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The Interface of Infectious Disease and Neuro-ophthalmology

Joseph R. Berger, MD

Five articles in this issue of the Journal of Neuro-Ophthalmology are interwoven by a common thread, namely, infectious disease as the underlying etiology of neuro-ophthalmic disorders. Affecting both the afferent and efferent visual systems, these reports encompass virtually every form of infectious agent ranging from viruses to parasites.

Sridhar et al (1) describe 3 patients seen in south Florida who developed neuro-ophthalmic complications of fungal disease. The entity they describe, allergic fungal sinusitis (AFS), is very different than the more familiar form of invasive fungal sinusitis. Invasive fungal sinusitis can be classified into 3 types (2). The acute (fulminant) type is characterized by headache, fever, nasal crusting, and epistaxis. One example is mucormycosis, characterized by hyphal invasion of blood vessels, vasculitis with thrombosis, and tissue infarction. Granulomatous invasive fungal sinusitis occurs with Aspergillus flavus infection and presents with proptosis in an immunocompetent host. Chronic invasive fungal sinusitis is distinguished by a prolonged course coupled with dense accumulation of hyphae and vascular invasion. It is associated with diabetes mellitus and corticosteroid treatment and may cause orbital apex syndrome. However, the patients described by Sridhar et al (1) had AFS. They developed painless visual loss, ophthalmoplegia, and ptosis due to allergic reaction to dematiaceous fungal sinus disease. This disorder is likely underrecognized and arises from several varieties of ubiquitous fungi. A number of features distinguish this disorder from the invasive fungal sinusitis. Patients with AFS are not immunocompromised, there appears to be a geographic distribution of AFS with most cases reported in hot humid environments, and it occurs as an allergic response to the fungus rather than as consequence of the organism’s capacity to invade and destroy tissue. While not a novel suggestion, the authors propose that hurricanes, by increasing the exposure to dematiaceous fungi, may predispose individuals to AFS. Importantly, AFS is a treatable disorder in which recovery follows surgical evacuation of the fungal mass and corticosteroid treatment. Since there have been no randomized controlled therapeutic trials for AFS, issues regarding duration of corticosteroid therapy and the role of antifungal agents remain unknown. These patients typically have an allergic diathesis, and immunotherapy directed against allergens to which they are sensitive may have a role in management (3).

Lyme disease would not be the first diagnosis to come to mind in a 90-year-old woman presenting with painless ptosis, but Xu et al (4) describe such a patient. They emphasize the importance of considering Lyme disease in the differential diagnosis of orbital cellulitis. This complication must be quite unusual as the authors were able to identify only 4 cases in their review of the literature. In the patient described by Xu et al (4), the serological studies for Lyme disease obtained proximate to the tick bite were negative. Six months later, at the time of presentation with orbital cellulitis, there was convincing evidence of serological conversion with Western blot (WB) for Borrelia burgdorferi immunoglobulin G (IgG). The sensitivity and standardization of immunoblots for Lyme have improved substantially with the use of recombinant antigens, and detection rates for serum antibodies varies between 20% and 50% in localized infection, 70%–90% in disseminated early disease, and approaches 100% in late disease (5). Several well-established antibiotic regimens, including oral antimicrobial therapy for European neuroborreliosis, have been demonstrated to be effective (6). Antimicrobial therapy for more than 4 weeks is unnecessary and is associated with significant morbidity.

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The author reports no conflicts of interest.
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A wide variety of ocular abnormalities have been described with cat scratch disease (7). Neuroretinitis is a frequent manifestation of cat scratch disease due to Bartonella henselae. Like Lyme disease, cat scratch disease also may be difficult to diagnose if one relies solely on serological studies. Neither patient reported by Gulati et al (8) in this issue of the Journal initially fulfilled serological criteria for B. henselae infection. Repeat testing supported the diagnosis in both cases and demonstrates the importance of having a high index of suspicion for this infection and pursuing the diagnosis with serial sampling. Several different serological tests are used for the diagnosis of cat scratch disease, including the immunofluorescence assay (IFA), the enzyme-linked immunosorbent assay, and WB analysis. The sensitivities of different IFAs range from 14% to 100%, depending on the antigen used, the cut-off chosen, and the test procedures (9). Alternatively, presumptive treatment based on reasonable clinical suspicion may be a necessary and appropriate course of action.

Elston et al (10) describe a 69-year-old Caucasian woman who presented with facial skin lesions and unilateral trigeminal and facial neuropathies coupled with a peripheral neuropathy and similar dermatological lesions over her extremities. Establishing the diagnosis of multibacillary leprosy required skin biopsy although her history of having lived in Indonesia for 8 years, an endemic area for leprosy, 3 years before returning to the United Kingdom and the nature of her clinical findings were highly suggestive of leprosy. Despite the appropriate antimicrobial therapy, complications attributable to Mycobacterium leprae seem to have progressed, but the patient succumbed to lung cancer within several months. When cranial nerve involvement occurs with leprosy, the trigeminal and facial nerves are most commonly involved (11). Eighteen percent of leprosy patients attending a neurology clinic in Vellore, India, had cranial nerve involvement (11). The patient described by Elston et al (10) illustrates the importance of obtaining a travel history. While leprosy is a treatable and a potentially curable disorder, persistent infection and relapse have been observed (12,13).

Every physician should recognize that nystagmus coupled with an altered level of consciousness might indicate an underlying seizure disorder. Lee et al (14) report a patient with herpes encephalitis who developed ictal nystagmus occurring with nonconvulsive status epilepticus. The diagnosis in their patient was not established with detection of herpes simplex virus (HSV) in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR), but rather by demonstrating IgG directed against HSV in the CSF. While CSF PCR for HSV is highly sensitive and specific, in the first 72 hours of illness, false-negative tests may occur (15). The electroencephalography findings reported by Lee et al (14) suggest that the ictal nystagmus was believed to have emanated from cortical saccade regions of the brain and resulted in nystagmus with the fast phase beating to the opposite side. While epileptic nystagmus complicating HSV encephalitis is unusual, physicians should be alert to the possibility of this CNS infection in any patient presenting with new onset seizure coupled with fever and headache.

These case reports and case series illustrate the importance of keeping infectious disease in the differential diagnosis of patients presenting with neuro-ophthalmic disorders. They illustrate the diversity of causative organisms, the variety of clinical manifestations confronting the neuro-ophthalmologist, and the difficulties encountered in establishing the diagnosis. Yet, it is essential that infectious conditions be recognized in a timely fashion as they are potentially entirely reversible if treated promptly and appropriately.

REFERENCES

Neuro-ophthalmic Manifestations of Fungal Disease Associated With Posthurricane Environment

Jayanth Sridhar, MD, Byron L. Lam, MD, Joshua Pasol, MD, Linda Sternau, MD

Background: Allergic fungal sinusitis (AFS) is thought to represent an immunologic response to exposure to dematiaceous fungi. These fungi are known to cause disease more frequently in hot and humid climates and seasons.

Methods: Three patients presented with unusual manifestations of fungal disease after exposure to environments recently affected by hurricanes.

Results: Two patients had AFS, 1 with gradual painless visual loss from an AFS mass extending into the suprasellar region and 1 with orbital apex syndrome. Another patient had invasive fungal disease and developed orbital apex syndrome.

Conclusions: These cases underscore the importance of clinical recognition of fungal disease in patients with sinus, orbital, or skull base involvement as well as its potential for causing permanent visual loss. This report suggests a potential association between fungal disease and tropical storm exposure.

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Fungal disease of the sinuses is classified into 4 subtypes: chronic noninvasive infection, chronic indolent infection, fulminant invasive disease, and allergic fungal sinusitis (AFS) (1). AFS is the most recently described form, thought originally to be an allergic response to Aspergillus species (2). It is now known that dematiaceous fungi, such as Bipolaris and Drechslera, are the principle organisms involved (3). AFS is relatively common, accounting for up to 7% of sinus disease in patients undergoing sinus surgery (4). The exact pathogenesis of AFS is unknown but is thought to involve both type 1 (immediate, IgE-mediated) and type 3 (immune complex, IgG-mediated) immunologic reactions to fungal antigens after fungal colonization of the sinuses (5).

AFS is usually seen in immunocompetent individuals with long-standing sinus disease symptoms (6). Most commonly, AFS occurs in hot and humid environments (7). The dematiaceous fungal species that cause AFS have been demonstrated to cause disease more frequently in warmer and more humid months as well (8). Despite being “noninvasive” by definition, AFS is not benign and may cause destructive inflammation extending through the sinuses into the orbit and cavernous sinus, leading to ophthalmoplegia (9,10).

We report 3 patients with fungal disease associated with exposure to posthurricane environments. Two patients had AFS, and 1 patient had invasive fungal infection. The cases underscore the importance of clinical recognition of fungal disease in patients with sinus, orbital, or skull base involvement as well as its potential for causing permanent visual loss.

CASE REPORTS

Case 1
A 25-year-old Miami schoolteacher presented with a 10-month history of painless vision loss in the left eye that worsened in the week prior to presentation. She had a history of seasonal allergies and migraine headache. She was present in Miami when both Hurricane Katrina and Wilma passed through south Florida and worked in a hurricane-damaged classroom.

Best-corrected visual acuity was 20/20, right eye, and 5/200, left eye, with a left relative afferent pupillary defect. Extraocular movements were full. The right fundus was normal, and the left optic disc had pallor and temporal cupping. Manual kinetic perimetry disclosed a left central scotoma, and optical coherence tomography was consistent with retinal nerve fiber layer thinning in the left eye.
MRI revealed a sphenoid sinus mass, hypointense on T2 images, extending superiorly displacing the pituitary gland and optic chiasm (Fig. 1). The lesion also extended posteriorly to displace and distend the prepontine cistern and compress the basilar artery.

The patient underwent transsphenoidal surgery with the removal of a large necrotic mass with bony fragments from the left sphenoid sinus. Histopathologic examination revealed septated fungal hyphae and several eosinophils mixed with mucus and necrotic material (Fig. 2). Fungal culture grew *Drechslera* species.

The patient was diagnosed with AFS and placed on intravenous methylprednisolone and oral voriconazole. The patient’s kinetic visual fields improved over the next few months, with near resolution of the left central scotoma. Repeat MRI 9 months after the surgery revealed persistent AFS, but the patient did not follow-up thereafter.

**Case 2**

A 58-year-old Caribbean woman was referred with a 6-month history of left-sided headache with recent development of diplopia. Medical history was remarkable for hypertension and hypothyroidism managed with oral medication. About 2 years prior to presentation, she worked in a hurricane-damaged hotel in the Cayman Islands and was involved in cleaning the damaged rooms.

Best-corrected visual acuity was 20/25, right eye, and 20/20, left eye, with no relative afferent pupillary defect. The patient had a left sixth nerve palsy and decreased sensation in the ophthalmic branch (V1) of the left trigeminal nerve. Ophthalmoscopic examination was unremarkable.

MRI showed left sphenoid and posterior ethmoid sinus expansion extending around the left internal carotid artery into the cavernous sinus. The sinuses appeared to be filled with a central nonenhancing material demonstrating peripheral mucosal enhancement (Fig. 3).

The patient underwent emergent left transsphenoidal decompression, with the removal of a large necrotic mass. Histopathology revealed numerous eosinophils and septate hyphal fragments consistent with AFS.

The patient was placed on a short course of intravenous methylprednisolone and a 1-year course of voriconazole. One month later, the patient’s sixth nerve palsy decreased and V1 sensation had resolved. At the 2-year follow-up, the patient was asymptomatic, with no headache or sinus congestion. MRI showed residual left sphenoid sinus disease.

**Case 3**

A 64-year-old Federal Emergency Management Agency (FEMA) inspector was referred with a 3-month history of vision loss in the right eye as well as right ptosis and ophthalmoplegia. He had been previously evaluated elsewhere for severe right-sided temporal headache associated with weight loss and was treated briefly with oral corticosteroids for presumed giant cell arteritis. Over the next 3 months, he experienced rapid deterioration of vision in the right eye followed by diplopia and ptosis. The patient was diabetic, and in the year prior to presentation, he had been working without any respiratory protection as an inspector of mold-infested trailers in the areas of Louisiana affected by Hurricane Katrina.

Visual acuity was no light perception (NLP), right eye, and 20/25, left eye. The right pupil demonstrated both an afferent and an efferent pupillary defect. There was a complete right upper lid ptosis with near-complete ophthalmoplegia with only minimal abduction of the right eye. The fundi were normal as was function of the trigeminal and facial nerves.

MRI revealed an enhanced area involving the right optic nerve and cavernous sinus (Fig. 4). The patient underwent...
transsphenoidal biopsy the following day that revealed fungal hyphae. He was treated with oral cortisone, oral voriconazole, and intravenous micafungin.

Two months later, the area of infection appeared more extensive on MRI and a right orbital exenteration was considered. The patient declined surgery, and medical therapy was changed to micafungin and voriconazole, both given intravenously for an additional 10 months. The patient’s headache and ophthalmoplegia gradually improved with full extraocular movements at 1 year following the initial presentation. Visual acuity remained NLP, right eye.

**DISCUSSION**

As our first 2 cases demonstrate, AFS must be considered in the differential diagnosis of patients who have sinus disease and ophthalmic symptoms and signs (11). As many as 17% of patients can present with orbital symptoms (12). Although proptosis is the most common orbital sign, diplopia and visual loss in the absence of proptosis and pain have been reported as presenting complaints (6,13). The pathophysiology of AFS involves destructive inflammation extending through the sinuses and orbit into the cavernous sinus and resulting in ophthalmoplegia (9,10). The mechanism of visual loss is thought to be secondary to either orbital inflammation causing a contiguous inflammatory optic neuritis or optic nerve ischemia secondary to increased intraorbital pressure (14).

If the diagnosis of AFS is suspected clinically, neuroimaging with attention to the paranasal sinuses and orbital structures is necessary. MRI classically reveals decreased T2 intensity in the involved sinus with high signal of the surrounding mucosa (15). This imaging finding is thought to be due to both the accumulation of desiccated mucosal secretions and high concentrations of manganese, iron, and calcium in

**FIG. 2.** Case 1. Histopathology of sphenoid sinus mass. A. Eosinophils mixed with mucus and necrotic material (hematoxylin and eosin, ×40). B. Septated fungal hyphae (Gomori methenamine silver, ×40).

**FIG. 3.** Case 2. Initial contrast-enhanced T1 axial (A) and coronal (B) MRI with fat suppression reveals left sphenoid and posterior ethmoid sinus disease with left orbital apex involvement.

the fungal concretions (16,17). Definitive diagnosis depends on positive fungal culture and histopathology of tissue revealing extensive mucin, eosinophils, and septate hyphae (18).

Treatment of AFS consists of surgical removal of the fungal mass and postoperative use of systemic corticosteroids to reduce risk of recurrence (19). There is no evidence to either support or discredit the use of intravenous and oral antifungal agents (19).

In Case 1, the patient lived in Miami and began developing symptoms 2 months after 2 major hurricanes affected the region. Ten months later, she presented with unilateral visual loss from an optic neuropathy secondary to suprasellar inflammatory process, an infrequently reported finding in AFS (6). Imaging is exceptionally helpful in guiding appropriate therapy because glucocorticoid treatment without surgery could have resulted in permanent vision loss (12).

In Case 2, our patient cleaned hurricane-damaged hotel rooms in the Cayman Islands. Eighteen months later, she began having severe headache, and in another 5 months, she presented with a right cavernous sinus syndrome. This was confirmed on MRI, and treatment was made early enough to prevent any further clinical deterioration. Orbital apex syndrome is a very uncommon manifestation of AFS, occurring in only 2% of AFS patients with orbital symptoms (9).

In Case 3, the patient had a prolonged stay in Louisiana in the aftermath of Hurricane Katrina. Nine months after starting his job with FEMA, he began experiencing right-sided temporal headache followed by right-sided blindness, ptosis, and ophthalmoplegia. MRI revealed enhancement of the right orbital apex, which led to a transphenoidal biopsy revealing fungal hyphae. The patient’s ophthalmoplegia resolved with treatment but there was no improvement in vision.

What factors might facilitate fungal disease occurring in the posthurricane environment? Soil-dwelling fungi that induce fungal disease and AFS have been shown to cause more disease in wetter and warmer months. It is known that a water-rich environment is conducive to the growth of mold species (8). Hurricanes can create such an environment due to flooding and water damage. In the aftermath of Hurricane Katrina, aspergillus species were found to be more concentrated than normal in both general urban air quality studies and tests of the air in homes undergoing renovation (20,21). Six months after Hurricane Katrina, a direct correlation was demonstrated between exposure to water-damaged homes and respiratory symptoms (22).

Although it is impossible to assign causality, our 3 patients may all have developed fungal disease secondary to living and working in areas recently affected by inclement weather and flooding. They developed signs and symptoms over a 3- to 18-month period, consistent with the slow indolent course of AFS and fungal infection.

In conclusion, fungal disease, including AFS, is an important diagnostic consideration in the otherwise healthy patient presenting with symptoms, including visual loss, diplopia, facial numbness, and unilateral temporal headache. A potential association between tropical storm exposure and fungal disease, including AFS, requires further investigation.

REFERENCES

Prevalence of Diabetes Mellitus in Biopsy-Positive Giant Cell Arteritis

Jared L. Matthews, MD, David N. Gilbert, MD, Bradley K. Farris, MD, R. Michael Siatkowski, MD

**Background:** We tested the hypothesis that patients with diabetes mellitus (DM) develop biopsy-positive giant cell arteritis (GCA) significantly less frequently than nondiabetic patients.

**Methods:** We compared the prevalence of DM in patients with positive temporal artery biopsy (TAB) with that in patients with negative TAB via a retrospective study of 215 patients who underwent TAB. Patients were classified as having biopsy-positive GCA if microscopic examination disclosed active or healed arteritis. Patients were classified as having DM if they had a diagnosis of diabetes in their medical history or were taking oral hypoglycemic medications and/or insulin at or before the time of biopsy. In addition, we performed a meta-analysis of 8 previously published articles with a total of 1,401 additional biopsy-proven cases of GCA in patients whose status was recorded as diabetic or nondiabetic.

**Results:** Of 44 cases with biopsy-positive GCA in our patient cohort, only 4 (9.1%) were diabetic at or before the time of biopsy. Of 171 patients with negative TAB, 61 (35.7%) had DM (P = 0.0006). The prevalence of DM among recorded cases of biopsy-positive GCA ranged from 0% to 13.8% in the 8 studies included in our meta-analysis, with a combined frequency of 89 diabetic patients in a total of 1,401 cases (6.35%).

**Conclusion:** The low frequency of a positive TAB in diabetic GCA suspects should be considered when formulating an index of suspicion in the evaluation of patients with possible GCA. More research is needed to delineate the nature of the interaction between DM and GCA.

**Giant cell arteritis (GCA) is the most common form of vasculitis in the Western world (1). GCA is a disease of older adults—it is exceedingly rare in persons younger than 50 years, and the greatest risk of developing the disease is seen among those aged 75–85 years (2). The pathologic signature of GCA is granulomatous inflammation of medium and large vessels. In the involved vasculature, intimal hyperplasia and luminal obstruction may lead to ischemic manifestations, including headache, jaw claudication, scalp tenderness, and temporal artery involvement (3). Permanent visual loss occurs in 10%–20% of patients (4–7). A majority of patients with GCA also present with a syndrome of systemic inflammation, which may variably include fever, fatigue, weight loss, anorexia, night sweats, depression, elevations in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, and thrombocytosis (8–11).**

These clinical signs can be particularly difficult to assess in the diabetic patient, since ESR and CRP levels in diabetic patients can be altered for reasons other than GCA (12,13). Additionally, focal temporal or facial pain can be a presentation of trigeminal nerve irritation or ischemia in diabetic patients, unrelated to GCA (14,15). Finally, a falsely high index of suspicion for GCA in diabetic patients may lead to the use of high-dose steroids until temporal artery biopsy (TAB) can be performed, complicating blood glucose control.

The clinical impression among many physicians is that diabetic patients presenting with symptoms suspicious for GCA are rarely found to have positive TABs. This has support in the medical literature. In a study assessing the influence of traditional risk factors for atherosclerosis on the development of ischemic complications in GCA, Gonzalez-Gay et al (16) noted a low prevalence of diabetes mellitus (DM) in their series of GCA patients [17 (8.1%) of 210 patients with biopsy-positive GCA]. A study by Duhaut et al (17) found that the prevalence of DM in women with GCA was approximately half that of sex- and age-matched controls (6.43% and 11.83%, respectively, $P = 0.042$).
While a multitude of studies have sought to identify predictive factors for positive TAB in patients with suspected GCA (18–24), to our knowledge, no studies have sought to determine, as a primary objective, the prevalence of DM among patients with biopsy-positive GCA compared with a control group of patients with negative TAB.

METHODS

Subjects undergoing TAB were identified by searching the medical records database of Dean A. McGee Eye Institute for all patients who had received a billing code for the procedure from November 1, 1992, to February 1, 2011. A total of 215 patients who had cumulatively undergone 226 biopsies were selected for inclusion. In each case, TAB was performed because GCA was suspected after a careful consideration of each patient’s history, symptoms, signs, and the results of ancillary tests, including laboratory values. Two patients were excluded—a 55-year-old man due to incomplete medical records and a 17-year-old woman who received a TAB during a workup that eventually resulted in the diagnosis of angioedema.

Data were analyzed as a case–control study. Cases were defined as patients whose TABs were read as having either active or healed arteritis. Controls were defined as patients with TAB negative for active or healed arteritis. In the 11 patients who underwent bilateral biopsy, only the second biopsy was included. The individual medical records were consulted to determine each patient’s status as diabetic or nondiabetic. Diabetic patients were defined as all patients with a diagnosis of DM in their medical history and/or all patients taking oral hypoglycemic medications and/or insulin at or before the time of biopsy. The prevalence of DM was determined for both cases and controls and compared via χ² test for statistical significance.

For each group of patients, the mean age and gender were calculated and included for comparison, as well as ESR and CRP levels (when available), and the number of patients within each group with decreased visual acuity at presentation.

A search of the medical literature was conducted via PubMed using the search terms biopsy positive giant cell arteritis, biopsy positive temporal arteritis, temporal artery biopsy, giant cell arteritis and diabetes, temporal arteritis and diabetes, and diabetes mellitus and temporal artery biopsy. Secondary searches of the bibliographies of all relevant articles were conducted to achieve greater inclusiveness. Articles were selected for inclusion in the meta-analysis if they contained both cases of biopsy-positive GCA and sufficient information to determine the percentage of diabetic patients among the biopsy-proven cases.

RESULTS

Of 215 patients who underwent TAB at our institution, 44 (20.5%) were found to have biopsy-positive GCA. Among these positive cases, 4 patients (9.1%) were diabetic at or before the time of biopsy. In the control group of 171 patients with negative TAB (79.5% of the total cohort), 61 (35.7%) were found to be diabetic [odds ratio (OR) = 0.18, P = 0.0006]. These results are depicted in Table 1.

Patients ranged in age from 46 to 91 years, with one patient younger than 50 years. Comparison of gender, age, ESR and CRP levels (at the time of initial presentation, when available), and number of patients presenting with decreased visual acuity is presented in Table 2. In the total cohort of 215 patients, ESR and CRP values were available for 189 and 140 patients, respectively.

Our meta-analysis included a total of 8 studies that reported both cases of biopsy-positive GCA and sufficient information to determine the frequency of DM among the positive cases (16–18,25–29). Taken together, these studies included a total of 1,401 cases of biopsy-positive GCA. Only 89 patients (6.35%) had a concurrent diagnosis of DM as it was variably defined within each study. The frequency of DM among biopsy-positive cases ranged from 0% to 13.8%. The statistics of each study are summarized in Table 3.

DISCUSSION

Our finding of a low prevalence of DM among patients with biopsy-positive GCA raises an important question: does this result reflect a true decrease in the likelihood of developing GCA or instead a greater tendency of diabetic patients to develop the biopsy-negative form of the disease? This question could be answered by comparing the prevalence of biopsy-negative GCA among diabetic patients with negative TAB with that of nondiabetic patients with negative TAB.

The frequency of DM in our control group (35.7%) was high when compared with the estimate of 24.1% of the general population of Oklahoma residents aged 60 years or older (30). The high prevalence in our controls is not surprising. Many underwent TAB in the course of a workup ultimately resulting in a diagnosis of non-arteritic anterior ischemic optic neuropathy (NAION), and diabetes is a well-known risk factor for NAION (31,32). Additionally, because ESR and CRP can be elevated in diabetic

| TABLE 1. Frequency of diabetes mellitus among cases and controls |
|---------------------|-------------|-----------|
|                    | TAB+       | TAB−      | Total |
| DM+                 | 4          | 61        | 65    |
| DM−                 | 40         | 110       | 150   |
| Total               | 44         | 171       | 215   |

Odds ratio = 0.18, 95% confidence interval = 0.062–0.528; P = 0.0006 (χ² test).
patients for reasons other than GCA (12,13), such eva-
tions may lead to a greater likelihood of TAB being per-
formed when diabetic patients present with symptoms
suggestive of GCA compared to nondiabetic patients. It
should be cautioned that our study population differs in
many ways from the general population. Our subjects were
overwhelmingly female and typically older than 70 years,
and our study included data from as far back as 1992, while
the data cited on the prevalence of DM in the general
population of Oklahoma contains a more uniform gender
distribution and greater ethnic diversity. The data for the
general population also is more recent (2003–2007), which
is problematic due to the fact that the prevalence of DM is
increasing over time (33). Nevertheless, our findings have
clinical relevance: they assist in formulating an index of
suspicion in potential GCA patients and raise caution assess-
ing diabetic patients with elevated ESR and CRP and those
with facial/scalp pain.

The exact nature of the interplay between GCA and DM
appears to be complex. In our literature review, we found
only one report comparing the rate of DM in positive TAB
cases with a control group of negative biopsies (25). The
difference in frequency of DM between cases and controls
in that study (10.7% and 19.1%, respectively) was not
statistically significant. In assessing the role of cardiovascular
risk factors in the pathogenesis of GCA, Duhaut et al (17)
found a similar proportion of cases and controls with DM
among men. This probably was due to the inclusion of both
biopsy-negative GCA patients and polymyalgia rheumatica
patients, as well as controls being population based, sex and
age matched, not those with negative biopsies. Despite this,
a history of DM was associated with a 50% reduction in the
odds of developing GCA in women (OR = 0.51, P = 0.042).
In another study, these investigators found that during the
course of a 3-year follow-up (mean = 23 months), patients
with biopsy-negative GCA were more likely to develop new-
onset DM than patients with biopsy-positive GCA (inci-
dence density, 17.66 cases/year/100 patients vs 8.00 cases/
year/100 patients, respectively, P = 0.0005) (18). Similarly,
in a study reviewing the final diagnoses rendered in a group
of biopsy-negative patients, Roth et al (34) found a high
prevalence of DM (5 of 33, 15%).

The pathogenesis of GCA as an antigen-driven inflam-
matory process has been well described, although the
inciting antigen has yet to be elucidated (35). Recent advan-
ces in our understanding of the pathogenesis of DM have
also characterized the disease within the paradigm of an
inflammatory disorder (36). There are several opportunities
for the two disorders to potentially overlap, and we offer
three testable hypotheses to explain the low frequency of
biopsy-positive patients among diabetic patients.

First, multiple studies have demonstrated that cytokine
profiles are a major determinant of GCA clinical phenotype
and disease severity (4,37–39). Cytokine profiles can also
influence TAB results. For example, a subgroup of GCA
patients with large artery involvement defined by subclavian
and axillary disease demonstrates a distinct cytokine pattern
marked by high levels of interleukin-2 gene transcripts in
arterial samples. These patients also demonstrate a low rate
of positive TAB of only 33% (39). Furthermore, alterations
in cytokine levels have also been observed in patients with
type 2 DM, with elevated levels of interleukin-1β, interleu-
kin-6, and CRP being predictive of the development of DM
(12,40). The commonality of derangements in inflam-
matory cytokines in both diseases raises an intriguing possi-
bility, and we therefore hypothesize that in individuals with
DM, the cytokine profile may be altered in such a way as to
preclude the development of GCA or, alternatively, shifted
toward a cytokine pattern more likely to result in biopsy-
negative disease.

Second, the T cells of diabetic patients may be less respon-
sive to the inciting antigens being presented by the dendritic
cells (DCs) of the arterial adventitia, a process that is under-
stood to be crucial in the development of GCA (35,40).
Studies have demonstrated a decreased responsiveness to vari-
ous antigens in the T cells of diabetic patients (41).

Third is the possibility that there is decreased activation
of DCs in patients with DM (42). The process of nonen-
zymatic glycosylation in hyperglycemic states has been well
described, and it is possible that diabetic patients may alter

TABLE 2. Gender, age, ESR, CRP, and number of patients with decreased visual acuity at presentation
undergoing temporal artery biopsy

<table>
<thead>
<tr>
<th></th>
<th>TAB−, DM−</th>
<th>TAB−, DM+</th>
<th>TAB+, DM−</th>
<th>TAB+, DM+</th>
<th>Study Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects</td>
<td>110 (51.2%)</td>
<td>61 (28.4%)</td>
<td>40 (18.6%)</td>
<td>4 (1.9%)</td>
<td>215</td>
</tr>
<tr>
<td>Biopsies performed</td>
<td>117</td>
<td>63</td>
<td>42</td>
<td>4</td>
<td>226</td>
</tr>
<tr>
<td>% Female</td>
<td>71</td>
<td>75.4</td>
<td>77.5</td>
<td>50</td>
<td>73</td>
</tr>
<tr>
<td>% Male</td>
<td>29</td>
<td>24.6</td>
<td>22.5</td>
<td>50</td>
<td>27</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>72.3</td>
<td>69.2</td>
<td>75.5</td>
<td>73.5</td>
<td>72.1</td>
</tr>
<tr>
<td>% 50 years of age or older</td>
<td>100</td>
<td>98.4</td>
<td>100</td>
<td>99.5</td>
<td></td>
</tr>
<tr>
<td>Mean ESR, mm/h</td>
<td>49.5 (n = 97)</td>
<td>56.9 (n = 53)</td>
<td>69.8 (n = 35)</td>
<td>56.3 (n = 4)</td>
<td>55.5 (n = 189)</td>
</tr>
<tr>
<td>Mean CRP, mg/L</td>
<td>21.4 (n = 68)</td>
<td>16.4 (n = 42)</td>
<td>42.3 (n = 26)</td>
<td>15.4 (n = 4)</td>
<td>23.6 (n = 140)</td>
</tr>
<tr>
<td>Decreased visual acuity at presentation</td>
<td>55 (50%)</td>
<td>34 (55.7%)</td>
<td>23 (57.5%)</td>
<td>4 (100%)</td>
<td>116 (54%)</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; TAB, temporal artery biopsy.
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Cases of TAB+ GCA</td>
<td>210</td>
<td>136</td>
<td>25</td>
<td>207</td>
<td>400*</td>
<td>40</td>
<td>28</td>
<td>145</td>
<td>44</td>
</tr>
<tr>
<td>Female</td>
<td>113 (53.8%)</td>
<td>101 (74.3%)</td>
<td>18 (72%)</td>
<td>157 (75.9%)</td>
<td>282 (70.5%)</td>
<td>25 (62.5%)</td>
<td>19 (68%)</td>
<td>108 (74.5%)</td>
<td>33 (75%)</td>
</tr>
<tr>
<td>Male</td>
<td>97 (46.2%)</td>
<td>35 (25.7%)</td>
<td>7 (28%)</td>
<td>50 (24.1%)</td>
<td>118 (29.5%)</td>
<td>15 (37.5%)</td>
<td>9 (32%)</td>
<td>37 (25.5%)</td>
<td>11 (25%)</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>74.6</td>
<td>73</td>
<td>72</td>
<td>75.2</td>
<td>74.4</td>
<td>72.8</td>
<td>Not available</td>
<td>75.7</td>
<td>75.3</td>
</tr>
<tr>
<td>Mean ESR, mm/h</td>
<td>93 (n = 210)</td>
<td>87</td>
<td>78</td>
<td>88 (n = 207)</td>
<td>Not available</td>
<td>91.1</td>
<td>Not available</td>
<td>87</td>
<td>68.4 (n = 39)</td>
</tr>
<tr>
<td>TAB+ cases with concurrent DM</td>
<td>17 (8.1%)</td>
<td>0</td>
<td>2 (8%)</td>
<td>14 (6.8%)</td>
<td>32* (8%)</td>
<td>1† (2.5%)</td>
<td>3 (10.7%)</td>
<td>20 (13.8%)</td>
<td>4 (9.1%)</td>
</tr>
<tr>
<td>Study definition of DM</td>
<td>Diagnosed with DM by family physician or plasma glucose greater than 140 mg/dL at the time of admission and verified by repeat test</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>Personal history of DM</td>
<td>1979 NIH National Diabetes Group Criteria</td>
<td>Not available</td>
<td>Not available</td>
<td>Medical history of DM in patient chart and/or oral diabetes medications in chart and/or insulin usage documented on or before TAB date</td>
</tr>
<tr>
<td>Control population</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>85 patients with biopsy-negative GCA as defined by fulfillment of at least 5 of 10 clinical criteria estimated to be 85% sensitive and 95% specific</td>
<td>281 population-based, individually sex- and age-matched controls</td>
<td>40 population-based, age, sex, body mass index, cardiovascular risk factor, and ethnically matched controls</td>
<td>Not available</td>
<td>171 patients with negative TAB</td>
</tr>
<tr>
<td>Concurrent DM in control population</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
<td>10 (11.8%)†</td>
<td>28 (9.96%)</td>
<td>3 (7.5%)§</td>
<td>129 (19.1%)</td>
<td>Not available</td>
<td>61 (35.7%)</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; NIH, National Institutes of Health; TAB, temporal artery biopsy.

*Includes TAB positive, TAB negative, and polymyalgia rheumatica cases.

†Met criteria for DM during ultrasound evaluation 32.5 months after completing steroid treatment.

‡P = 0.15 in comparison between cases and controls.

§P = 0.62 in comparison between cases and controls.
the inciting antigen(s) of GCA, rendering them unable to activate vascular DCs. It is also possible that multiple mechanisms are involved. The potential interaction of GCA and DM clearly is a subject that merits further study.

REFERENCES
Differentiation of Optic Disc Edema From Optic Nerve Head Drusen With Spectral-Domain Optical Coherence Tomography

Ozge Sarac, MD, Yelda Y. Tasci, MD, Canan Gurdal, MD, Izzet Can, MD

Background: To assess the efficacy of quantitative analysis of the optic nerve head and peripapillary retinal nerve fiber layer (RNFL) with the spectral-domain optical coherence tomography (SD-OCT) in differentiating optic disc edema (ODE) from optic nerve head drusen (ONHD).

Methods: Prospective clinical study. Twenty-five eyes of 25 ODE patients (group 1), 25 eyes of 25 ONHD patients (group 2), and 25 eyes of 25 healthy subjects were included. The thickness of the peripapillary RNFL, the thickness of the subretinal hyporeflective space (SHYPS), the area of the SHYPS, the horizontal length of the optic nerve head, and the angle between the temporal RNFL and the optic nerve head (α-angle) were evaluated with SD-OCT.

Results: The mean RNFL thickness was significantly greater in group 1 when compared with group 2 and control group (P < 0.001). The receiver operating characteristic curve areas for temporal and nasal RNFL thicknesses in differentiating group 1 and group 2 were 0.819 and 0.851, respectively (for temporal RNFL thickness 101.5 μm: sensitivity 92%, specificity 65%; for nasal RNFL thickness 74.5 μm: sensitivity 92%, specificity 47%). The mean SHYPS thickness, SHYPS area, and degree of the α-angle were greater in group 1 when compared with group 2 (P < 0.05). For the SHYPS thickness >464 μm: 85% sensitivity and 60% specificity; for the SHYPS area >811 μm²: 85% sensitivity and 85% specificity; and for the α-angle >141°: 77% sensitivity and 95% specificity were obtained.

Conclusion: The quantitative analysis of the optic nerve head and peripapillary RNFL with SD-OCT can provide useful data in differentiating ODE from ONHD.

Optic disc edema (ODE) is usually due to increased intracranial pressure or an optic neuropathy that may necessitate neurologic or systemic evaluation and medical or surgical treatment. Optic nerve head drusen (ONHD) are laminated calcified hyaline bodies that form anterior to the lamina cribrosa of the optic nerve and are not associated with neurologic disease, yet may simulate ODE (1–4).

During patient evaluation, differentiation of ODE from ONHD is crucial. Examination techniques commonly performed in the diagnosis of ONHD are B-scan ultrasonography, fluorescein angiography, and CT (1,5). Application of optical coherence tomography (OCT), a noninvasive imaging technique that creates images closely resembling histologic sections, recently has achieved increasing popularity in differentiating ODE vs ONHD. OCT parameters studied included peripapillary retinal nerve fiber layer (RNFL) thickness (6,7) and direct visualization of the optic nerve head (8).

We assessed the efficacy of spectral-domain optical coherence tomography (SD-OCT) in differentiating ODE and ONHD by visualizing the optic nerve head and the peripapillary RNFL. In addition, we sought to identify SD-OCT features that would differentiate ODE from ONHD.

METHODS

This prospective study was conducted in compliance with the institutional and government review board regulations, informed consent regulations, and the Declaration of Helsinki. Written informed consent was obtained from all patients and control subjects.

Twenty-five eyes of 25 ODE patients (11 with papilledema, 8 with nonarteritic anterior ischemic optic neuropathy, and 6 with optic neuritis), 25 eyes of 25 ONHD patients, and 25 eyes of 25 normal subjects were recruited from the Department of Neuro-Ophthalmology of Yildirim Beyazit University, Ataturk Hospital, from December 2009...
to April 2011. Patients with ODE formed group 1, and patients with ONHD formed group 2. The degree of ODE was variable from subtle to severe. In bilateral asymmetric cases, only the more edematous optic disc was evaluated, and in bilateral symmetric cases, only the right eye was included for study. Those excluded were patients younger than 7 years or older than 70 years and individuals with high hyperopia (greater than +7.00 diopters [D]) or high myopia (greater than −6.00 D).

All patients underwent complete ophthalmologic examination, including visual acuity testing, slit-lamp examination, dilated funduscopy, color fundus photography, autofluorescence imaging, and ocular echography. Supplemental testing included visual fields and fluorescein angiography. Patients suspected of having a neurologic disorder underwent neurologic examination, brain CT imaging, and cerebrospinal fluid analysis. If the diagnosis of ONHD could not be made with funduscopy, it was established by fulfilling at least 2 of the following 4 criteria: autofluorescence on fundus photography, calcification on B-scan ultrasonography or CT, and normal opening pressure on lumbar puncture. Patients with ODE who were included in the study had documented resolution of ODE during the follow-up period.

Patients were evaluated with SD-OCT (RTVue, software version 2.7; Optovue, Inc, Fremont, CA) imaging the optic disc and the peripapillary RNFL. This instrument takes 26,000 A-scans per second, with a frame rate of 256 to 4,096 A-scans per frame. It has a depth resolution of 5 μm and a transverse resolution of 15 μm. The scan range is 2–2.3 mm in depth and 2–12 mm in the transverse plane. The scan beam wavelength is 840 ± 10 nm (9).

All OCT measurements were performed by a single examiner (Y.Y.T.). Each participant was instructed to fixate on an external target positioned in the primary position. Multiple horizontal and vertical scans centered 3.45 mm diameter (radius, 1.73 mm) on the optic disc were performed. The configurations of the optic nerve head and retinal layers around the optic nerve head and the average peripapillary RNFL thickness of the superior, inferior, nasal, and temporal quadrants in group 1, group 2, and the control groups were evaluated. The hyporeflective space located between the sensory retina and the retinal pigment epithelium and choriocapillaris complex, designated as the subretinal hyporeflective space (SHYPS), was determined in groups 1 and 2 (10). With the caliper tool provided by the SD-OCT, the thickness (Fig. 1A) and area (Fig. 1B) of the SHYPS were measured. The thickness of the SHYPS was measured from the highest point in each patient. The angle between the retinal pigment epithelium and the outer nuclear layer at the optic nerve head margin, termed the α-angle (Fig. 1C), was measured manually with a caliper tool from the computer screen in the section where the optic nerve head had the highest configuration. Finally, the horizontal length of the optic nerve was determined (Fig. 1D).

Statistical analysis was performed using the Statistical Package for Social Sciences software (version 16.0; SPSS, Inc, Chicago, IL). The significance of the difference in the RNFL thickness and optic nerve head parameters were assessed by the analysis of variance test between the study groups and the control group. Differences were considered statistically significant at $P \leq 0.05$.

![FIG. 1. SD-OCT in a patient with ODE. (A) thickness (arrow) of the SHYPS, (B) area of SHYPS, (C) α-angle: the angle between the RNFL and the optic nerve head margin, (D) horizontal length of the optic nerve head. SHYPS, subretinal hyporeflective space.](image-url)
RESULTS

Group 1 was composed of 17 women (68%) and 8 men (32%), and group 2 included 15 women (60%) and 10 men (40%). The average age in group 1 was 38.13 ± 18.84 years (range, 19–61 years) and that in group 2 was 29.29 ± 15.58 years (range, 7–55 years). The control group consisted of 15 women (60%) and 10 men (40%), with an average age of 32.53 ± 15.05 years (range, 18–52 years).

The mean RNFL thickness was significantly greater in group 1 when compared with group 2 and the control group (P < 0.001; Table 1). No statistically significant difference between group 2 and the control group was seen (P = 0.320; Table 1). While differentiating groups 1 and 2, the receiver operating characteristic (ROC) curve areas were calculated in each quadrant for the RNFL thickness. The ROC curve area for temporal RNFL thickness was 0.819. When the cutoff point for temporal RNFL thickness was set at 101.5 μm, 92% sensitivity and 65% specificity were obtained. The area under the ROC curve for nasal RNFL thickness was 0.851 (for RNFL thickness >74.5 μm: sensitivity 92%, specificity 47%).

The mean thickness of the highest point of the SHYPS was 582.27 ± 208.16 μm in group 1 and 456.77 ± 112.07 μm in group 2 (P = 0.04). When the cutoff point for the thickness of the highest point of the SHYPS was set at 464 μm, 85% sensitivity and 60% specificity were obtained. The mean area of the SHYPS was 1,110 ± 210 μm² in group 1 and it was decreased to 620 ± 120 μm² in group 2 (P = 0.008). The area under the ROC curve for nasal RNFL thickness was 0.851 (for area >811 μm²: sensitivity 85%, specificity 89%).

The mean degree of the α-angle was 145.77 ± 6.34° in group 1 compared with 131.18 ± 11.89° in group 2 (P < 0.001). The area under the ROC curve for this parameter was 0.851 (for angle >141°: sensitivity 77%, specificity 95%).

The mean horizontal length of the optic nerve head was 2,530 ± 830 μm in group 1. The value was 1,920 ± 241 μm in group 2 and 1,530 ± 200 μm in the control subjects. The differences between groups 1 and 2 (P = 0.007) and group 1 and the control group (P < 0.01) were statistically significant. The mean horizontal length of the optic nerve head was positively correlated with the mean RNFL thickness (r = 0.557, P < 0.001), the mean SHYPS thickness (r = 0.757, P < 0.001), and the mean area of the SHYPS (r = 0.927, P < 0.001).

DISCUSSION

ONHD are a common, benign, congenital anomaly of the optic nerve, which rarely lead to decreased visual acuity (1,11). It is thought that the formation of ONHD is caused by axoplasmic transport alteration and axonal degeneration in the presence of a small scleral canal (12). In affected patients, the configuration of the optic nerve head is variable, and the drusen may be visible on the disc surface or buried within the disc.

It is buried ONHD that may simulate ODE and lead to diagnostic uncertainty. Techniques to differentiate these 2 conditions include fundoscopy, optic disc autofluorescence, fluorescein angiography, B-scan ultrasonography, and CT scanning. B-scan ultrasonography has been shown to be superior to autofluorescence and CT (13). In recent years, there have been a number of reports evaluating OCT to distinguish between ODE and ONHD, focused primarily on measurements of the peripapillary RNFL thickness (6,8,10,14). RNFL thickness, especially in the nasal quadrant, has been shown to be decreased in ONHD when compared with ODE (8). In some patients with ONHD, photoreceptor changes also have been documented (15).

Using OCT, Savini et al (10) identified the SHYPS, a hyporeflective space located between the sensory retina and the retinal pigment epithelium and choriocapillaris in ODE patients. Johnson et al (7) found a decrease in the mean SHYPS thickness in ONHD patients compared with those with ODE. They considered the extravasated fluid from the optic nerve head, percolating into and elevating the subretinal space, as the most plausible cause for the increased SHYPS thickness. These investigators characterized the OCT appearance of ODE as an elevated optic nerve head with a smooth internal contour and a SHYPS

| TABLE 1. RNFL thickness in patients with ODE, ONHD, and controls |
|---------------------|---------------------|-----------------|------------------|------------------|
|                     | ODE (μ)             | ONHD            | P (ODE vs ONHD)  | P (ODE vs Controls) |
| Temporal            | 132.87 ± 25.43      | 102.24 ± 31.76  | 0.012            | 0.946             |
| Superotemporal      | 182.87 ± 50.85      | 165.77 ± 56.6   | 0.056            | 0.032             |
| Inferotemporal      | 187.4 ± 50.67       | 183.3 ± 31.26   | 0.957            | 0.001             |
| Nasal               | 133.2 ± 52.68       | 87.12 ± 28.8    | 0.003            | 0.724             |
| Superonasal         | 177.47 ± 51.4       | 148.65 ± 38.3   | 0.069            | 0.090             |
| Inferonasal         | 181.47 ± 56.39      | 149.47 ± 18.25  | 0.998            | 0.001             |
| Average             | 156.87 ± 31.59      | 128.24 ± 29.85  | 0.320            |                   |

ODE, optic disc edema; ONHD, optic nerve head drusen; RNFL, retinal nerve fiber layer
thickness under the optic nerve head with a gradient taper away from the disc. A “lumpy bumpy” internal optic nerve contour and a more abrupt taper of the SHYPS (Fig. 2) were suggestive of ONHD (7). We differentiated ODE from ONHD using quantitative measures obtained with SD-OCT: peripapillary RNFL thickness, SHYPS thickness, area of the SHYPS, and degree of the α-angle.

Measuring RNFL thickness with SD-OCT, differentiation of ODE from ONHD ranged in sensitivity from 77% to 92% (temporal and nasal RNFL thicknesses greater than 101.5 and 74.5 μm, respectively) and specificity from 47% to 95% (α-angle greater than 141°). The mean RNFL thickness was higher in ODE patients in all quadrants when compared with that of ONHD patients. When we evaluated the respective peripapillary RNFL thicknesses, the ROC curve showed that the temporal and nasal RNFL thicknesses were the most important parameters for differentiating these 2 disorders. The temporal RNFL thickness greater than 101.5 μm had 92% sensitivity and 65% specificity. The nasal RNFL thickness greater than 74.5 μm had 92% sensitivity and 47% specificity. Johnson et al (7) reported 80% specificity and 70% sensitivity for the temporal and nasal RNFL thickness greater than 97 μm and nasal RNFL thickness greater than 86 μm for the differentiation of ONHD from ODE. Lee et al (8) investigated the differentiation of ONHD from ODE with SD-OCT and demonstrated the nasal RNFL thickness as the most important factor. They detected 80.0% sensitivity and 88.9% specificity for nasal RNFL thickness greater than 78.0 μm.

Measuring the thickness of the SHYPS also helped distinguish between ODE and ONHD, being greater in ODE patients. SHYPS thickness greater than 464 μm had 85% sensitivity and 60% specificity. Johnson et al (7) measured the SHYPS thickness at radii of 0.75, 1.5, and 2 mm in ONHD and ODE patients and reported the sensitivity and specificity for the 2-mm radius for SHYPS thickness as 70% and 90%, respectively (for SHYPS thickness >169 μm). Their cutoff point for this parameter was thinner than that of 464 μm in our study.

The area of the SHYPS and the α-angle were significantly higher in ODE patients than in patients with ONHD. These 2 parameters had the highest specificity values. The area of the SHYPS greater than 811 μm² had 89% specificity and proved to be a better method of distinguishing ODE from ONHD than the thickness of the SHYPS, both in our study and previous reports (7,8). Measurement of the α-angle was also a highly predictive parameter as a measurement greater than 141° had a 95% specificity.

While the horizontal length of the optic nerve head in ODE patients was significantly greater than that in patients with ONHD and control subjects, it did not distinguish between patients with ONHD and control subjects. Our findings are in agreement with those of Floyd et al (16) and do not support the hypothesis that ONHD patients have a small scleral canal that causes a crowding effect on axonal transport or neural development.

We recognize the limitations of our study. First, the sample sizes were small with wide age range in all groups. Second, measurement of the α-angle was performed manually. Third, we did not evaluate the qualitative parameters of the optic nerve head and the peripapillary RNFL. Despite these limitations, we believe that our study presents promising findings in support of the use of SD-OCT in differentiating ODE from ONHD. Further studies with large patient groups are needed to validate the proposed cutoff values that we obtained.

REFERENCES

FIG. 2. SD-OCT in a patient with ONHD. Note the lumpy-bumpy internal contour of the optic nerve head and an abrupt decline in the border of the SHYPS.


Safety of Prednisone for Ocular Myasthenia Gravis

Beau B. Bruce, MD, MS, Mark J. Kupersmith, MD

Background: Treatment with chronic corticosteroids has been associated with frequent significant adverse effects. We hypothesized that a long-term low-dose prednisone regimen for ocular myasthenia gravis (OMG) would have a low rate of major side effects.

Methods: Consecutive OMG patients from a single institution over a 16-year period and treated with >1 month of daily prednisone were included. Steroid-related complications were defined as the development/worsening of conditions requiring alteration to medical therapy. Serious complications included conditions requiring emergency care, hospitalization, or surgery.

Results: Eighty-three patients with follow-up period ranging from 1 to 271 months (median, 58 months) were included. Fifty-eight (70%) patients had follow-up period of >24 months. The maximum prednisone dose ranged from 10 to 60 mg. Tapering to ≤10 mg/d required ≤4 months for all but 2 patients. Median average daily dose following the initial course was 5 mg daily (interquartile range, 4–7.5 mg). During the first 2 years, there were 24.5 complications per 100 person-years. Only one patient had a serious complication within the first 2 years (2-year cumulative risk, 1%), but this individual was not following the recommended regimen.

Conclusions: Low-dose prednisone for OMG has an acceptable side-effect profile and causes few serious complications (2-year risk, ~1%). However, patients need monitoring to detect the relatively common, but less serious, complications (2-year risk, ~3%) to adjust medical therapy in a timely fashion.

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Methods

Consecutive patients with OMG evaluated and managed at the Institute for Neurology and Neurosurgery at Roosevelt Hospital and New York Eye and Ear Infirmary by one of the investigators (M.J.K.) were considered for inclusion. The study was approved by the Institutional Review Board at St. Luke’s Roosevelt Hospital. Patients who were begun on prednisone between October 1984 and December 2010 and treated with a minimum of 1 month of daily prednisone were included. OMG was diagnosed on the basis of having ptosis, binocular diplopia, or extraocular motility limitation confirmed by ice test, edrophonium test, repetitive nerve stimulation electromyography, single-fiber electromyography, or positive acetylcholine receptor antibody testing (13,14).
Patients had their last clinical assessment between August 1996 and June 2011. In general, patients were evaluated monthly for the first 3 months and thereafter every 6 months.

Patients were not randomized to therapy. Those with diplopia or with ptosis that blocked the visual axis and were unresponsive to pyridostigmine were treated with prednisone. Patients were not given corticosteroids if they refused or had a contraindication, including active infection, gastrointestinal ulcer, history of tuberculosis, diabetes mellitus that was difficult to control, severe hypertension, or congestive heart failure. Patients with a history of a positive purified protein derivative or one or more calcified lesions, suggestive of healed tuberculosis, on the chest CT received 300 mg of isoniazid and 50 mg of pyridoxine concomitantly with prednisone. Patients were prescribed a daily H2 blocker (ranitidine hydrochloride, nizatidine, or famotidine) and 1000–1500 mg of calcium daily as long as they took prednisone. If baseline bone mineral density (not done in all patients) showed osteopenia of the lumbar spine or hips, biphosphonate therapy was also prescribed.

Complications of steroids were defined as the development of or worsening of any of the following conditions that required a change in management (e.g., addition of a medication): osteopenia, osteoporosis, bone fracture, hypertension, diabetes mellitus, gastrointestinal disturbance, psychosis, depression, dementia, infection (other than viral upper respiratory infection), elevated intraocular pressure, glaucoma, or cataract. Serious complications included conditions requiring emergency care, hospitalization, or surgery.

Statistical analysis was performed using R: a language and environment for statistical computing (R Foundation for Statistical Computing, http://www.r-project.org). We performed univariate analyses to produce summary measures for continuous measures (medians, interquartile ranges, and ranges) and proportions. Significance was defined as the 0.05 level. Person-time for incidence rates was determined using time of prednisone initiation as the start of follow-up and using either the number of weeks to last follow-up (censored) or the development of the first complication (event) as the end of person-time. Kaplan–Meier plots were used for graphical presentation of the survival curves. Confidence limits were calculated using the normal approximation of the Poisson distribution.

RESULTS

Eighty-three patients with confirmed OMG were included. Median age at diagnosis was 61 years (interquartile range, 46.5–73 years; range, 16–87 years). Sixty (72%) patients were men. Follow-up period ranged from 1 to 271 months with a median of 58 months. Fifty-eight (70%) patients required exactly 3 months to taper prednisone. Patients were on a maximum daily dose of prednisone ranging from 10 to 60 mg (all but 3 patients were on a maximum dose of 40–60 mg). Tapering from this dose to 10 mg/d required 4 months or less for all but 2 of the patients and a significant majority of the patients (58/83, 70%) required exactly 3 months to taper to 10 mg. The median average daily dose following the initial course was 5 mg daily (interquartile range, 4–7.5 mg).

Twenty-nine (35%) patients developed a complication (Table 1) that could potentially be related to steroid use within the total period of follow-up (439 person-years) corresponding to a rate of 6.6 complications per 100 person-years (95% confidence interval [CI], 4.2–9.0; Fig. 1A). Nine (31%) of these 29 patients developed more than 1 complication during the total period of follow-up. Within the first 2 years, the complication rate was 24.5 per 100 person-years (26 complications during the 106 person-years accumulated during the first 2 years of study; 95% CI, 15.0–33.9; Fig. 1A, inset). There were 10 complications in the first year (1-year cumulative risk, 12%), and 3 during the second year (2-year cumulative risk, 16%).

Three patients had serious complications during the total period of follow-up corresponding to a rate of 0.7 serious complications per 100 person-years (95% CI, 0.0–1.5; Fig. 1B). None occurred during the first year (1-year cumulative risk, 0%) and only one occurred during the second year (2-year cumulative risk, 1%). The rate within the first 2 years was 2.2 serious complications per 100 person-years (95% CI, 0.0–4.7; Fig. 1B, inset). The one patient who had a serious complication during this period developed severe hypertension complicated by myocardial infarction during month 12. However, this patient was not following the recommended prednisone regimen, instead taking 20–40 mg daily throughout the time prior to his associated complication by obtaining prednisone from multiple practitioners.

DISCUSSION

Our retrospective study demonstrated a low rate of serious complications related to a low-dose steroid regimen for OMG. Seventy percent of our patients had more than 2 years of follow-up. Assuming a constant rate of 2.2 serious complications per 100 person-years during a 2-year study, we have extrapolated our results to a larger patient cohort. If we assume a sample size of 231 patients, we would expect 4.3% (10/231; 95% CI, 0%–9%) of the patient treated with steroids to develop a serious complication that could be related to steroids. However, because the one patient in our study with a serious complication during the first 2 years was not following the low-dose regimen, we believe that the lower rate of 0.7 serious complications per 100 person-years seen over the entire study period represents a more accurate estimate. Given these assumptions, we would expect only 1.4% (3/231) of subjects to develop a serious complication.

Our data suggest that the use of a low-dose corticosteroid regimen has an acceptable side-effect profile for the treatment of OMG. This is in contrast to the frequent adverse effects seen with the relatively long-term high-dose...
corticosteroid regimens (15,16). Many clinicians are wary of the adverse effects of chronic corticosteroid use and frequently prescribe only pyridostigmine. Although this can be helpful for ptosis, it is rarely completely successful in relieving diplopia and fails to alter the underlying autoimmune process that leads to GMG in patients who first present with OMG (6,17).

Our study was limited because it was retrospective and represented a single center’s experience. There may have been patient selection bias, although we included patients without regard to having detectable acetylcholine receptor–binding antibody. Finally, the use of retrospective data from standard office visits, rather than systematic data collection, limits our ability to detect all other adverse effects of prednisone.

In conclusion, it appears that a low-dose prednisone regimen for the treatment of OMG causes few serious complications. Patients need monitoring for relatively common, but less serious, complications to ensure that these issues are detected early and allow for timely adjustment of medical therapy.

Table 1: Summary of complications possibly related to prednisone

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Onset (mo)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>9</td>
<td>Rx alendronate</td>
</tr>
<tr>
<td>30</td>
<td>125</td>
<td>Rx calcium + vitamin D</td>
</tr>
<tr>
<td>43</td>
<td>30</td>
<td>Rx risedronate</td>
</tr>
<tr>
<td>44*</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>69*</td>
<td>42</td>
<td>Rx alendronate</td>
</tr>
<tr>
<td>70</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3*</td>
<td>11</td>
<td>Rx alendronate</td>
</tr>
<tr>
<td>25</td>
<td>24</td>
<td>Rx calcium + vitamin D (improved later)</td>
</tr>
<tr>
<td>38</td>
<td>25</td>
<td>Rx alendronate</td>
</tr>
<tr>
<td>53*</td>
<td>72</td>
<td>Rx risedronate</td>
</tr>
<tr>
<td>76</td>
<td>70</td>
<td>Baseline osteoporosis, on alendronate, complicated by fracture</td>
</tr>
<tr>
<td>80*</td>
<td>23</td>
<td>Rx alendronate</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>2 years after stopping prednisone</td>
</tr>
<tr>
<td>3*</td>
<td>50</td>
<td>Rx pioglitazone</td>
</tr>
<tr>
<td>15</td>
<td>120</td>
<td>Rx metformin + insulin</td>
</tr>
<tr>
<td>19</td>
<td>48</td>
<td>Rx 4 oral agents</td>
</tr>
<tr>
<td>44*</td>
<td>1</td>
<td>Transient, no Rx</td>
</tr>
<tr>
<td>60</td>
<td>48</td>
<td>Rx oral agent (4 oral agents by year 8)</td>
</tr>
<tr>
<td>61</td>
<td>4</td>
<td>Rx metformin + pioglitazone</td>
</tr>
<tr>
<td>62*</td>
<td>12</td>
<td>Rx glyburide + insulin</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Rx 2 agents</td>
</tr>
<tr>
<td>27*</td>
<td>36</td>
<td>Rx additional oral agent</td>
</tr>
<tr>
<td>35</td>
<td>1</td>
<td>Increased propranolol</td>
</tr>
<tr>
<td>62*</td>
<td>1</td>
<td>Rx metoprolol + captopril, complicated by myocardial infarction</td>
</tr>
<tr>
<td>63</td>
<td>1</td>
<td>Rx lisinopril</td>
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<tr>
<td>78*</td>
<td>1</td>
<td>Rx valsartan</td>
</tr>
<tr>
<td>80*</td>
<td>24</td>
<td>Rx oral agent</td>
</tr>
<tr>
<td>Psychological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>78*</td>
<td>1</td>
<td>Agitation, no Rx</td>
</tr>
<tr>
<td>Cataract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53*</td>
<td>65</td>
<td>Nuclear sclerosis only</td>
</tr>
<tr>
<td>69*</td>
<td>72</td>
<td>Nuclear sclerosis only</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27*</td>
<td>36</td>
<td>Ocular hypertension</td>
</tr>
<tr>
<td>69*</td>
<td>48</td>
<td>Ocular hypertension</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>Lid cellulitis requiring hospitalization</td>
</tr>
</tbody>
</table>

Serious complications are indicated in bold.
*Patients with ≥2 complications.
FIG. 1. Kaplan–Meier survival curves for all (A) and major (B) complications (solid lines) during the study, with 95% confidence intervals (dashed lines). Hashes on solid line represent censored observations. Inset: complications during first 2 years.

REFERENCES


Magnetic Resonance Imaging of Optic Neuritis in Patients With Neuromyelitis Optica Versus Multiple Sclerosis

Sangeeta Khanna, MD, Aseem Sharma, MD, Julie Huecker, MS, Mae Gordon, PhD, Robert T. Naismith, MD, Gregory P. Van Stavern, MD

Background: Patients with neuromyelitis optica (NMO) and multiple sclerosis (MS) both can present with acute optic neuritis (ON), while differing considerably in their prognosis and management. The clinical course, serologic testing results, and brain and spinal cord imaging of these diseases have been well documented. The purpose of this study was to look systematically for any differences in the imaging appearance of the optic nerve in NMO and MS-related ON.

Methods: Magnetic resonance imaging (MRI) of brain and orbits obtained within 6 weeks of acute ON in patients with securely diagnosed NMO (n = 6) and MS (n = 11) were retrospectively analyzed by a neuroradiologist masked to the clinical diagnosis. Standardized scoring system was used to assess and analyze the extent and nature of optic pathway involvement.

Results: No significant differences were observed in the presence, degree, or the type of signal alteration and contrast enhancement of the affected nerve segments between NMO and MS groups. There was a trend toward more posterior involvement of the optic nerve in the NMO group with chiasmatic enhancement exclusively seen in NMO patients.

Conclusion: We found a higher propensity of NMO-related ON to affect more posterior parts of the optic nerve, including chiasm, and have simultaneous bilateral disease. Further study with larger sample sizes is needed.

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Optic neuritis (ON) may be the initial presenting feature of both multiple sclerosis (MS) and neuromyelitis optica (NMO). Distinction between the 2 conditions is important, as both diseases differ in pathophysiology, visual and neurologic outcome, and response to treatment (1–3). Early recognition and treatment with immunosuppression can reduce the burden of disease. The clinical spectrum of NMO has expanded considerably with the advent of the NMO immunoglobulin G (IgG) antibody, a sensitive and highly specific test that helps distinguish NMO from MS. The diagnostic criteria for NMO (4) now include a history of ON with history of acute myelitis and 2 of 3 supportive criteria: 1) a contiguous spinal cord MRI lesion extending over at least 3 vertebral segments antibody, 2) a brain MRI that does not meet the criteria for MS, and 3) NMO–IgG seropositivity.

Early diagnosis may be critical when making treatment decisions, but there is still debate regarding whether all patients with demyelinating ON need to be screened for NMO. Some recommend testing all patients with ON and aggressive immunosuppression in patients with positive NMO titers (without conclusive evidence of NMO) (5). Others have argued that NMO antibody testing is not warranted in every patient because NMO-related isolated ON is rare (5). Clinical parameters such as bilateral onset and poor visual outcomes are often clues to NMO-related ON but are not present in all such patients. A recent study from Brazil demonstrated much higher likelihood of severe residual visual field deficit on automated perimetry after ON related to NMO versus MS (6). Ratchford et al (7) studied a cohort of patients with MS-related ON and NMO-related ON and found significantly greater thinning of retinal nerve fiber layer using optical coherence tomography (OCT) in NMO patients. Such studies highlight the need for clinical parameters to better guide diagnostic testing.
MRI plays a critical role in the diagnosis of MS and NMO. Although ON can be diagnosed by clinical features, fat-suppressed orbital MRI shows characteristic findings, including signal change and enhancement of the optic nerve in 95% of the patients, and is often included in the work-up of ON patients (8). Previous studies (8,9) have attempted to use length of enhancement and signal change to predict visual outcome, with variable results. However, no prior research has been done using similar methods to predict neurologic outcome, whether the patient is destined to develop NMO or MS. The goal of this study was to identify any distinctive features of optic nerve imaging with MRI in acute ON in a cohort of securely diagnosed NMO and MS patients.

MATERIALS AND METHODS

This is a retrospective case study. A chart review consisted of securely diagnosed NMO patients examined and followed by an MS specialist (R.T.N.) between 2006 and 2010. Of the 27 patients with NMO, 6 with NMO-related ON who had neuroimaging done within 6 weeks of onset of visual symptoms were identified and included in the study. Eleven patients with securely diagnosed MS (McDonald criteria) (10) imaged within 6 weeks of onset of ON also were included. Six weeks was chosen because that is the time frame in which acute findings (such as contrast enhancement of the involved nerve) are most prominent. The MRI of these patients was analyzed by a neuroradiologist (A.S.) masked to the clinical diagnosis. After the protocol was approved by the institutional review board, a retrospective chart review performed to determine the age, sex, race, and the laterality of involvement clinically and to confirm the diagnoses. A standardized scoring system was developed and used to assess and analyze the extent and nature of the optic pathway involvement detected with MRI.

MRI was done with a 1.5 Tesla magnet (Siemens AG, Munich, Germany). All patients underwent MRI of the brain and orbits with 5-mm slice thickness. Images included with and without contrast T1 axial, T2 axial, axial fat-suppressed FLAIR, and contrasted T1 coronal. In addition, 10 of the 17 patients had orbital MRI with 3-mm slice thickness. These studies included contrast-enhanced T1 axial and coronal, contrast-enhanced fat-suppressed T1, and fat-suppressed T2.

We compared the MRI optic pathway imaging characteristics between the 2 groups. The parameters assessed were as follows:

1. Optic nerve enhancement.
2. Degree of optic nerve enhancement: The maximally affected segment of nerve was assessed and graded subjectively using level of extraocular muscle enhancement as a reference. 0, none; 1, subtle; 2, definite < muscles; 3, definite > muscles.
3. Presence of optic nerve thickening. The affected optic nerve segment was compared with contralateral unaffected nerve or ipsilateral unaffected segment in bilateral cases.
4. Presence of hyperintensity on FLAIR.
5. Degree of hyperintensity on FLAIR: Hyperintensity of signal change was subjectively graded on a scale of 0–3 ranging from no change in signal (0) to marked change in signal (3).
6. Extent of optic nerve involvement: classified as 0, none; 1, up to one-third; 2, one-third to two-thirds; 3, two-third or greater.
7. Optic nerve head swelling.
8. Segment of nerve most affected (retrobulbar/canalicul/intracranial).
9. Laterality of involvement.
10. Chiasmal involvement.
11. Optic tract involvement.

Fisher exact test (categorical variables) and t tests (continuous variables) were used to test for statistical significance.

RESULTS

Six patients were included in the NMO group and 11 patients in the MS group. The patient characteristics are summarized in Table 1. All patients underwent brain MRI within 6 weeks (range, 4 days to 6 weeks) of an episode of ON. Seven of 11 MS patients and 3 of 6 NMO patients had dedicated orbital MRI in additional brain MRI. Four of 6 NMO patients had unilateral optic nerve involvement, and 2 had bilateral disease. All 11 MS patients had unilateral disease. No significant differences were observed between the 2 groups regarding the presence, degree, extent, or the type of signal alteration and contrast enhancement of the affected optic nerve segments. The most important comparison parameters are shown in Table 2. There was a trend toward more posterior optic nerve involvement in the NMO group, with chiasmal enhancement exclusively seen in NMO-related ON (3 patients, P = 0.0179). Optic nerve head enhancement was not seen in either group.

The mean difference in the thickness of the most affected segment compared with unaffected contralateral nerve was higher in MS (mean 0.7182 ± 0.7) versus NMO

| TABLE 1. Demographic characteristics of NMO and MS patients with ON |
|--------------------------|--------------------------|--------------------------|
| Characteristics          | NMO (n = 6)              | MS (n = 11)              |
| Age, mean (SD), y        | 39 (18.4)                | 39 (16.7)                |
| Female gender, n (%)     | 5 (83.3)                 | 8 (72.7)                 |
| Race, n (%)              |                           |                          |
| African American         | 4 (66.7)                 | 4 (36.4)                 |
| Caucasian                | 2 (33.3)                 | 7 (63.6)                 |

MS, multiple sclerosis; NMO, neuromyelitis optica; ON, optic neuritis.

TABLE 2. MRI characteristics of ON in patients with NMO and MS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NMO (n = 6), %</th>
<th>MS (n = 11), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of nerve enhancement*</td>
<td>4 (80.0)</td>
<td>8 (88.9)</td>
</tr>
<tr>
<td>Presence of nerve thickening</td>
<td>4 (66.7)</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>Hyperintensity of nerve on FLAIR</td>
<td>6 (100.0)</td>
<td>9 (81.8)</td>
</tr>
<tr>
<td>Chiasmal involvement*</td>
<td>3 (60.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Optic tract involvement</td>
<td>1 (16.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Optic nerve head swelling</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Most affected segment is retrobulbar</td>
<td>0 (0)</td>
<td>3 (27.0)</td>
</tr>
<tr>
<td>Most affected segment is canalicular</td>
<td>4 (80.0)</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>Most affected segment is intracranial</td>
<td>1 (20.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bilateral disease on MRI</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Extent of nerve involvement &lt; one-third</td>
<td>4 (66.7)</td>
<td>5 (45.5)</td>
</tr>
<tr>
<td>Extent of nerve involvement one-third to two-third</td>
<td>1 (16.7)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Extent of nerve involvement &gt; two-third</td>
<td>1 (16.7)</td>
<td>2 (18.2)</td>
</tr>
</tbody>
</table>

*1 NMO and 2 MS patients had indeterminate call on nerve enhancement. One patient in NMO group had indeterminate call on chiasmal enhancement. The percentage reflects the number positive out of those with determinate call and the percent may be higher than actual number but is more reflective of the true call. Because of a small sample size, the statistical power of comparisons above is low; hence, the P values are not meaningful and have not been included here.

MS, multiple sclerosis; NMO, neuromyelitis optica; ON, optic neuritis.

(mean 0.375 ± 0.33), but this was not statistically significant. The characteristic MRI features of 1 representative MS and 1 NMO patient are shown in Figures 1 and 2, respectively.

DISCUSSION

In patients with ON caused by NMO and MS, our study showed that there were no distinguishing optic nerve features on MRI. However, bilateral optic nerve and chiasmal enhancement were seen only in our NMO cohort of patients.

To our knowledge, there is no prior systematic comparison of imaging of acute ON in securely diagnosed NMO versus MS. Prior MRI studies have looked at imaging findings in acute ON but have not systematically included or excluded NMO. Kupersmith et al (8) reviewed MRI findings in 107 patients with acute ON and found abnormal optic nerve enhancement in 94% of affected nerves. The percent of abnormal contrast enhancement in our study is similar but slightly less at 80% (NMO patients) to 88.9% (MS patients). One hundred percent of our NMO and 82% of our MS patients showed optic nerve hyperintensity on FLAIR sequences. Although Kupersmith et al found that location and length of optic nerve enhancement are not predictive of visual recovery, a prior report (9) suggested that abnormal signal length >17.5 mm and canalicular location are associated with poor or slow recovery from ON even if treated with steroids (9). In the study by Kupersmith et al (8), 17 of 107 patients had probable or definite MS at the time of presentation. It is unclear whether patients were systemically evaluated for NMO. Although NMO patients have poorer visual recovery and more loss of nerve fibers on OCT with each ON episode (2,7), we did not...

FIG. 1. MRI in MS. Contrast-enhanced fat-suppressed T1 MRIs show enhancement of the canalicular and intracranial right optic nerve (arrow) in the axial projection (A) and the intracranial portion (arrowhead) in the coronal view (B). Axial FLAIR image through the brain demonstrates hyperintense foci in the white matter representing demyelination plaques (C).
detect any significant difference in the length of involved segment of optic nerve between the MS and NMO patients. However, a trend toward more posterior location and chiasmal enhancement was noted in our NMO cohort.

Chiasmal involvement previously has been reported in NMO (11), and it has also been described in MS based on autopsy and clinical and imaging evidence. Most of these reports were prior to 1991, when NMO had not yet been defined as an entity distinct from MS (12). However, in 2009, Kawasaki et al (13) reported a series of 20 patients with idiopathic chiasmal neuritis and found that 40% developed clinically definite MS, with follow-up ranging from 3 months to 3 years. This series did not exclude NMO patients, and 1 patient developed a myelopathy. In our study, chiasmal enhancement/enlargement was exclusively present in the NMO group.

We found simultaneous bilateral enhancement of the optic nerves only in our NMO patients. In a study of 427 patients with MS, simultaneous bilateral disease was rare, noted in only 2 patients (0.42%) (14). This suggests that simultaneous bilateral optic nerve enhancement in a monocularly symptomatic patient should warrant careful evaluation for NMO. In our study, 1 of the 2 patients with bilateral optic nerve enhancement had clinical findings of unilateral ON.

In conclusion, our study suggests that bilateral optic nerve or chiasmal enhancement on MRI might prompt further patient evaluation for NMO. The strength of our study is that we have only included securely diagnosed NMO or MS patients, and MRI studies were reviewed by neuroradiologist who was blinded to the clinical diagnosis. Limitations of our study include its retrospective nature, small patient cohort, and absence of dedicated orbital imaging protocol in all patients. Although studies with larger sample size and standardized imaging are warranted, our findings might serve as a useful guide in clinical decision making when managing patients with acute ON.

REFERENCES


Auditory-Olfactory Synesthesia Coexisting With Auditory-Visual Synesthesia

Thomas E. Jackson, MRCOphth, Soupramanien Sandramouli, FRCOphth

Abstract: Synesthesia is an unusual condition in which stimulation of one sensory modality causes an experience in another sensory modality or when a sensation in one sensory modality causes another sensation within the same modality. We describe a previously unreported association of auditory-olfactory synesthesia coexisting with auditory-visual synesthesia. Given that many types of synesthesias involve vision, it is important that the clinician provide these patients with the necessary information and support that is available.

CASE REPORT

A 30-year-old man was referred to the ophthalmology clinic with a history of "seeing sounds." From approximately 5 years, he experienced shapes and colors whenever he heard sounds. All sounds created images, some more distracting than others. These were rarely static and tended to move across his visual field before slowly fading. He had originally thought that this was a normal sensation but later realized that it was unique to him.

Certain sounds were experienced as shapes in his vision. Voices created a collection of circles that rippled across the lower part of his vision and became stacked on top of each other when more than one voice was heard. Shouting caused the circles to be scattered across his whole field of vision and were more difficult to ignore. Clicking sounds such as a light switch or hard shoes on a floor were seen as a square, while treading on grass was a small triangle and treading on gravel or ripping paper was a larger triangle. Other sounds were seen as numbers: an untuned television, for example, was 1, 9, and 20; deep bass sounds were the number 400; and a washing machine was 1, 9, and 5.

The patient was usually able to ignore the images, but there were times that he described "sensory overload" when they became overpowering. If he was in a room with a number of children playing and shouting, he experienced so many images that his vision became cluttered and overwhelmed to the point that he needed to leave. Similarly, he found it too difficult to visit the local shopping center and described himself as a solitary individual who had always been prone to spending long periods of time alone in his bedroom. He worked as a computer programmer but found it hard to concentrate because of the constant images created by background office noise; he coped by listening on headphones a repeating list of music tracks. Although the music continued to create images, these were predictable and interfered less with his work. He also drank large volumes of caffeinated drinks, which helped him remain focused on a particular task while blocking out other sensations, but the caffeine frequently interrupted his regular sleep pattern.

On further questioning, the patient reported that certain sounds elicited smells. He described the sound of a drill smelling like bleach, a vacuum cleaner like vomit, and...
music like food. These smells could also be overpowering, and the strong smell of bleach had caused him to vomit on a number of occasions. The auditory-visual and auditory-olfactory sensations were unidirectional such that sights or smells did not stimulate other sensory modalities.

He had mild asthma, was a nonsmoker, and denied any alcohol or drug use. On examination, the visual acuity was normal, and the ophthalmic examination was unremarkable.

**DISCUSSION**

The first known reference to synesthesia was in 1690 (1), and it was described in detail by Francis Galton in 1880 (2). Synesthesia was repeatedly dismissed as a fictitious condition, and it is only recently that brain imaging techniques, including the use of functional magnetic resonance imaging (fMRI) (3,4) and positron emission tomography (PET) (5) have confirmed that it is a genuine condition.

Synesthesia may occur between any 2 sensory modalities or within the same sensory modality, and at least 61 different combinations have been reported, many of which involve the visual system (Table 1) (6). This is the first reported case of auditory-visual synesthesia coexisting with auditory-olfactory synesthesia.

The incidence of synesthesia has been reported as between 1% and 4% (7); however, it remains controversial with estimates of anywhere from 1 in 20 to 1 in 250,000 (8). Some forms of synesthesia are more prevalent than others; the most common is grapheme-color synesthesia, where graphemes (numbers, letters, or symbols) generate the sensation of a color, so the number 3 may cause the sensation of green or the letter “e” may cause the sensation of blue. The pairing of color to grapheme may vary between synesthetes but remains constant for each individual.

Auditory-visual synesthesia is another common form of synesthesia. In some patients, such as in our case, any auditory stimulus triggers a visual perception, but there are also forms of auditory-visual synesthesia where the auditory stimulus is limited to voices or music (chords, keys, or individual notes). The composer Nikolai Rimsky-Korsakov, for example, experienced the key of C major as white and the key of B major as gloomy dark blue with a steel shine, while jazz-rock guitarist Tony DeCaprio experienced individual notes as different colors (1).

Synesthesia is usually unidirectional; however, there are cases in which it is bidirectional, for example, numbers give an experience of colors and colors also give an experience of numbers. The pairing is automatic and present since childhood.

Brain imaging techniques in patients with both auditory-color and grapheme-color synesthesia involved small numbers of patients but showed changes in the visual association pathways and not in the primary visual cortex. fMRI found visual association areas V4 and V8 to be activated by a word or grapheme stimulus (3,4) while PET scans found the posterior inferior temporal gyrus and parieto-occipital junction to be activated (5). Beeli et al (9) used electrodiagnostic testing patients with auditory-color synesthesia and demonstrated activation of the color area V4 and the posterior inferior temporal during color perception elicited by auditory stimuli. While imaging techniques have illustrated abnormal brain activity, the neural basis remains unclear. It may be a problem of anatomy in which failure to prune early abundant connections in the normal infant brain may result in extra connection between brain regions. Alternatively, it may be attributable to disinhibition of existing pathways that are normally masked in the adult brain (10). A further possibility is that there are multisensory brain regions that bind together different sensory stimuli to build a complete picture and that problems in this area may lead to synesthesia (11).

It is interesting that most synesthetes prefer not to be cured of their condition and, in fact, synesthesia can be a help rather than a hindrance. Grapheme-color synesthetes are often better at remembering numbers, whereas other types of synesthesia are linked to musical and artistic ability with a number of famous people thought to have been synesthetes, including composer Franz Liszt, pianist Duke Ellington, and artist David Hockney (6).

Synesthesia is a complex condition with no current treatment options. Our patient has spent a lifetime developing various coping strategies to manage his condition. He was not looking for a treatment, but what he really sought was a formal diagnosis to help him understand his condition and to allow him to explain it to others. Information and support can help patients understand this condition, and there

**TABLE 1. Types of synesthesia involving vision**

<table>
<thead>
<tr>
<th>Triggering Stimulus</th>
<th>Resultant Experience</th>
<th>Prevalence Among Synesthetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graphemes</td>
<td>Color</td>
<td>64.4</td>
</tr>
<tr>
<td>Music</td>
<td>Visual</td>
<td>27.7</td>
</tr>
<tr>
<td>General sounds</td>
<td>Visual</td>
<td>15.3</td>
</tr>
<tr>
<td>Voice</td>
<td>Visual</td>
<td>7.5</td>
</tr>
<tr>
<td>Personalities</td>
<td>Visual</td>
<td>6.4</td>
</tr>
<tr>
<td>Flavors</td>
<td>Visual</td>
<td>6.3</td>
</tr>
<tr>
<td>Smells</td>
<td>Visual</td>
<td>6.3</td>
</tr>
<tr>
<td>Pain</td>
<td>Visual</td>
<td>5.6</td>
</tr>
<tr>
<td>Touch</td>
<td>Visual</td>
<td>3.8</td>
</tr>
<tr>
<td>Emotions</td>
<td>Visual</td>
<td>2.9</td>
</tr>
<tr>
<td>Visual</td>
<td>Auditory</td>
<td>2.6</td>
</tr>
<tr>
<td>Temperature</td>
<td>Visual</td>
<td>2.2</td>
</tr>
<tr>
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<tr>
<td>Visual</td>
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</tr>
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</tr>
<tr>
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<td>Kinetics</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Modified from Day (6).
are a number of useful websites, including the American Synesthesia Association (http://www.synesthesia.info) and Synesthesia (http://www.daysyn.com). Many countries also have their own synesthesia associations that offer local support and annual conferences. For clinicians, further information regarding this complex subject is available in a number of good review articles (1,12).

Synesthesia is a condition that is rarely diagnosed by ophthalmologists because of its rare presentation. It is important that ophthalmologists recognize synesthesia to provide patients with necessary information and support that is available.

REFERENCES
Up-Down Asymmetry of Saccadic Contrapulsion in Lateral Medullary Syndrome

Diego Kaski, BSc, MRCP, Paul Bentley, MRCP, PhD, Russell Lane, MD, FRCP, Adolfo Bronstein, PhD, FRCP

Abstract: We report greater amplitude of horizontal contrapulsion on upward vs. downward vertical saccades in a patient with saccadic contrapulsion as a result of a focal demyelinating lesion of the left dorsolateral medulla. The vertical asymmetry in horizontal saccadic contrapulsion likely relates to an imbalance of fastigial oculomotor inputs on horizontal burst neurons during vertical saccades as reported in non-human primates. Our finding suggests that such asymmetry is also present in humans and provides insight into the pathophysiology of saccade generation.

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Saccadic lateropulsion is most commonly seen with dorsolateral medullary lesions (usually infarctions) and is a hallmark of Wallenberg syndrome. In the case of dorsolateral medullary lesions, it consists of ipsilesional hypermetric saccades, contralateral hypometric saccades, and ipsilesional deviation of vertical saccades (1). The pathophysiological mechanism of saccadic lateropulsion is thought to relate to dysfunction of ipsilateral fastigial nucleus or its afferent pathways (2). However, lesions involving the fastigial nucleus can lead to both ipsilateral and contralateral saccadic lateropulsion depending on whether they involve crossed or uncrossed afferent olivocerebellar pathways (3). We describe a patient with saccadic contrapulsion caused by a well-defined lesion involving the left dorsolateral medulla. We noted increased amplitude of horizontal contrapulsion on upward vs. downward vertical saccades and hypothesize that this relates to an imbalance of fastigial oculomotor inputs on horizontal burst neurons during vertical saccades.

CASE REPORT

A 36-year-old man presented with acute onset of leftward room tilt, nausea, and vomiting. Two days earlier, he had noticed left-sided paresthesia involving the arm, face, and tongue. Examination revealed left beating horizontal and left torsional nystagmus present in all directions of gaze but most marked on left gaze. Saccades were predominantly hypermetric. There was a rightward deviation of the eyes on vertical saccades. Clinically, the ability to suppress the vestibulo-ocular reflex was impaired bilaterally. Sensation was reduced to pain and light touch over the left side of the face. The left gag reflex was depressed, and the patient was dysarthric. Examination of the limbs revealed a left-sided hemiparesis and right-sided hypesthesia to pain and temperature, in addition to dysdiadochokinesia and limb dysmetria on the left. The gait was broad based and spastic.

The cerebrospinal fluid (CSF) revealed a moderately increased protein level of 0.69 g/L (normal, 0.15–0.45 g/L), and oligoclonal bands were present in the CSF and serum. Magnetic resonance imaging (MRI) showed a lesion extending from the origin of the seventh and eighth cranial nerves 1.5 cm caudally to the cervical cord (C1) (Fig. 1). The diagnosis was consistent with demyelination, although the clinical and neuroimaging findings did not satisfy the MacDonald criteria for multiple sclerosis.

Three years later, the patient’s saccadic eye movements were recorded using binocular video-oculography acquired at 50 frames per second (see Supplemental Digital Content 2, http://links.lww.com/WNO/A46). There had been no neurologic events during this period, and the patient was taking pregabalin and amitriptyline at the time of the eye movements.
movement recording. During upward vertical saccades, the eyes deviated to the right (Fig. 2 A, C). The magnitude of the rightward deviation increased with the amplitude of the vertical saccade. Large downward saccades also deviated to the right but to a smaller extent (Fig. 2. B, D) (see Video, Supplemental Digital Content 3, http://links.lww.com/WNO/A45). The horizontal asymmetry of upward vs. downward saccades did not change when the eyes were examined clinically in the left ear down, right ear down, and head down (pitch) positions. No torsional ocular deviation or nystagmus was observed in primary gaze or during the examination.

For horizontal saccades, there was right-beating nystagmus on right gaze (with a slow phase velocity [SPV] of 10°/s at 30° eccentricity) and left-beating nystagmus on left gaze (at 30° eccentricity, the SPV = 10°/s in the light; 20–30°/s in the dark). A small left-beating nystagmus was observed in primary gaze in the dark (SPV <3°/s). Horizontal centrifugal saccades were often hypermetric, with a nystagmic glissade back to the target position. Centripetal saccades from a right eccentric position often began with a rightward movement of the eyes, overshot the central target, and then finally reached the central position with an exponential decay. Centripetal saccades from a left eccentric position were hypermetric. The patient has been followed for 11 years with no change in the pattern or direction of saccadic contrapulsion.

DISCUSSION

We describe a patient with contralesional saccadic lateropulsion caused by a well-defined lesion probably demyelinating,
Gravity affects the eyes such that downward eye movements are facilitated, and upward movements are restrained (5). It is known from studies in primates that upward directed saccades have a tendency to undershoot, whereas downward saccades overshoot (2), consistent with a gravitational effect. As a result, there exist 2 excitatory circuits for upward saccades and only 1 for downward saccades (5). The lesion in our patient could have involved the “antigravity” pathway, thus making upward saccades more susceptible to horizontal deviations. Similarly, Gresty et al (6) reported a patient with a left-sided medulloblastoma in whom horizontal hypometric saccades to the left normalized when lying with right ear down, implying that the metrics of saccades were under the influence of an abnormal otolith signal (6). On this basis, the greater upward lateropulsion observed in our patient could also be related to otolith influences on the oculomotor system. However, this could not be confirmed, as there was no change in the magnitude or polarity of the lateropulsion during head tilt (face forward, up, down, right, or left). In support of our clinical finding, a recent study found no change in the amplitude or direction of ocular lateropulsion with static postural shifts in patients with peripheral or central vestibular lesions (7).

Another explanation for our findings may be due to an apparent in-built horizontal bias during vertical saccades that is regulated by the vermis and released after lesions involving this region. Behavioral data confirm the activity of horizontal excitatory burst neurons during pure vertical saccades (8). Monkeys with lesions of the oculomotor vermis, which projects to the fastigial oculomotor region (FOR), had distorted saccade trajectories with greater horizontal deviations during upward-directed vs. downward-directed saccades (9). This asymmetry may reflect an imbalance in FOR inhibitory inputs on the horizontal burst neurons during vertical saccades. Such an asymmetry may underlie the bias in horizontally distorted vertical saccades observed in our patient, although the exact mechanisms involved are unknown.

ACKNOWLEDGMENTS

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REFERENCES

Neuronal Programmed Cell Death-1 Ligand Expression Regulates Retinal Ganglion Cell Number in Neonatal and Adult Mice

Caroline W. Sham, MD, PhD, Ann M. Chan, MS, Jacky M. K. Kwong, PhD, Joseph Caprioli, MD, Steven Nusinowitz, PhD, Bryan Chen, BS, Janice G. Lee, MD, Nishant M. Gandhi, MD, Louise M. Francisco, PhD, Arlene H. Sharpe, MD, PhD, Ling Chen, MD, PhD, Jonathan Braun, MD, PhD, Lynn K. Gordon, MD, PhD

Objectives: During mouse retina maturation, the final number of retinal ganglion cells (RGCs) is determined by highly regulated programmed cell death. Previous studies demonstrated that the immunoregulatory receptor programmed cell death-1 (PD-1) promotes developmental RGC death. To identify the functional signaling partner(s) for PD-1, we identified retinal expression of PD-1 ligands and examined the effect of PD-1 ligand expression on RGC number. We also explored the hypothesis that PD-1 signaling promotes the development of functional visual circuitry.

Methods: Characterization of retinal and brain programmed cell death-1 ligand 1 (PD-L1) expression were examined by immunofluorescence on tissue sections. The contribution of PD-ligands, PD-L1, and programmed cell death-1 ligand 2 (PD-L2) to RGC number was examined in PD-ligand knockout mice lacking 1 or both ligands. Retinal architecture was assessed by spectral-domain optical coherence tomography, and retinal function was analyzed by electroretinography in wild-type and PD-L1/L2 double-deficient mice.

Results: PD-L1 expression is found throughout the neonatal retina and persists in adult RGCs, bipolar interneurons, and Müller glia. In the absence of both PD-ligands, there is a significant numerical increase in RGCs (34% at postnatal day 2 [P2] and 18% in adult), as compared to wild type, and PD-ligands have redundant function in this process. Despite the increased RGC number, adult PD-L1/L2 double-knockout mice have normal retinal architecture and outer retina function.

Conclusion: This study demonstrates that PD-L1 and PD-L2 together impact the final number of RGCs in adult mice and supports a novel role for active promotion of neuronal cell death through PD-1 receptor-ligand engagement.

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In the developing central nervous system (CNS), many more neurons are created than are necessary to form functional circuits. Excess neurons are eliminated by carefully regulated apoptotic programmed cell death (PCD) in a process called developmental cell death (1). Murine postnatal retina maturation is an example of ontogenic cell death, providing a model to study PCD in the CNS (2). PCD has been particularly explored well in retinal ganglion cells (RGCs), as about half of RGCs born will die by this process (3). To survive and form functional circuitry, RGCs must project axons to the brain, synapse on target cells, and avoid elimination by synaptic pruning (2). A variety of cell surface interactions are known to positively and negatively influence this developmental sequence. Cell surface adhesion γ-protocadherin proteins (4), neurotrophic support (5), and electrical activity (6) are all required for proper
RGC survival. In contrast to these influences, molecules decorating cell processes, such as complement initiating factor C1q (7), CD3ζ, and MHCI (8) and neuronal pentraxins (9), act to promote synaptic refinement. Additionally, the p75NTR neurotrophin (10) and programmed cell death-1 (PD-1) (11) receptors act to promote RGC death.

PD-1 is a membrane-associated coinhibitory receptor, expressed on a number of hematopoietic cells including T cells, B cells, and macrophages (12) and on neurons of the CNS (11,13). In the immune system setting, PD-1 engagement with 1 of the 2 ligands, PD-L1 or PD-L2, acts to attenuate immune responses and thus has broad immunoregulatory roles in peripheral tolerance, as well as immunity to chronic infections, tumors, and organ transplants (12). We previously reported that PD-1 receptor ligation promotes RGC apoptosis during early postnatal development and identified PD-L1 and PD-L2 gene expression throughout retina maturation (11), suggesting that either one or both PD-ligands engage functionally with PD-1 in the retina. In this study, we identify the cellular expression of PD-ligand proteins and demonstrate an increased RGC number in the absence of PD-L1 and PD-L2.

METHODS

Animals

Knockout mice were constructed in the C57BL/6 background, as previously described: PD-1−/−, PD-L1−/−, PD-L2−/−, and PD-L1/L2−/− (14-16). Animals used for each experiment are described in Table 1. Wild-type (WT) embryonic and adult age-matched C57BL/6 mice were purchased from Charles River Laboratory. All animal experiments were reviewed and approved by the University of California, Los Angeles, Chancellor’s Animal Research Committee, in adherence to the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research.

Animal Perfusion

Mice were deeply anesthetized with intraperitoneal sodium pentobarbital (80 mg/kg of Nembutal) and perfused transcardially with 10 mL of 4% paraformaldehyde (PFA) in phosphate buffered saline (PBS) for 5 minutes.

Immunofluorescence Staining

Paraformaldehyde-fixed, frozen vertical retina sections of 7-μm thickness were prepared from postnatal day 2 (P2) and adult (P56) animals. Staining and epifluorescent imaging were performed as previously described (11). Antibodies used, including PD-L2 antibodies tested, are listed in Table 2. For brain sections, adult (P56) WT male mice were perfused, brains were dissected, postfixed in 4% PFA/PBS overnight at 4°C, cryoprotected in 30% sucrose/PBS, and embedded in optical coherence tomography (OCT) medium (Sakura Finetek). Serial coronal sections of 25 μm were collected at the level of the superior colliculus (SCs) at

| TABLE 1. Summary of experimental animal (mice) studies showing the effect of programmed cell death-1 ligands on retinal ganglion cell number |
|-------------------------------------------------|-----------------|-----------|-----------------|-----------------|
| Experiment                                      | Strain          | Age       | Age Rationale   | Result           |
| Retinal PD-L1 expression by IF                  | WT              | P2        | Age-match RGC quantification | Expressed in GCL cell bodies and neuroblast layer neuropil |
| Brain PD-1 and PD-L1 expression by IF           | WT              | P56       | Age-match brain expression | Expressed in RGCs, bipolar cells, and Müller glia |
| RGC quantification by IF                        | WT              | P2        | Peak RGC death | Increased RGC number in PD-1−/− and PD-L1/L2−/− |
| Axon counting by electron microscopy            | WT              | P28       | Establish baseline for future experiments | Increased RGC number in PD-L1/L2−/− |
| ERG and SD-OCT                                  | WT              | P42       | Knockout animal availability | Normal outer retina function and architecture in PD-1−/− and PD-L1/L2−/− |
Bregma −4.1 to −4.4 mm; coordinates were determined using the Allen Mouse Brain reference atlas (26). Immunofluorescence staining was performed for PD-1 and PD-L1, using the same method as for retina sections, with the exception that all slide washing was performed with agitation.

**Optic Nerve Axon Analysis**

Adult (P28) WT, PD-1−/−, and PD-L1/L2−/− mice were perfused. Optic nerves were dissected, postfixed in 1% osmium tetroxide, stained with 1% potassium ferricyanide, dehydrated in ethanol and acetone, and embedded in epoxy resin. Ultrathin (70 nm) optic nerve sections were obtained with a microtome (Reichert Ultracut) at approximately 400 mm posterior to the eye globe, placed on slotted grids, and counterstained with 1% uranyl acetate and Sato lead. Images were obtained using transmission electron microscopy (Tecnai; FEI). For each section, 20 micrographs were taken at ×21,000 at representative optic nerve regions: central (4), midperipheral (8), and peripheral (8). No positional adjustments were made. Images included blood vessels and glial cells. Micrographs were digitized using a 2K charge-coupled device (Photometrics Inc). Analysis was performed according to published methods (27).

Semi-thin (1 μm) optic nerve sections were stained with 1% toluidine blue (Sigma-Aldrich). To determine axon density, axons located within a counting frame (8 × 8 μm) and intersecting the upper and right frame edges were counted manually in a blinded manner. Mean axon density was calculated as total axons divided by total area.

**Nissl Staining**

To stain all neuronal cell bodies, every fourth coronal brain section was Nissl stained as previously described (28), with 0.1% cresyl violet (Sigma-Aldrich). Structures were localized using Nissl stains in conjunction with the Allen Mouse Brain reference atlas (26).

**Imaging and Quantification of Immunofluorescence Staining**

Retina sections were imaged at ×400 magnification, yielding an image width of 262 μm. Quantification of ganglion cell layer (GCL) cell types, RGCs and displaced amacrine cells, and statistical analysis were performed as previously described (11). Semithin optic nerve sections were imaged at ×400 magnification, and cross-sectional area was measured by outlining the nerve border with image acquisition software (DP2-BSW, Olympus) and repeated on 3 consecutive sections. Brain sections were imaged at ×100 magnification. All images were obtained with light or epifluorescent microscopy (BX51, Olympus).

**Retina Architecture**

Following euthanasia, eyes were rapidly enucleated and immediately fixed in 4% PFA. Paraffin embedding, sectioning at 4 μm thickness, and hematoxylin and eosin (H&E) staining were performed by UCLA’s Translational Pathology Core Laboratory (TPCL). Images were obtained at ×400 magnification by light microscopy, as above.

**Electroretinogram**

Adult (6 week-old) WT and PD-L1/L2−/− male mice were dark-adapted overnight for full-field flash electroretinogram (ERG) recording as previously described (29). Briefly, ERGs were recorded using a gold electrode touching the corneal surface referenced to a gold electrode in the mouth. Scotopic rod-mediated responses were obtained to blue

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**TABLE 2.** Primary antibodies used for immunofluorescence staining (13,17–25).

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Dilution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-mouse PD-1 (clone 29F.1A12, rat IgG2α) (17)</td>
<td>1:200</td>
<td>Gift of Gordon Freeman, MD, PhD (Boston, MA)</td>
</tr>
<tr>
<td>Anti-PD-L1/CD274 (rabbit polyclonal) (17)</td>
<td>1:750</td>
<td>Lifespan Biosciences, #LS-B480</td>
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<td>Anti-mouse Bm3a (clone 5A 3.2, mouse IgG1) (18)</td>
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<td>Millipore/Chemicon</td>
</tr>
<tr>
<td>Anti-mouse AP2α (clone 3B5, mouse IgG2b) (19)</td>
<td>1:20</td>
<td>Developmental Studies</td>
</tr>
<tr>
<td>Anti-Calbindin D28K (clone CB-955 (formerly CL-300), mouse IgG1) (20)</td>
<td>1:1000</td>
<td>Sigma-Aldrich</td>
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<td>Anti-PKCa (clone H-7, mouse IgG1) (21,22)</td>
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<td>Anti-G protein Goα (clone 2A, mouse IgG1) (23)</td>
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<td>Anti-glutamine synthetase (clone GS-6, mouse IgG2a) (24,25)</td>
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<td>Species- or isotype-specific Alexa Fluor 488 or 594</td>
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<tr>
<td>Anti-mouse PD-L2 (clone TY25, rat IgG2a) (13,17)</td>
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<tr>
<td>Anti-human PD-L2 (clone 24F.7G12, mouse IgG2α)</td>
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<td>Gift of Gordon Freeman, MD, PhD (Boston, MA)</td>
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FIG. 1. PD-L1 expression in the neonatal mouse retina and brain by immunofluorescence staining. A. PD-1 (green) and PD-L1 (red) expression at P2 in the central retina, at the level of the optic nerve. B. PD-L1 (green) and the following retinal cell type markers (all in red): Brn3a for RGCs, AP2α for amacrine cells, Calbindin D28K (D28K) for horizontal cells, PKCα for rod bipolar cells, Goα for optic nerve bipolar cells, glutamine synthetase (GS) for Müller glia. White arrows indicate cells shown at higher magnification inset into each panel. All images were taken at the level of the optic nerve, at the midpoint between the optic nerve head (ONH) and periphery. C. Coronal section of the superior colliculus at Bregma −4.3 mm, after Allen Mouse Brain Atlas coordinates. Panels from left to right show: 1) Nissl stain, 2) PD-1 (green) and PD-L1 (red) expression by immunofluorescence, with DAPI counterstain (blue), 3) same as second image, without DAPI, and 4) secondary only negative control, where PD-1 and PD-L1 primary antibodies were omitted, and the white box indicates area shown at higher magnification.
flashes (Wratten 47A, λ_max = 470 nm, Eastman Kodak). After a 5-minute light adaptation, cone-mediated responses were recorded. Analysis was performed using custom software (29). Amplitude of dark-adapted b wave was plotted against flash intensity and resulting intensity-response function was fit with a Naka-Rushton equation to derive V_max (maximum saturated amplitude) and k (semisaturation intensity).

Spectral-Domain Optical Coherence Tomography
Spectral-domain OCT (SD-OCT) imaging (Bioptigen) was performed. Animals were anesthetized and left pupils dilated with atropine (1% wt/vol atropine sulfate ophthalmic solution). Recordings were taken with a 50° field of view, yielding a 1.5-mm-diameter image. En face view C-scans were recorded with the optic nerve head (ONH) centered in the image and consisted of 100 two-dimensional B-scans, which in turn consisted of 800 one-dimensional A-scans. Total scan time was approximately 5 seconds. Retinal layers were measured at 0.2 mm eccentricity from the ONH with analysis software (Software Suite; Bioptigen). At 0.6 mm eccentricity from the ONH, in both temporal and superior orientations, no differences were noted between WT and PD-L1/L2−/− total retina thickness (P = 0.83 and 0.43, respectively), thus representative central measurements are reported. Retina layer analysis was performed referencing published mouse OCT images (30). “Inner retina” was defined as the distance from the inner limiting membrane to the inner nuclear layer (INL), and “outer retina” was defined as the distance from the outer plexiform layer (OPL) to the retinal pigment epithelium.

Statistical Analysis
A graphing program (Prism 5; GraphPad) was used for data visualization and statistical analysis. For immunofluorescence quantification, optic nerve axon counts, and retina architecture analysis, a Student t test was used to compare groups. For ERG data, mean and standard error of the mean (SEM) were plotted at each frequency, and Boltzmann sigmoidal curves were fitted to the data. For scotopic ERG, an unpaired t test was used to compare V_max and k between WT and PD-L1/L2−/− mice. For timing and photopic ERG amplitude, 2-way analysis of variance was used to evaluate difference between WT and PD-L1/L2−/− mice.

RESULTS

PD-L1 Is Expressed in RGCs, Bipolar Interneurons, and Müller Glia of the Mature Mouse Retina
Retinal expression of Pdcd1lg1 (PD-L1 gene) has been reported (11), identifying it as a neuronal PD-ligand. To determine potential locations for PD-1 ligation, PD-L1 protein localization was characterized in the mouse retina and SCs, the major target of rodent optic nerve axons (31). During postnatal retina maturation, a wave of RGC death occurs, peaking at P2–P5 (32). At P2, coincident with this peak, PD-L1 expression is found in the GCL in a non-nuclear distribution and in the neuroblast layer distributed on the neuropil colocalizing with PD-1 receptor expression (Fig. 1A). In addition, PD-L1 is expressed in cell processes of the incipient inner plexiform layer (Fig. 1A). In the mature retina, PD-L1 expression persists and is restricted to the inner retina layers (Fig. 1B). Since PD-L1 was found across the INL, inner plexiform layer, and GCL, immunofluorescence (IF) double labeling with GCL and INL cell type markers was performed. PD-L1 was found to be expressed in many but not all cell types. PD-L1 expression did not colocalize with 2 types of interneurons: AP2α-positive amacrine cells and calbindin D28K-positive horizontal cells (Fig. 1B). However, PD-L1 expression did colocalize with 2 neuronal cell types: Brn3α-positive RGCs, and both protein kinase C (PKC) α-positive rod bipolar axonal terminals and Goc-positive optical nerve (ON) bipolar dendrites, and in addition, 1 glial cell type: glutamine synthetase–positive Müller cell bodies and processes (Fig. 1B). Within the OPL, PD-L1 expression was observed at ON cone bipolar terminals of cone pedicle synapses, as evidenced by colocalization with the ON bipolar marker Goc, which labels both ON cone and rod bipolars (33) but not with the rod bipolar marker PKCo. Although neuronal Pdcd1lg2 (PD-L2 gene) expression has been previously described (11), PD-L2 protein expression was below the threshold of detection by IF using several anti-PD-L2 antibodies (Table 2). Since RGCs express both PD-1 and PD-L1 and extend axons to the brain via the optic nerve, we next explored expression of the PD-1 signaling system in the superficial layers of the SCs, the location to which the majority of mouse RGCs project (31). Both PD-1 and PD-L1 are expressed across the SCs, including the stratum opticum, which contains afferent optic nerve fibers of RGCs (Fig. 1C, D).
expression pattern supports the possibility that PD-1:PD-L1 engagement can also occur at the axon terminals of RGCs. Within the SCs, higher resolution imaging will be necessary to determine the subcellular localization of PD-1 and PD-L1 and also the spatial relationship of cells expressing each molecule.

**Absence of Both PD-Ligands Results in Persistent Increase in RGC Number**

To test the importance of PD-L1 GCL expression during peak RGC apoptosis, we next tested the functional role of PD-ligands in developmental RGC death and predicted that similar to that reported previously for PD-1 receptor knockout (PD-1\(^{2/2}\)) mice (11), the genetic absence of PD-ligands would increase RGC survival in the neonatal period. GCL layer compartments were assessed during the development of the PD-L1 and PD-L2 double-knockout (PD-L1\(\text{L}2^{2/2}\)) mouse retina, in comparison to WT controls, by immunofluorescent staining for the RGC and amacrine cell markers Brn3a and AP2\(\alpha\), respectively (Fig. 2A). At P2, the PD-L1\(\text{L}2^{2/2}\) retina has a significant increase in RGC number compared to WT (34 ± 2.9%; \(P = 0.006\); Fig. 2B), measured by the number of Brn3a-positive nuclei per millimeter. Given that these observations for PD-L1\(\text{L}2^{2/2}\) mirror the previously reported PD-1\(^{2/2}\) phenotype (11), we were surprised to observe that in contrast to the PD-1\(^{2/2}\) adult retina, PD-L1\(\text{L}2^{2/2}\) adult retinas have a significant increase in RGC number compared to WT (18 ± 5.4%; \(P = 0.04\); Fig. 2C). To confirm this increase, optic nerve axon counting was performed and showed that adult PD-L1\(\text{L}2^{2/2}\) had significantly increased mean axon density, as compared to WT (Fig. 3C; \(P = 0.01\)).

To determine which PD-ligand contributes to the adult phenotype, we examined retinas from single PD-ligand knockouts, PD-L1\(^{2/2}\), and PD-L2\(^{2/2}\) and found that neither had a difference in RGC number as compared to WT (\(P = 0.07\) and 0.14, respectively; Fig. 2C). A significant number of displaced amacrine cells also reside in the GCL.

**FIG. 2.** Increased RGCs in the neonatal and adult retina of PD-L1\(\text{L}2^{2/2}\) mice. A. Immunofluorescence staining for Brn3a (green) and AP2\(\alpha\) (red) in P2 and adult (P56) retina of WT, PD-1\(^{2/2}\), and PD-L1\(\text{L}2^{2/2}\) mice, with DAPI nuclear counterstain (blue). Scale bars = 50 \(\mu\)m. B. Quantification of RGC number (Brn3a/mm) in WT, PD-1\(^{2/2}\) mice at P2. Quantification of RGC number (Brn3a/mm, B, C) and amacrine cell number (AP2/mm, D) in the adult retina. Three mice per strain were analyzed at each time point. For each quantified readout, the mean and standard error of the mean were plotted. *Significant \(P\) value in comparing each knockout to WT; *\(P \leq 0.04\), **\(P = 0.006\).
so we also examined amacrine cell number in the absence of PD-1 ligation. In the adult retina, there were no significant differences in amacrine cell number between any of the knockout strains, as compared to WT ($P = 0.4$ for all knockout strains; Fig. 2D). These findings suggest that PD-L1 and PD-L2 have redundant roles in RGC cell death, and their concurrent absence is associated with a persistent increase in RGC number of the mature retina.

**Normal Gross Retina Architecture and Function in the PD-L1/L2$^{2/-}$ Adult Mouse**

The observed increase in the numbers of RGCs in the PD-L1/L2$^{2/-}$ animals prompted further evaluation of the functional significance of this observation. We first explored if the normal highly organized, laminated retina structure was present in the mature adult PD-L1/L2$^{2/-}$ retina by H&E stain and found the gross architecture to be normal, as compared to WT (Fig. 4A). Retina architecture of 6-week-old PD-L1/L2$^{2/-}$ and WT mice was visualized in vivo by SD-OCT. Reconstructed vertical sections (Fig. 4B, D) and en face fundus images (Fig. 4C, E) both appeared grossly normal in PD-L1/L2$^{2/-}$ mice (Fig. 4D, E). There were no significant differences in inner or outer retina layer thickness between PD-L1/L2$^{2/-}$ and WT (Fig. 4F, G), and concordantly, no significant differences when either the inner (Figs. 3, 4H) or outer (Figs. 3, 4I) retina was broken down to nuclear and nonnuclear layer components.

Since we observed PD-L1 expression colocalizing with PKCa-positive rod bipolar axon terminals and Goxa-positive ON bipolar dendrites, we next investigated middle and outer retina function using standard ERG. Representative ERGs recorded from PD-L1/L2$^{2/-}$ mice are shown in Figure 5A. No statistically significant differences in rod-mediated retinal function were observed between PD-L1/L2$^{2/-}$ and WT adult mice (Fig. 5B, C), although the PD-L1/L2$^{2/-}$ demonstrated a weak trend in the direction of reduced response amplitude ($V_{\text{max}}$) and photoreceptor sensitivity ($k$) ($P = 0.68$ for $V_{\text{max}}$ and $P = 0.07$ for $k$; Fig. 5B). Correspondingly, there were no statistically significant differences in cone-mediated function (Fig. 5C; $P = 0.46$). Finally, we analyzed the timing of peak components of the rod-mediated and cone-mediated ERGs and found no statistically significant differences ($P = 0.16$ and 0.71, respectively). These data collectively demonstrate that retinal structure and outer retinal function are both normal in adult PD-L1/L2$^{2/-}$ mice.

**DISCUSSION**

Developmental RGC death in mice is a highly regulated process, generating the correct number of surviving RGCs...
FIG. 4. Retina architecture in PD-1 and PD-ligand knockout mice. A. Hematoxylin and eosin stain showing gross retina architecture of WT and PD-L1/L2^−/− adult mice. Representative B-scan images at the level of the optic nerve head showing a retina cross-section from WT (B) and PD-L1/L2^−/− (D) mice. White arrows indicate Bergmeister papilla, a remnant of fetal hyaloid vasculature commonly observed in C57BL/6 mice on spectral-domain optical coherence tomographic imaging. Representative en face C-scans showing fundus images from WT (C) and PD-L1/L2^−/− (E) mice, with the horizontal green line indicating orientation of respective B-scans. F. Cropped view of WT (B) and PD-L1/L2^−/− (D) B-scans, labeled to indicate retinal layers and landmarks used for quantification of layer thickness. Quantification of inner, outer, and total retina thickness (G), and nuclear layer and nonnuclear layer components of the inner or outer retina (H or I, respectively). GC/IPL, ganglion cell and inner plexiform layers; INL, OPL, ONL, as defined above in Fig. 1; IS/OS, photoreceptor inner and outer segments; OLM, outer limiting membrane; ns, not significant; RPE/CC, retinal pigment epithelium and choriocapillaris. Scale bars = 50 µm (A), 100 µm (both x- and y-axes, B, D, F), or 200 µm (C, E).
necessary to form functional connections with the optic tectum and visual cortex (3). According to the neurotrophic hypothesis, RGC death results from the lack of available extracellular neurotrophic support (35). The discovery of a neurotrophic death–promoting signal, nerve growth factor engagement with p75NTR, introduced the additional hypothesis that soluble neurotrophic ligands can provide an active death trigger for retinal neurons (36). Our work introduces an important refinement to this idea, where receptor engagement with a cell-associated ligand can also promote developmental RGC death. We refer to this hypothesis as “active selection” of neuronal elimination.

PD-1 ligation blockade in vitro was found to decrease RGC apoptosis during peak RGC death (11), supporting a role for PD-1 receptor-ligand interaction in this process. This work, summarized in Table 1, presents strong evidence that PD-L1, PD-L1, and PD-L2 are the functional neuronal ligands for PD-1, acting within the GCL to influence RGC-specific developmental cell death. Furthermore, PD-L1 is expressed in the developing and mature retina, suggesting potential for engagement with PD-1 receptor during these times. We hypothesize several potential locations for PD-1 ligation within the retina. First, developmental ligation between GCL cell types could lead to cell death. Second, in the mature retina, PD-L1 on rod bipolar could potentially interact with PD-1 on AP2α-positive glycinergic AII amacrine cells (11,37). Third, PD-L1 on Müller glia, which ensheath all retinal cell types (38), could engage PD-1–positive RGCs and/or amacrine cells (11). PD-L1 expression at cone bipolar terminals suggests a potential role for PD-L1 in cone pathway visual responses. The presence of PD-L1 in the mature retina, along with PD-1 receptor (11), suggests additional roles for PD-1 ligation beyond developmental RGC cell death. Since the PD-L1/L2−/− retina has normal gross function by ERG, PD-ligands are not required for wiring functional circuitry within the retina. Further studies are necessary to assess whether PD-1 ligation has a role in defining retina-brain projections, perhaps through synaptic refinement, similar to other cell surface immune molecules in the CNS (8).

Perturbations of neurotrophic support (39–41), neurotrophic death (10,42), or PD-1 signaling (11) cause transient changes in RGC survival in vivo. However, none of these cell surface survival modulators are sufficient to influence the final number of RGCs in the mature adult retina. Here, we provide the first evidence for a receptor-ligand signal having a more persistent effect on RGC numbers. Genetic absence of both PD-ligands yields an 18% increase in RGCs in the mature adult retina. However, this difference is modest compared to inactivation of intracellular apoptotic machinery, where RGC numbers can be increased 50%–226%, as reviewed (3).

The observation that the absence of both PD-ligands had a persistent effect on RGC survival, while the absence of
PD-1 receptor only has a transient early developmental effect (11) led us to hypothesize the presence of another neuronal PD-ligand receptor functioning during the final phase of developmental cell death. One strong candidate is another B7 family costimulatory ligand B7-1, shown to interact with PD-L1 (but not PD-L2) in lymphocytes, with ligation resulting in similar immunoinhibitory effects as PD-1 ligation (43). Defining additional PD-ligand interacting molecules in the retina, including B7-1, and which elicit an “active selection” death signal are questions for future investigation.

PD-L1 expression in Müller glia is intriguing, as this cell type has both protective and detrimental roles in retinal disease (44). We hypothesize that PD-1 ligation could act to downregulate Müller glia activity in settings of retinal damage. Although PD-L1 expression was characterized in this study, we were unable to reliably detect PD-L2 protein expression by immunofluorescence in the developing and mature mouse retina. Genetic evidence that PD-L2 is functionally redundant with PD-L1 in promoting RGC death, in combination with identification of PD-L2 gene expression, will require further characterization of neuronal PD-L2 protein expression. In summary, our work solidifies the role of PD-ligands in RGC developmental cell death and provides impetus to explore the role of the PD-1 signaling pathway in neurodegenerative retinal disease.

ACKNOWLEDGMENTS

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Optic Disc Doubling

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FIG. 1. A. The left optic disc has an intact neuroretinal rim (C/D ratio = 0.5), but the inferotemporal venular trunk is absent. More inferiorly, there is a rudimentary optic disc and an area of retinal pigment epithelial atrophy that bridges the 2 discs. There is a single foveal avascular zone corresponding to the true optic disc at a level slightly lower than normal with a macular pigment epithelial detachment. The inferotemporal portion of the perifoveal capillary net is formed by tributaries from the superotemporal vascular arcade of the rudimentary disc. B and C. Fundus fluorescein angiogram of the left eye showing simultaneous and similar filling patterns of both the main and accessory vascular systems with pooling in the pigment epithelial detachment. D. Automated visual field of the left eye demonstrating an additional blind spot corresponding to the rudimentary disc with a contiguous arcuate scotoma superiorly. E. Optical coherence tomography line scan, passing obliquely across both optic discs, showing 2 craters of similar configuration but different depths. F. B-scan ultrasound of the left eye showing a single optic nerve shadow; a second optic nerve was not detected in additional planes. The patient declined orbital MRI.
Abstract: Many developmental defects can simulate the optic disc (optic disc pseudodoubling). True optic disc duplication with 2 independent retinal vasculatures is rare. Associated optic nerve duplication is rarer still and seen in lower vertebrates. We report a rare case of unilateral double optic discs with a single optic nerve in the left eye of a 41-year-old man, otherwise asymptomatic in the affected eye.

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Many developmental defects can simulate the optic disc (optic disc pseudodoubling) including peripapillary coloboma and scarring (1–3). True optic disc duplication with 2 independent retinal vasculatures is rare (4).

We document such a case in the asymptomatic left eye of a 41-year-old man (Fig. 1). Visual acuity was 20/20 bilaterally, and pupillary reactions were normal, as were anterior segment examinations and the right fundus appearance. The patient’s general health was excellent, and medical history was unremarkable.

REFERENCES
Primary Dural Lymphoma Masquerading as a Meningioma

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Abstract: A 39-year-old woman noted painless, progressive blurred vision in the temporal aspect of her right visual field for 1 year. Medical history was significant for hypertension treated with enalapril. The woman was a professional banker, entertainer, and singer from Trinidad. She denied the use of tobacco or illicit drugs.

Visual acuity was 20/25, right eye, and 20/20, left eye. She had diminished color vision in the right eye with a 0.6 log unit relative afferent pupillary defect. Extraocular movements were full, and external and anterior segment examinations were unremarkable. Intraocular pressure was 19 mm Hg bilaterally. Automated visual field of the right eye showed central and temporal loss (Fig. 1) while the left field was normal. There was mild optic disc pallor in the right eye, and the left fundus was normal.

The results of brain magnetic resonance imaging (MRI) were felt to most likely represent en plaque meningioma of the planum sphenoidale, compressing the right optic nerve (Fig. 2A–C). Other diagnostic considerations included a lymphoproliferative disorder, sarcoidosis, and nonspecific inflammation (pseudotumor).

Three days later, a right fronto-orbital craniotomy was performed to debulk the tumor. The surgical findings appeared typical of an en plaque meningioma (Fig. 3).

The pathologic specimen revealed an infiltrate of small basophilic cells (Fig. 4A). Staining for epithelial membrane antigen was negative for cells of meningoepithelial origin. CD20 stained the majority of the cells, indicating a B-cell proliferation with a few interspersed reactive T cells (Fig. 4B). The cells were highlighted by CD138, indicating plasmacytoid differentiation (Fig. 4C). Ki67, a nuclear protein only present during active phases of the cell cycle, showed a moderate proliferative index (Fig. 4D). Molecular analysis and polymerase chain reaction detected immunoglobulin (IGH and IGK) gene rearrangements. The histology and genetic results confirmed the diagnosis of B-cell lymphoma.

Staging, including bone marrow biopsy and whole-body positron emission tomography–computed tomography, showed no evidence of systemic disease. The patient was treated with 45 Gy of intensity-modulated radiation therapy. Eighteen months later, visual acuity was 20/25, right eye, and 20/20, left eye. The right visual field deficit with involvement of the right optic canal, orbital apex, and cavernous sinus with extension to the left optic canal (Fig. 2A–C). Other diagnostic considerations included a lymphoproliferative disorder, sarcoidosis, and nonspecific inflammation (pseudotumor).

FIG. 1. Automated visual field of the right eye shows a cecocentral scotoma and temporal field depression.
remained stable. The MRI showed successful debulking of the tumor with no evidence of recurrence (Fig. 2D–F).

Lymphomas arising primarily from the meninges without brain or systemic involvement are rare and differ biologically from other central nervous system (CNS) lymphomas (1,2). When they do occur, they typically consist of a low-grade B-cell lymphoma (1), as in our case. Primary dural lymphoma (PDL) typically has an indolent course and generally can be cured with local therapy (3). It differs from other types of CNS lymphoma (either primary or metastatic), which are typically aggressive, high-grade neoplasms with a poor prognosis.

The pathogenesis of PDL is not well understood. The dura is devoid of lymphoid tissue, as opposed to the gastrointestinal tract, where histologically similar marginal zone lymphomas typically originate from chronic antigenic stimulation (1). It has been hypothesized that meningoepithelial cells, which are present throughout the arachnoid membrane, may give rise to these neoplasms in a similar fashion (2).

PDL is initially often diagnosed as meningioma because of its virtually identical MRI features, including a dural tail (4). Thus, in cases of suspected meningioma, it is prudent to obtain a pathologic specimen whenever possible or clinically warranted.

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If a lymphomatous neoplasm is suspected on the initial pathology, further testing should be done to identify the precise histologic subtype. A meticulous search for an occult source is critical because this will determine treatment and prognosis.

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FIG. 4. Histopathologic specimen. A. The tumor is composed primarily of small basophilic cells (hematoxylin and eosin, ×200). B. Immunostaining shows a lymphoid cell population with predominance of CD20+ B cells (brown) and few interspersed CD3+ T cells (red) (×400). C. Many cells stain positive for CD138, indicating plasmacytoid differentiation (×400). D. Staining for Ki67 shows a moderate proliferative index (×200).
Cat Scratch Neuroretinitis: The Role of Acute and Convalescent Titers for Diagnosis

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Abstract: Cat scratch neuroretinitis (CSN) is a clinical diagnosis supported by serological testing. We present 2 cases of CSN in which initial acute titers were negative or equivocal for Bartonella henselae while convalescent titers were shown to be positive. We report these cases to emphasize that a single acute negative titer is insufficient to exclude the diagnosis of CSN and that convalescent titers should be obtained in patients for whom there is a high clinical suspicion of the disease.


CASE REPORTS

Case 1
A 43-year-old woman developed acute unilateral loss of vision in the lower portion of her right visual field. Medical history was significant for hypertension, gastric ulcers, degenerative arthritis, and anxiety. Her medications included paroxetine, aspirin, and olmesartan. She reported being scratched by kittens 2 weeks previously and had cat scratches on her lower extremities. She denied fever, malaise, weakness, regional lymphadenopathy, or flu-like symptoms.

Visual acuity was 20/25, right eye, and 20/20, left eye. The pupils were isocoric and reactive to light with a small right relative afferent pupillary defect. External examination, ocular motility, and slit-lamp biomicroscopy were normal. Automated visual field testing showed an inferior altitudinal visual field in the right eye while the left field was normal. The right fundus showed optic disc edema with peripapillary hemorrhage and exudate (Fig. 1), and the left fundus was unremarkable.

MRI of the brain and orbits was normal except for an old lacunar infarct in the left midbrain. Serological studies for Bartonella henselae were equivocal for IgG, 1:128 (positive $\geq$ 1:256), and negative for IgM, <1:16 (positive > 1:16). The patient was started on azithromycin (500 mg daily for 5 days). Two weeks later, convalescent serologies were positive for Bartonella henselae IgG, 1:256 (positive $\geq$ 1:256), and remained negative for IgM, <1:16 (positive > 1:16). The
patient’s signs and symptoms progressively improved, and 2 weeks later, vision was 20/20 in each eye, with normal visual field testing.

**Case 2**

A 6-year-old boy developed blurry vision after being hospitalized for surgical drainage of a psoas muscle abscess. Medical history was significant for esotropia, corrected with strabismus surgery, and congenital left ptosis but no history of amblyopia. Visual acuity was 20/40, right eye, and count fingers, left eye. He correctly identified 4/8 Ishihara color plates with the right eye and none with the left eye. Pupils were isocoric and reactive to light with a left relative afferent pupillary defect. The patient had a left esotropia of 10–12 prism diopters with full extraocular movements. Funduscopy of the right eye showed optic disc edema with a macular star of exudate (Fig. 2A). On the left eye, there was an inflammatory lesion obscuring the optic disc and exudates in the macula (Fig. 2B).

Initial *B. henselae* serological results were negative for IgG, <1:64 (positive ≥ 1:256), and IgM, <1:64 (positive > 1:64). The patient was started on azithromycin (60 mg daily for 4 weeks) and rifampin (175 mg twice daily for 4 weeks). Repeat testing 2 weeks later showed convalescent titers to *B. henselae* of IgG, >1:1024 (positive ≥ 1:256), and remained negative for IgM, <1:64 (positive > 1:64). Over the following month, the patient’s vision improved to 20/40, right eye, and 20/30, left eye. There was resolution of the optic disc swelling in the right eye and reduction in the size of the lesion overlying the left optic nerve head (Fig. 3).

**DISCUSSION**

Serology antibody testing for *B. henselae* is used to support a clinical diagnosis of CSD (9). Elevated IgM titer is evidence for an acute infection, but by 3 months, only 4% of CSD patients have a positive IgM (10). In contrast, the IgG antibody level rises following the IgM titers and then will decrease with time. Yet the IgG titer may remain positive for 2 or more years following the onset of symptoms (10). In patients for whom there is a high suspicion of CSD, it is our practice to obtain a convalescent titer 2 weeks following a negative initial result, as the initial test may have been performed before IgG titers have risen and after IgM titers return to normal. It is important to note that a high seroprevalence in the general population limits the utility of a single IgG titer (11). In addition, there appears to be limited association between the serological titers and either the clinical manifestations of CSD or the duration of symptoms (10), so titers alone should not be used to measure the outcome or prognosis of disease.

Despite these limitations, the Centers for Disease Control and Prevention recommend that a single highly elevated IgG or a positive IgM antibody titer is generally sufficient to confirm CSD (12,13). A 4-fold change in IgG antibody titer in acute and convalescent serum samples is also used as laboratory criteria for recent infection (11–14).
Two types of serological diagnostic tests are available for B. henselae: indirect fluorescence assay (IFA) and enzyme immunoassay (EIA). Both have been documented to have low sensitivity in establishing the diagnosis of CSD (11,15–19). For the EIA test, IgM sensitivities range from 65% to 71% with IgG sensitivities from 9.5% to 28% (11,15,19). The IFA test, which is more commonly used, has been shown to have similar low sensitivities with IgM values ranging from 46% to 53% and IgG values from 32% to 67% (11,19). This may be due to the fact that some patients may remain serologically positive long after recovery, while others never mount a detectable response (11). The short duration of the rise in IgM antibodies is also problematic, and negative or equivocal results should not exclude infection (18).

In patients with a high likelihood of CSD, acute and convalescent titers are strongly recommended. Laboratory testing with polymerase chain reaction (PCR) also might be valuable in patients with negative serologic results (11). This technique has been reported to be highly specific and sensitive for detecting Bartonella DNA in lymph node specimens (11). PCR has also detected Bartonella species in iris tissue and aqueous humor (7,20). In our clinical practice, we have not used PCR in this setting.

REFERENCES

Lyme-Associated Orbital Inflammation Presenting as Painless Subacute Unilateral Ptosis

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Abstract: A 90-year-old woman presented with subacute painless left ptosis. Examination of the left eye revealed ptosis with loss of the superior eyelid sulcus, 2 mm of proptosis, mild tenderness with retropulsion, and optic disc edema. Levator function and extraocular movements were normal, and there was no relative afferent pupillary defect. MRI demonstrated thickening of the extraocular muscles in the left orbit with lacrimal gland enlargement and mild enhancement of the optic nerve sheath. Serology revealed a positive enzyme-linked immunosorbent assay for Lyme antibodies and a positive Western blot of Lyme IgG titer. The patient recalled a tick bite 6 months earlier, at which time Lyme serologies were negative. After 3 weeks of intravenous ceftriaxone, she had a significant improvement and a full recovery by 3 months. Lyme disease should be included in the differential diagnosis of orbital inflammation, especially in Lyme-endemic areas.

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CASE REPORT

A 90-year-old woman from Connecticut presented with subacute painless left eyelid ptosis and increased tearing for 1 month accompanied by mild fatigue and unintentional weight loss. She recalled a tick bite to her right ear 6 months earlier without associated erythema migrans; although Lyme titers were negative, she was treated presumptively with a 3-week course of 100 mg of oral doxycycline twice daily.

Ophthalmologic examination revealed visual acuity of 20/25, right eye, and 20/50, left eye. Pupils were 2 mm and reactive on the right eye and postsurgically irregularly dilated on the left eye. There was no relative afferent pupillary defect. Color vision was normal in the right eye and reduced in the left eye. On slit-lamp examination, posterior lenses were present and there was no evidence of uveitis. Extraocular movements were full. There was no resistance to retropulsion of the globes, although there was tenderness on the left eye with retropulsion and 2 mm of left proptosis. There was loss of the left superior lid sulcus, and left ptosis was present with a margin reflex distance-1 (MRD-1) of 5 mm on the right and 2 mm on the left (Fig. 1). Levator function was 15 mm bilaterally. Cranial nerves V and VII were intact bilaterally. Funduscopic examination on the left eye demonstrated mild optic disc edema with peripapillary hemorrhages (Fig. 2), while the right fundus was normal. Automated visual field testing was unreliable while confrontation fields were full. MRI demonstrated increased thickness of the extraocular muscles in the left orbit with mild enlargement of the lacrimal gland and contrast enhancement of the optic nerve sheath (Fig. 3).

Laboratory results revealed a positive enzyme-linked immunosorbent assay for Lyme antibodies (Lyme index 5.08; normal range, <1.00), with a positive Western blot for B. burgdorferi IgG (8 bands) and negative IgM. Complete blood count, angiotensin-converting enzyme, rapid

FIG. 1. At presentation, the patient had 3 mm of left ptosis with the loss of the superior eyelid sulcus.
plasma reagin, C-reactive protein, erythrocyte sedimentation rate, antineutrophil cytoplasmic antibody, myasthenia gravis panel, and thyroid panel (T4, thyroid-stimulating hormone, anti-thyroid peroxidase, antithyroglobulin) were unremarkable.

The patient was treated with a 3-week course of 1,500 mg of intravenous ceftriaxone daily. At a 3-week follow-up visit, her vision on the left eye had improved to 20/25 with normal color vision. MRD-1 on the left increased to 3.5 mm. At 3 months, the patient’s ptosis (Fig. 4) and optic disc edema had completely resolved.

**DISCUSSION**

Seidenberg and Leib (1) first described Lyme-associated orbital myositis in a 5-year-old girl in 1990. Our literature search revealed 4 cases of serologically confirmed Lyme-associated orbital inflammation, all of which had a component of orbital myositis (2–5). Lyme antibodies are usually detected 6 weeks after the initial infection. This may explain the negative Lyme titer 6 months prior to our patient’s presentation and her later seroconversion. The most common presentation of orbital myositis is acute and unilateral, with symptoms of orbital and periorbital pain worsening with ocular movement (85%–100% of cases), diplopia (50%–100% of cases), mild proptosis of 1–2 mm (30%–56% of cases), swollen eyelids, and conjunctival hyperemia (6). Our patient’s presentation was unusual, as her primary complaint was unilateral painless ptosis without diplopia. The initial differential diagnosis also included neoplasm, thyroid orbitopathy, myasthenia gravis, and levator aponeurosis dehiscence. The diffuse thickening of extraocular muscles seen on MRI was previously reported in other orbital Lyme myositis cases (4,7). Unilateral optic disc edema and optic nerve sheath enhancement suggested a diagnosis of optic perineuritis. Optic perineuritis can spare central visual field and acuity and thus may account for our not seeing a relative afferent pupil defect or a central scotoma on visual field testing.

The reported cases of Lyme orbital myositis can be categorized as manifestations of early disseminated disease or late disease. Although 2 g of intravenous ceftriaxone daily or 20–24 million units of penicillin G daily are typically recommended as first-line agents for ophthalmic or neurologic disease, there are no clear recommendations for the treatment of orbital disease without ocular or neurologic involvement (8). Successful treatment of Lyme orbital inflammation with either 3–4 weeks of oral doxycycline (3,4,7) or 2–3 weeks of intravenous ceftriaxone (2,5) has been reported. In our case, the history of prior doxycycline treatment at the time of the initial tick bite prompted intravenous ceftriaxone treatment.

**REFERENCES**

Nonconvulsive Status Epilepticus Presenting as Epileptic Nystagmus in a Patient With Herpes Encephalitis

Ju-Hee Lee, MD, Do-Hyun Nam, MD, Sun-Young Oh, MD, Byung-Soo Shin, MD, Man-Wook Seo, MD, Seul-Ki Jeong, MD, Jun-Young Lee, MD

Abstract: Epileptic nystagmus (EN) is characterized by rhythmic ocular oscillations or quick, repetitive eye movements secondary to seizure activity. The fast component of EN is known to be contralateral to the epileptogenic focus. There are few reports EN occurring patients in nonconvulsive status epilepticus (NCSE). We report such a patient in the setting of herpes encephalitis.

CASE REPORT

A 19-year-old girl was admitted to hospital for headache, fever, and altered mental status, which occurred several days previously. With onset of symptoms, she complained of a right homonymous hemianopia, and her mental status deteriorated steadily into stuporous state. At the time of initial examination, she was afebrile. Cerebrospinal fluid examination revealed white blood cell count of 19/mm$^3$ and herpes simplex virus IgG titer of 2.6 IU/mL. Brain MRI demonstrated high signal intensities involving portions of the left temporal and occipital lobes (Fig. 1).

Diagnosed with herpes encephalitis, the patient was given intravenous acyclovir. Despite treatment, she continued to deteriorate clinically. She had no response to painful stimuli and developed spontaneous conjugate right-beating nystagmus with tonic deviation toward the right side. The slow component of nystagmus did not cross the midline. Her head paroxysmally deviated to the right along with her eyes and showed episodic bilateral eyelid elevation. EEG revealed spiky rhythmic alpha activity in the left posterior region of the head, which evolved into repetitive sharp waves (Fig. 2). We felt that the patient had NCSE with EN and administered intravenous phenytoin and lorazepam. This led to almost immediate suppression of ictal activity and disappearance of nystagmus with progressive improvement of cognitive function.

DISCUSSION

Depending on the clinical characteristics of EN, there are 3 different mechanisms for generation of this eye movement disorder. First, EN may be due to epileptic discharges in the cortical saccade regions of the frontal...
eye field (frontal precentral sulcus), the parietal eye field (anterior angular sulcus), or posterior parietal cortex (inferior parietal lobule) (4). Activation of these regions induces nystagmus with the fast phase beating opposite to the side of the epileptic focus. This is followed by an ipsilateral centripetal slow drift of the eyes that do not cross the midline (8,13). Second, EN may be caused by epileptic discharges in the temporo-parieto-occipital junction. Activation of this region induces ipsilateral smooth pursuit eye movements, which cross the midline (11). This is followed by secondary, reflexive contraversive saccades. Third, EN may arise from epileptic discharges in the optokinetic region, a projection from temporal–occipital cortex to the nucleus of the optic tract (11).

In our patient, EN onset was probably due to the first mechanism. This is supported by the MRI findings and the tonic deviation of the eyes to the right, the slow phase of the nystagmus that did not cross the midline, and the onset of ictal discharges localized over the parieto-occipital electrodes.

Despite many cases of EN, it has infrequently been associated with NCSE (4). This may in part be due to the lack of diagnostic criteria for NCSE (14), particularly when dealing with an obtunded/comatose patient. NCSE should be considered in any patient with unexplained altered mental status or coma with or without abnormal motor activity. This diagnosis requires a high index of suspicion and must be verified with an EEG (15).

FIG. 1. Axial (A) and coronal (B) FLAIR MRI show an area of high signal involving the left hippocampus and parahippocampal and lingual gyri.

FIG. 2. EEG shows spiky rhythmic alpha activity in the left posterior head region, which evolved into repetitive sharp waves. Nystagmus was observed in the right frontopolar channel (boxed recordings).
REFERENCES


Clinical Observation

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Reversible Prolonged Bilateral Inferior Altitudinal Visual Field Defects Associated With Migraine

Hartej S. Sethi, MD, Byron L. Lam, MD, Jose G. Romano, MD

Abstract: A 14-year-old girl with a history of migraine headaches and methylphenidate use presented with 2 episodes of prolonged but completely reversible inferior altitudinal homonymous visual field loss, lasting 5 days and 4.5 weeks, respectively. Neuroimaging studies were unremarkable. We discuss the potential causes of our patient's visual symptoms and speculate and hypothesize that it may represent an atypical manifestation of migraine, perhaps related to a channelopathy.


Transient visual field defects are a relatively common accompaniment of migraine headaches. These usually last a few minutes to an hour, but prolonged visual field loss has rarely been described (1). Visual field defects that persist are usually caused by permanent visual pathway damage. We present a patient with reversible, recurrent, prolonged, bilateral, inferior altitudinal visual field defect that initially was thought to represent cerebral ischemia and discuss potential mechanisms causing this rare manifestation of migraine.

CASE REPORT

A 14 year-old girl experienced sudden onset of change in color perception described “as if seeing through a dark red lens” in the lower visual fields of both eyes. The patient had no associated symptoms and had no headaches. Medical history was remarkable for a 5-year history of throbbing headaches and associated with photophobia and phonophobia. The headaches usually lasted a few hours, were often preceded by 30 minutes of nausea and scintillating scotomas, and were triggered by stress and the smell of chocolate. They were relieved by ibuprofen and sleep, and there was a strong paternal family history of migraine. The patient had been diagnosed with attention-deficit hyperactivity disorder and for which she was taking methylphenidate.

One day after the onset of symptoms, the patient’s visual acuity was 20/20 in each eye with no relative afferent papillary defect. Ocular motility and anterior segment examinations were normal as were intraocular pressures (16 mm Hg, right eye; 15 mm Hg, left eye). Automated perimetry (24-2 threshold, SITA-standard strategy; Zeiss-Humphrey Division, Dublin, CA) showed bilateral homonymous inferior visual field defects (Fig. 1). The fundi were normal.

Two days after the onset of symptoms, MRI with FLAIR, diffusion weighted and T1 with and without contrast sequences of the brain, and fat saturation of orbits were unremarkable. The visual field defects resolved over the next 5 days.

Five and a half months later, while in school, the patient developed sudden painless loss of the lower half of the visual field in each eye. She had no other symptoms, including headache, nausea, or vomiting. The patient was still on methylphenidate for attention-deficit disorder. Three days later, the patient’s visual acuity was 20/20 bilaterally, with a normal ophthalmic examination. Automated perimetry (30-2 SITA standard) showed dense bilateral inferior field defects (Fig. 2A). General physical and neurologic examinations were normal.

Repeat brain and orbital MRI with and without contrast was normal. Magnetic resonance angiogram of the neck, transthoracic echocardiogram, transcranial electroencephalogram, and a shunt detection study with transcranial Doppler failed to show any abnormality. Extensive laboratory testing, including complete blood count, serum chemistries, a hypercoagulable and rheumatologic panels, serum lactic acid and pyruvic acid levels, was normal.

Three weeks after the onset of symptoms, the patient retained 20/20 acuity in each eye, and the visual field defects were smaller (Fig. 2B). Over the following week, her visual field defects resolved.
The patient’s methylphenidate was discontinued, and she was placed on aspirin and topiramate. She developed vomiting, and a metabolic panel showed slight hypoglycemia and metabolic acidosis. This resolved after topiramate was stopped, and she has not had any visual episodes over the ensuing 16 months.

**DISCUSSION**

In our patient, the history of headaches and the recurrent nature of the events suggested a migrainous etiology of the prolonged bilateral episodes of inferior visual field loss. Other diagnostic considerations included stroke, occipital seizures, glaucoma, optic neuropathy, metabolic encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).

All of these were unlikely in the setting of normal MRI studies, laboratory testing, ophthalmologic examination, and electroencephalogram.

Visual symptoms are a frequent manifestation of migraine with aura (classic migraine). Visual accompaniments of migraine with aura include unformed flashes of lights (photopsias), enlarging blind spots with shimmering edges (scintillating scotomas), formations of dazzling zigzag lines (fortification spectra or teichopsia), and blurred, shimmering, or cloudy vision. These visual phenomena spread or migrate across the visual field over several minutes. Less commonly, there are more complex visual disturbances such as metamorphopsia and palinopsia (2,3). Negative visual field defects, seen less often, are usually of short duration and frequently homonymous, indicating a cortical origin. They are followed by the typical migraine headache, but occasionally, the headache may be mild or absent, and the episode is termed a migraine aura without headache. This can present a diagnostic dilemma, as seen in our patient.

Persistent aura without infarction is a rare but recognized entity. It is described in the International Classification of Headache Disorders, 2nd edition (ICHD-II) (1) as typical aura symptoms in patients with migraine with aura lasting more than 7 days in the absence of neuroimaging evidence of infarction. We are aware of 28 cases of prolonged visual phenomena probably related to migraine (4–15). However, in most described cases, the visual phenomena had “positive” characteristics of scintillation, photopsias, or scintillation. Only 4 of these had persistent “negative” symptoms of visual field loss (12–15), and altitudinal defects were described in 2 (14,15). One of these patients had persistent visual field defects at 6-month follow-up, and the other had complete resolution at 4 months.

Our understanding of the pathophysiology of the visual aura of migraine is incomplete. Alteration in neuronal or glial ion channels lowers the threshold for depolarization in certain cerebral cortical locations. This results in a wave of depolarization followed by inhibition (cortical spreading...
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depression). Imaging studies have demonstrated changes consistent with cortical spreading depression that correlate with migraine aura (16). There is consensus that during the migraine aura, brief transient cerebral hyperemia occurs, followed promptly by a decrease in regional blood flow lasting up to a few hours (17–19). These findings suggest that vascular mechanisms do not play a central role in prolonged migrainous aura. It is more likely the result of neuronal depression in contiguous cortical areas, although the responsible mechanisms for this phenomenon are not well understood (20,21).

The best-studied model for migrainous aura is familial hemiplegic migraine (FHM). In this condition, hemiplegia associated with migraine can last from minutes to hours, but symptoms lasting 4 weeks have been reported (22). The molecular correlates of FHM have been elucidated; 3 genes that transcribe membrane ion channel proteins have been implicated: CACNA1A (FHM type 1), ATP1A2 (FHM type 2), and SCN1A (22). In a mouse model of FHM type 1, subcortical spread of cortical depression to the striatum with reverberation of the spreading depression waves has been demonstrated (23). Such reverberation of spreading depression between cortical and subcortical structures could explain the prolonged nature of this depression in certain cases (24). The ATP1A2 mutation has a greater association with prolonged aura in hemiplegic migraine compared to other mutations (25). It is possible that such ion channel abnormalities that result in prolonged neuronal suppression play an important role in migrainous defects.

Our patient was taking methylphenidate during both episodes of prolonged visual field loss. Cerebral vasculitis and stroke associated with methylphenidate use have been reported anecdotally in children (26) and adults (27,28), but no strokes occurred among 128,000 children taking methylphenidate in a large cohort study using administrative databases (29). As methylphenidate is related to amphetamines and stroke is associated with adrenergic agents, the suggestion that methylphenidate can cause stroke is not surprising. However, this is unlikely to be the cause of the prolonged visual field defects in our patient given their repetitive nature and normal neuroimaging studies. In fact, a pilot study of the use of amphetamines in migraine patients showed the use to be of benefit without serious adverse effects (30). Another possible association is that of aminergic-induced hallucinations that have been sporadically reported with methylphenidate, but these are short lived and resolve with discontinuation of the agent (31,32); the absence of positive visual phenomena and the altitudinal component of the deficit in our case argue against this explanation.

In conclusion, we have described a case of recurrent, prolonged, and completely reversible homonymous altitudinal visual field defects. We suggest that this is a manifestation of migraine and propose that an underlying channopathy may predispose to these unusual symptoms. Perhaps, future registries can advance the phenotypic and genetic characterization of cases such as ours.

REFERENCES


Magnetic Resonance Imaging of Luxury Perfusion of the Optic Nerve Head in Anterior Ischemic Optic Neuropathy

Oren S. Yovel, MD, Miriam Katz, MD, Hana Leiba, MD

Abstract: A 49-year-old woman with painless reduction in visual acuity in her left eye was found to have nonarteritic anterior ischemic optic neuropathy (NAION). Fluorescein angiography revealed optic disc capillary leakage consistent with “luxury perfusion.” Contrast-enhanced FLAIR magnetic resonance imaging (MRI) showed marked enhancement of the left optic disc. Resolution of the optic disc edema and the MRI abnormalities followed a similar time course. This report appears unique in documenting the MRI findings of luxury perfusion in NAION.

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Although magnetic resonance imaging (MRI) is the modality of choice in the assessment of various optic neuropathies, its role is limited in the diagnostic evaluation of NAION. The use of diffusion-weighted imaging (DWI) has shown promise in detecting optic nerve ischemia (1–3). We report a patient with NAION who developed luxury perfusion of the affected optic disc with marked enhancement of the optic nerve head on contrasted FLAIR MRI.

CASE REPORT

A 49-year-old woman presented with painless blurred vision in her left eye for 6 days. Her medical history included mild iron deficiency anemia and elevated cholesterol.

Visual acuity was 20/25, right eye, and 20/30, left eye. While color vision was intact bilaterally, there was a left relative afferent pupillary defect. Slit-lamp examination and intraocular pressure were normal in both eyes. Automated visual field testing showed superior and inferior field loss in the left eye (Fig. 1). The right optic disc was normal with a cup-to-disc ratio of 0.1, and the left optic disc was swollen (Fig. 2). No other neurologic or systemic deficits were found.

Fundus fluorescein angiography revealed hyperemia and leakage from the upper portion of the left optic disc (Fig. 3). Precontrast and postcontrast T1 MRI images of the orbits showed bulging of the left optic nerve head, and postcontrast FLAIR revealed high signal within the left optic disc (Fig. 4).

Three weeks later, visual acuity and visual fields were unchanged, but there was a slight decline in color vision in the left eye. The left disc was now pale with the resolution of edema. One month after the presentation, MRI revealed a decrease in the size and signal intensity of the left optic nerve head (Fig. 5).

DISCUSSION

Rizzo et al (4) examined the MRI findings in a cohort of patients with NAION using FLAIR and T2 images. They detected signal abnormalities in the orbital segment of the optic nerve in 5 of 32 patients, but none involving the optic disc. There have been few reports (1,2) of restricted diffusion of the optic disc with DWI in patients with NAION. It is in the setting of papilledema that increased signal abnormalities have been detected in the optic nerve head (5–7). These are often accompanied by other neuroimaging findings including flattening of the posterior sclera, vertical tortuosity of the orbital optic nerve, and empty sella (6).

Luxury perfusion has been described as “a vascular response to ischemia characterized by dilation of blood vessels and increased perfusion in a region surrounding an infarct” (8). It consists of dilated blood vessels at the interface of infarct and normal tissue and has been described in the heart (9) and brain (10) and initially in NAION by Smith (11). Luxury perfusion in NAION is felt to be...
a vascular autoregulatory response to increase oxygenation in ischemic portions of the optic disc.

In our patient, fluorescein angiography showed numerous dilated blood vessels in the upper portion of the affected disc, corresponding to the region of spared visual field. Luxury perfusion may have contributed to some preservation of optic nerve function including visual acuity and inferior visual field.

It is unclear why enhancement of the left optic disc was not seen on contrast-enhanced T1 MRI but was seen on
FLAIR. It may be that there are unique properties of luxury perfusion resulting in contrast enhancement on FLAIR sequences. For example, Mathers et al (12) examined 105 patients with various diseases of the brain and found that superficial meningeal enhancement often was better seen with contrasted FLAIR versus T1 images. Whether the neuroimaging findings documented in our patient are unique to luxury perfusion in NAION awaits further study.

REFERENCES

**FIG. 4.** Axial (A) and sagittal (B) contrasted, fat-suppressed FLAIR images disclose hyperintense signal of the left optic nerve head.

**FIG. 5.** One month later, axial contrasted, fat-suppressed FLAIR MRI shows diminished size and signal of the left optic disc.
The Immunopathology of Giant Cell Arteritis: Diagnostic and Therapeutic Implications

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Abstract: Giant cell arteritis (GCA) is an important cause of preventable blindness, most commonly due to anterior ischemic optic neuropathy. Ischemic tissue injury is the end result of a process that begins within the walls of susceptible arteries in which local dendritic cells (DCs) recruit and activate CD4 T cells that, in turn, direct the activity of effector macrophages. In response to the immune attack, the blood vessel forms lumen-stenosing intima. Multiple cascades of excessive T-cell reactivity contribute to the autoimmune features of giant cell arteritis with TH1 and TH17 immunity responsible for the early phase and TH1 immunity promoting chronic-smoldering inflammation. These cascades are only partially overlapping, supporting the concept that a multitude of instigators induce and sustain vascular inflammation. The artery actively participates in the abnormal immune response through endogenous immune sentinels, so-called vascular DCs embedded in the adventitia. Advancing age, the strongest of all risk factors for GCA, contributes to both, the dysfunction of the immune system and the vascular system. Expansion of the therapeutic armamentarium for GCA needs to focus on approaches that mitigate the impact of the aging artery and adapt to the needs of the immunosenescent host.

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Giant cell arteritis (GCA) is an autoimmune syndrome (1). Recognizing and managing GCA remain an ophthalmologic emergency because the disease can quickly progress to irreversible vision loss, diplopia, or stroke (2). If the underlying vasculitis is promptly treated, vision loss may be reversible and the fellow eye, also at high risk for involvement, can be protected.

The disease process underlying GCA is a granulomatous inflammation, which is typically positioned within the wall layers of medium and large arteries. Granulomatous infiltrates are composed of CD4 T cells and highly activated macrophages, often including multinucleated giant cells. The vascular wall, generally an immune-privileged site, responds to the attack with a response-to-injury program, which culminates in hyperplasia of the intimal layer, leading to luminal compromise and vessel occlusion.

In the majority of patients with GCA, the arteritis is associated with a syndrome of systemic inflammation, which results in the constitutional symptoms and the well-described laboratory abnormalities, such as elevated acute phase markers (sedimentation rate, C-reactive protein). This systemic component is relatively easy to treat with currently available immunosuppressive regimens. In contrast, the vascular complications of GCA remain a major clinical challenge. Recent data suggest that wall-centered inflammation persists chronically. Luminal stenosis/occlusion results in ischemia, and involvement of different vessels supplying the eye, optic nerve, and brain leads to different ocular findings and patterns of vision loss. Extracranial vessel involvement can cause headache, jaw claudication, eye pain, scalp infarction, and other ischemic presentations. GCA aortitis leads to aneurysm formation with the associated risk for dissection and rupture.

While formerly suspected to represent a granulomatous reaction to a yet unidentified instigator, it is now clear that the immunopathogenesis of GCA reaches a much higher degree of complexity. Separable lineages of dysfunctional immune cells have been implicated in driving the disease, making it highly unlikely that a single etiologic agent induces GCA (3). At least 2 distinct immune processes govern early...
and late disease, emphasizing the need to search for a variety of inciting events. Probably the most important observation in GCA research has come from the recognition that the blood vessel regulates disease susceptibility and progression through immune-stromal communications.

A much improved understanding of the immunopathology of GCA, which has emerged over the last decade, is impacting the diagnostic approach to patients suspected to have GCA or diagnosed with GCA. Immunologic studies suggest a much more chronic course of the disease than previously appreciated (4). Accordingly, current therapeutic strategies, while successful in managing acute disease, need to be adapted to longer term goals. An overriding challenge is the advanced age of the affected patient population. While immune aging emerges as one of the underlying pathogenic principles in conferring risk for GCA, it also restricts the potential use of more aggressive means to immunosuppress vessel-wall centered chronic inflammation.

**DISEASE RISK FACTORS IN GCA**

**Age**

By far the strongest risk factor to develop GCA is the age of the patient (Table 1) (5). Individuals younger than 50 years seem to be almost completely protected, whereas the 7th and 8th decade of life are high-risk periods. Exceptions to this rule are patients diagnosed with Takayasu’s arteritis that have a vasculitis similar to GCA. They are typically in the 2nd to 4th decade of life and current diagnostic criteria require a disease onset before 40 years of age. Similar to fundamental differences in age of onset, the geographic regions of the world with high-risk populations for GCA or Takayasu’s arteritis are almost mutually exclusive, supporting the concept that the 2 diseases affect two nonoverlapping host populations and thus must have critical differences in etiology and pathogenesis.

Aging leads to a profound remodeling of the immune system with weakening of adaptive immunity because of thymic involution, abating ability to maintain tolerance, and resurgence of less sophisticated innate defense mechanisms (6,7). Also, progressive accumulation of chronic infections reshapes the immune system, detracts from the ability to devote immune responses toward new antigens, and promotes a progressive rearrangement of naive and memory immune cell populations.

Whether an aged immune system is more likely to generate granulomatous reactions and whether aged macrophages are more susceptible to fuse into giant cells are not entirely understood. Equally important is the inherent immune function of the blood vessel wall and the impact that age-related structural changes have on cell trafficking, cell survival, and cell–cell communications. Interactions between the aging immune system and the aging arterial wall rely on fundamentally different molecular networks. The coordinated senescence of the immune system and the vascular tree may be the critical factor in allowing GCA to occur (8).

**Sex**

Women are at much higher risk of developing granulomatous arteritis of the medium and large arteries with a 3:1 female-to-male risk ratio (Table 1). Hormonal and reproductive factors are suspected to participate in disease risk, but mechanistic concepts and data are lacking. Considering that almost all patients are postmenopausal, one would have to postulate a role for sex-dependent imprinting of either the immune system or the vascular system that renders the host susceptible many decades later.

**Genetic Factors**

Data from the early 1990s have established that GCA is an human leukocyte antigen (HLA)-associated disease implicating the strongest of all immune response genes in pathogenesis (Table 1) (9). The GCA risk haplotype is HLA-DR4—a haplotype also found enriched among patients with the autoimmune syndrome rheumatoid arthritis. Interestingly, despite this common genetic risk, GCA and rheumatoid arthritis seldom co-occur, suggesting that HLA-DR4 can serve more than one role in biasing immune responses toward inflammation and tissue injury. An extended list of possible non-HLA disease risk genes have been examined over the last decade. Some are present at higher frequency.

**TABLE 1. Risk factors for GCA**

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factor</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>Older than 50 years</td>
</tr>
<tr>
<td>Sex</td>
<td>3:1 female-to-male ratio</td>
</tr>
<tr>
<td>Genetic</td>
<td>HLA-DR4 haplotype; multiple immune response gene polymorphisms with low risk ratio</td>
</tr>
<tr>
<td>Geography</td>
<td>High incidence region: Iceland, Sweden, Norway, Denmark; Intermediate incidence region: Middle Europe; low incidence region: Japan</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td>High risk: Caucasian</td>
</tr>
<tr>
<td></td>
<td>Low risk: African American</td>
</tr>
<tr>
<td>Immune aging</td>
<td>Remodeled adaptive immune system; hyperactive innate immune system</td>
</tr>
<tr>
<td>Vascular aging</td>
<td>?Altered vascular dendritic cell function</td>
</tr>
<tr>
<td></td>
<td>?Altered matrix composition</td>
</tr>
<tr>
<td></td>
<td>?Endothelial dysfunction</td>
</tr>
<tr>
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<td>?Altered smooth muscle cell behavior</td>
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in patients than controls, but the overriding theme has been that such polymorphisms contribute only a relatively small risk. The described disease risk genes all seem to be connected to the host’s ability to generate immune responses, emphasizing the central role of immunity in the pathogenesis of GCA.

Noninherited Risk Factors
In 1932, Horton (10), at the Mayo Clinic, obtained the first temporal artery biopsy and recognized the combination of headaches, fever, weakness, anemia, and painful tender scalp vessels as a novel disease entity. Early on, he was convinced that his first 2 patients had actinomycosis but later abandoned this diagnosis (11). Since then, there has been intense interest in whether GCA is precipitated by an infectious agent. Episodically, reports surface that attract attention to a bacterial or viral pathogen as the etiologic agent. So far, none of such reports has been confirmed in subsequent studies and in independent cohorts (12,13). The explicit sensitivity of the disease to high doses of corticosteroids makes a classical infectious pathogenesis unlikely. Also, the very strict age dependence of GCA questions how an infection could exclusively occur in individuals older than 50 years. This does not exclude an indirect role of the infectious burden in disease pathogenesis. Accumulative infection of the host with multiple organisms could well reprogram the host’s immune system such that subsequent noninfectious triggers would elicit tissue-damaging inflammatory reactions.

Deciphering the relationship between GCA and infectious organisms is complicated by the fact that chronic inflammatory lesions may serve as “waste depositories.” Phagocytic cells loaded with pathogen-derived materials may end up in chronic inflammatory infiltrates due to nonspecific recruitment signals; yet, their cargo has no contribution in initiating or sustaining disease (14).

The geographic variations of GCA across the world, with an impressively high prevalence in the Northern latitudes (Table 1) (15,16), raises the question how environmental factors affect disease risk. Sun exposure has been discussed as a potential risk factor. However, the observation that Scandinavians migrating from Sweden, Norway, and Denmark to Midwestern states of the United States brought with them the increased susceptibility to GCA is best compatible with the host immune system as the predominant risk determinant.

Dysfunctional Immunity in GCA
The immunopathogenesis of GCA is driven by 3 cell types: dendritic cells (DCs), CD4 T cells, and macrophages (17,18). While classical components of a granulomatous reaction, the distribution of these cell types is unique in that the dendritic cell is supplied by the blood vessel, determining the tropism of the disease for the transmural part of human arteries. In the translation of tissue inflammation into vascular disease, the immune system seems less important than the artery. The arterial wall responds to the immune attack with a vigorous remodeling program causing luminal stenosis and occlusion. This rule does not hold for the aorta where GCA aortitis almost always results in aneurysmal deformation, dissection, or even rupture. Pathogenic events underlying the systemic manifestations of GCA are less well understood. Polymyalgia rheumatica (PMR) has recently been associated with the accumulation of inflammatory cytokines in the interstitial fluid of painful muscles (19). Anemia, thrombocytosis, and elevated liver function tests point toward involvement of the bone marrow and the liver. Whether these are distant effects mediated by circulating inflammatory cytokines or reflect in situ inflammation is not yet known.

Initiation of Vascular Inflammation
GCA begins with the activation of DCs, so-called vasDC, that are embedded in the vessel wall (Fig. 1A) (20,21). They function as sentinels and monitor the tissue environment for danger signals. They are positioned at the media–adventitial junction, in close proximity to the vasa vasorum network. They are phagocytic and are equipped with surface receptors dedicated to the binding of danger signals. Such danger signals may arise from a variety of sources, including infectious agents, products of tissue breakdown, metabolic abnormalities, and deposition of irritating agents. VasDC functionally are more similar to myeloid DC but may represent a separate type of tissue-residing DC.

Once activated, vasDC produce chemokines to attract other immune cells that have access to the vessel wall through the vasa vasorum. VasDC upregulate the molecular machinery to stimulate T cells by upregulating CD40, CD83, CD80, CD86, and possibly many more receptors and ligands that ultimately shape the nature of the immune response. VasDC in GCA-affected arteries display 2 abnormalities. They break the rule of DC tissue mobility in that they fail to leave the peripheral tissue site to migrate to lymph nodes but acquire a fully-developed phenotype of highly-activated DC while positioned in the artery (21). This phenomenon has been described as trapping. Also, they bring adaptive immunity to a tissue microenvironment that is normally protected from in situ immune activation. Considering the enormously high price the host pays for engaging the immune system in the arterial wall, healthy vasDC display a phenotype of suppressing immunity and participate in the artery’s immune privilege.

VasDC have been implicated in defining the tissue tropism of GCA. In a study comparing the expression profile of Toll-like receptors (TLR), typically expressed by DC, in 6 different vascular territories (temporal, carotid, subclavian, aorta, mesenteric, iliac), each vascular region was found to have a typifying TLR signature (22). This has given rise to the novel concept that human arteries have immune sensing functions and that each vascular region specializes in particular danger signals. As a consequence, each human artery interacts with the immune system in a specific fashion making it susceptible to vessel-specific immune abnormalities.
In a model system of GCA, which relies on human arteries being engrafted into immune-compromised mice, the required components of vascular inflammation have been defined (20,22–24). Arteries lacking vasDC are protected from inflammatory attack. VasDC require activation. Pathogen-derived molecular patterns serve this purpose through distant activation, and infection is not necessary. The activation conditions of the vasDC dictate the architecture and the aggressiveness of the subsequent vasculitis. Not all human T cells and macrophages can cause vasculitis in this model. Those initiating vasculitis are functionally selected. The molecular determinants of that functional selection are currently unknown but could represent ideal biomarkers of disease risk and inflammatory burden.

**Distinct T-Cell Lineages in Early and Chronic GCA**

T cells are a condicio sine qua non in GCA (25). The majority of T cells arise from the CD4 T-cell subpopulation and displays a memory phenotype in the transmural lesion. Experimental evidence strongly supports that T cells undergo clonal proliferation in temporal artery lesions and that only selected T cells do so—by far the best evidence that this process is antigen specific (26).

Recent data advance the idea that T-cell biology allows the dissection of the arteritis into early and late GCA (Fig. 1A, B). In patients undergoing repeated temporal artery biopsy, one harvested at diagnosis and one while on chronic treatment, there is fundamental change in the composition of the T-cell infiltrate (4). Early GCA is characterized by the presence of 2 T-cell lineages, TH1 cells and TH17 cells. These T-cell lineages are defined through the production of marker cytokines (interferon [IFN]-γ and interleukin [IL]-17, respectively). IFN-γ– and IL-17–releasing T cells have distinct immunoregulatory potential and interact with distinct partner cells. In late GCA, with the second biopsy taken 3, 6, 9, or 12 months after the initiation of corticosteroid therapy, TH17 cells are no longer present. Instead, chronic GCA is a “pure” TH1 disease. These findings strongly endorse the concept that GCA: 1) has several disease phases; 2) multiple molecular networks sustain vasculitis; 3) is not self-limited; and 4) the therapeutic management needs to adapt to the disease stage.

Little is known about the tissue injury that is mediated by IL-17–secreting T cells. IL-17 receptors are broadly distributed on a variety of cell types, but vascular smooth muscle cells (VSMC), fibroblasts, and endothelial cells are likely affected by IL-17 stimulation. In contrast, substantial information has been collected on the action of IFN-γ in GCA. Temporal arteries with high tissue IFN-γ are found in patients with ischemic symptoms, including vision loss, whereas patients with predominance of PMR or fever, favor production of IL-2 (27,28). IFN-γ levels in the tissue correlate with neoangiogenesis, which is part of the vessel wall remodeling, and supports the outgrowth of the hyperplastic intima. Tissue IFN-γ production is relatively resistant to several clinically applied and experimental therapies, including corticosteroids, salicylic acid, and NOTCH pathway inhibitors (23,29). Persistence of IFN-γ production in the mural
lesions signifies the chronicity of GCA and emphasizes the central position of activated T cells in the disease process. Major cellular targets of IFN-\(\gamma\) are monocytes and macrophages, and giant cell formation is mediated by IFN-\(\gamma\). Inflammation-caused tissue damage results from activation of macrophages that mediate cellular injury and matrix destruction and regulate the formation of new microvessels. Temporal artery specimens may show a classical panarteritis but in a subset of cases the inflammatory infiltrate is mostly arranged around the vasa vasorum in the adventitia (30). In experimental GCA, these 2 types of arteritis—panarteritis and periarteritis—can be induced according to the initial activation that triggers vasDC (24). TLR4 ligands consistently cause panarteritis. Periarteritis emerges after stimulating vasDC with TLR5 ligands. Whether differences in the microarchitecture of vasculitis are a result of distinct T cells mediating the disease or are a consequence of differential activation programs in vasDC remains to be determined.

**Vasculitic Macrophages in GCA**

Granulomas are typically composed of activated T cells and macrophages. Multinucleated giant cells are derived from highly activated macrophages that fuse together. The spectrum of macrophage products and functions relevant in the arteritis is broad (Fig. 2), but some correlation exists between the physical location of the macrophages and their functional contribution (31,32). Different macrophage subtypes may be recruited to the artery. Alternatively, specifics of the microenvironment in different regions of the vessel wall, such as matrix proteins and 3-dimensional configurations, may guide macrophage differentiation. Macrophages in the adventitia have been reported to be engaged in the production of classical proinflammatory cytokines, such as IL-6 and IL-1\(\beta\). Macrophages in the medial layer are mostly devoted to the digestion of cellular structures and elastic membranes (33). Production of metalloproteinases has been assigned to such macrophages. They have also been implicated in the local production of reactive oxygen species (34,35).Nitrotyrosine has been described, mostly colocalizing with endothelial cells in newly formed microvessels (36).

Macrophages recruited to the expanding intimal layer are focused on cell growth–promoting actions. They produce platelet-derived growth factor and basic fibroblast growth factor, needed to stimulate the dedifferentiation, migration, and proliferation of medial smooth muscle cells (37). Macrophages residing at the media–intima junction also supply vascular endothelial growth factor, enabling the sprouting of new microvessels and securing oxygen supply for the wall remodeling process (38).

Recent progress in macrophage biology has established that monocytes differentiate along different pathways to generate M1 and M2 macrophages. M1 macrophages specialize in proinflammatory actions, whereas M2 macrophages are responsible for the removal of debris and repair activity in the tissue site. It is unknown whether macrophages in the GCA lesions differentiate in situ, which signals regulate their functional commitment, how long they survive, and how they contribute to the distinct phases of the disease. Results from the second-side temporal artery biopsy study (4) reveal that IL-1\(\beta\) and IL-6 production are explicitly susceptible to corticosteroid therapy. In contrast, production of the T-cell polarizing cytokine IL-12 is almost unaffected by steroids, suggesting that macrophages display similar differences in steroid responsiveness and resistance as T cells.

**Dysfunction of Vascular Cells in GCA**

The strict tissue tropism of GCA strongly suggests that the immune system is only one component in the disease process and that the disease microenvironment is equally important. The arteries targeted by the vasculitic reaction contribute through several pathways. The artery’s role is nonredundant, and it is likely that the permissibility of the vascular tissues is the ultimate checkpoint in GCA.

**Endothelial Cells**

The immune reaction leading to GCA enters the blood vessel wall through the vasa vasorum, with no evidence of participation of the macroendothelium. T-cell activation

---

**FIG. 2.** Vasculitic macrophages in giant cell arteritis (GCA). A multitude of macrophages contributes to the inflammatory infiltrates in GCA. Location within the vascular wall layers is associated with functional specialization. Adventitial macrophages produce proinflammatory cytokines (e.g., interleukin [IL]-6, IL-1). Macrophages caught in the media drive matrix and fiber destruction by the release of metalloproteinases and expose the tissue to reactive oxygen and nitrogen species. Macrophages recruited to the intima provide growth factors (PDGF, VEGF, FGF) needed to support myofibroblast outgrowth and the development of a capillary system to supply oxygen, metabolites and cells for the expanding intima. bFGF, Basic fibroblast growth factor; IEL, internal elastic lamina; MMP, matrix metalloproteinases; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor.
occurs exclusively in the adventitia, and human arteries stripped of the adventitial layer fail to sense danger signals (22). To enter the vessel wall, immune cells need to migrate from the capillary network of the vasa vasorum tree. How this process is enabled by microendothelial cells is currently unknown. Once the remodeling program of the vascular wall is initiated, new capillaries are formed. They can serve as an entrance port for T cells and macrophages and thus accelerate granuloma formation (39).

**Vascular Dendritic Cells**

Through their vessel-specific distribution and their selective portfolio of danger signals to which they respond, vasDC are prime candidates to control tissue tropism of GCA. They are localized between the vasa vasorum and the media, at the junction of the adventitial and media and thus lie in the path of incoming T cells and macrophages. They are critically involved in chemoattracting immune cells and no vessel wall inflammation can be initiated without them. There are numerous questions regarding their origin, survival times, turnover, and age-related changes that await investigation.

**Vascular Smooth Muscle Cells**

VSMC are active participants in the granulomatous reactions in that they serve as signal-sending and signal-receiving cells (40). Their major involvement lies in a phenotypic switch from a contractile into a migratory and secretory cell. The formation of the lumen-compromising intimal hyperplasia requires myofibroblasts, a dedifferentiated form of VSMC. Previous studies have implicated them in regulating the response of the arterial wall to oxidative stress. Specifically, they upregulate the enzyme aldose reductase to deal with oxidative alterations of cellular proteins (34). In a recent study, another VSMC-centered pathway, the NOTCH–NOTCH ligand pathway, was described as an amplification loop to sustain vasculitis (41). Components of the NOTCH signaling pathway regulate critical aspects of vascular formation and morphogenesis in development. Notch1, Notch4, Jagged1, Delta-like1, and Delta-like4 participate in arterial cell fate induction and determine the selection of endothelial tip and stalk cells during sprouting angiogenesis. CD4 T cells from patients with GCA spontaneously express the Notch1 receptor, enabling them to communicate with Notch ligand–positive cells. Vascular cells, in particular VSMC, are a rich source of Notch receptors and ligands. Developing VSMC express Notch3 receptors (Notch3 mutations cause CADA-SIL, a cerebral arteriopathy with subcortical infarcts and leukoencephalopathy), and mature VSMC have the ligand Jagged1 and the receptor Notch2 on their surface. This provides ideal conditions for immune–stromal communications between T cells and VSMC. Gene expression profiling has demonstrated that Notch1, Jagged1, and Delta-like1 are abundantly expressed in temporal arteries affected by GCA, and molecular studies support the notion that the Notch pathway is actively signaling in the inflamed arteries. Blockade of Notch signaling through an enzyme blocker relevant for a cleavage event that liberates the Notch intracellular domain effectively suppressed adaptive and innate immunity in vasculitis.

**Therapies of the Future**

GCA is a disease with a broad spectrum of clinical manifestations, as well as diagnostic and therapeutic challenges (see Supplemental Digital Content, http://links.lww.com/WNO/A47). While corticosteroids are highly effective in treating GCA, it would be preferable to have a more targeted approach (Table 2). Steroids promptly suppress IL-6, IL-1, IL-23, and IL-17, but they fail to control the production of IL-12 and IFN-γ, which seem critical in supporting chronic vasculitis. New treatment approaches are required that can safely target TH1 immunity without compromising protective immunity for the host. Inflammatory cascades that derive from communication between the vessel wall and the immune system should be addressed. Preclinical studies suggest that inhibition of such immune–stromal interactions can successfully disrupt vasculitis (41). Equally unexplored are the response-to-injury pathways that the artery launches in an attempt to repair wall damage. Interfering with the formation of intimal hyperplasia, blocking the formation of new microvessels in the injured wall, and suppressing oxidative damage all have the potential to counteract the deleterious consequences of vascular inflammation without further compromising the immune system of the elderly patient. Ultimately, an attempt needs to be made to reestablish the immune privilege of the arterial wall. Here, vasDC emerge as the therapeutic target. Understanding how they protect arteries from detrimental immune attack could open an entirely new paradigm in the management of GCA.

**TABLE 2.** Corticosteroid therapy in GCA

<table>
<thead>
<tr>
<th>Therapeutic Target</th>
<th>Responsiveness to Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>yes</td>
</tr>
<tr>
<td>IL-1β</td>
<td>yes</td>
</tr>
<tr>
<td>IL-23</td>
<td>yes</td>
</tr>
<tr>
<td>IL-12</td>
<td>no</td>
</tr>
<tr>
<td>IL-17</td>
<td>yes</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>no</td>
</tr>
<tr>
<td>ROS</td>
<td>unknown</td>
</tr>
<tr>
<td>VEGF</td>
<td>unknown</td>
</tr>
<tr>
<td>PDGF</td>
<td>unknown</td>
</tr>
<tr>
<td>MMP</td>
<td>unknown</td>
</tr>
<tr>
<td>Aldose reductase</td>
<td>unknown</td>
</tr>
<tr>
<td>NOTCH pathway</td>
<td>partially</td>
</tr>
</tbody>
</table>
To access the remainder of this article, please see Supplemental Digital Content, http://links.lww.com/WNO/A47.

REFERENCES

Background: Many neurological disorders show deficits in ocular motor function. In the past, evaluation has been limited to assessing abnormalities largely generated by pathology of the brainstem and cerebellum. In disorders that primarily or substantially, affect the cerebral hemispheres, disruption of cognitive processes occur, often early in the clinical course. While neuropsychological testing traditionally is used to measure cognitive performance, the cerebral influences on the ocular motor system provides another quantitative paradigm. This review explores the relationship between cognitive sensory processing and execution of planned ocular motor tests in Parkinson's disease, Huntington's disease and multiple sclerosis and explores areas of clinical utility.

Methods: Review of the literature regarding cognitive and ocular motor abnormalities in neurological disease.

Results: The literature indicates that in systems degeneration there are abnormalities of cognitive processing, defined both by conventional behavioural testing and by assessment of cognitive function utilizing ocular motor studies, which characterise those processes. Moreover, in diffuse disease, in processes such as multiple sclerosis, the assessment of cognitive processes involved in ocular motor function may well provide an added level of sensitivity indicating more widespread pathology than would be apparent with conventional clinical assessment.

Conclusions: Assessment of cognitive function in the ocular motor system may provide insight into cerebral function, in health and disease, and may provide both diagnostic information and permit quantification of deficit in future.

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are also parallel projections to single sensory mode association cortices and to multimodal association sensory cortices, both of which feed forward (and backward) providing complex parallel processing and parsing of preferred sensory responses. All this information is integrated with voluntary willed (top-down) activity, before a motor action is generated. Moreover, there are circuits through the basal ganglia and back to cortex via thalamus, for the somatic motor system, and to the superior colliculus via substantia nigra pars reticulata, for the ocular motor system (4) (Fig. 1). This system of intermediary processing, bridging the gap between sensation and action, including a range of processes like memory, attention, language, thought and emotion, is what we recognize as cognition (3).

Many aspects of cognition not only depend upon processing of real-time domain sensory events but also the interpretation of these events on the basis of previous experience. This involves circuits through frontal and prefrontal cortex with wide-ranging inputs from other areas (5,6). In reality, cognition is the interaction of top-down with bottom-up inputs, with reciprocal modulation both in real time and over time, with the resultant motor responses.

This review explores the evaluation of cognitive processes in the ocular motor system in Parkinson disease, primarily a basal ganglia disorder, Huntington disease, a degenerative disease of basal ganglia and cortex, and MS, a widespread multilesion demyelinating disorder.

CLINICAL AND ANATOMICAL ISSUES

Neuro-ophtalmologists are experienced in the diagnosis of disease based upon characteristic eye movement abnormalities. Almost exclusively, this involves extraocular muscles, cranial nerves, peripheral nerves, brainstem, and cerebellum. In general, we do not use eye movement abnormalities to any substantial degree in the evaluation of cerebral hemispheric pathology.

There is a developing literature regarding focal hemispheric lesions of cortex and deep nuclei and white matter, which produce specific abnormalities of cognitive control of eye movements. Presumably, focal abnormalities either interrupt crucial pathways or damage nodal sites of convergence and cognitive parsing of data. Documentation of such deficits may provide insight into the pathophysiology of neurodegeneration and multifocal disease.

The ocular motor networks substantially overlie the hemispheric attentional systems in frontal, temporal, and parietal lobes (7), interacting at many levels (8–17). Cognitive processes are most readily examined with saccades. Smooth pursuit eye movements, in the past considered to have a different control system, have more recently been postulated as merely a different outcome of the same cognitive processes (18,19). Saccadic testing paradigms include shifting of attention, endogenous, top-down voluntary saccades, reflexive, bottom-up saccades, working memory, spatial and temporal, and inhibition of nonsalient distractors. Documentation of performance can provide insight into hemispheric structural integrity.

In broad terms, frontal cortex regions of interest include the frontal eye fields (FEFs), supplementary eye fields (SEFs), and dorsolateral prefrontal cortex (DLPFC), with inputs from orbital and medial frontal cortex to these areas (6). Studies of the FEFs indicate they have a role in the generation of “top-down” driven saccades, such as those spontaneously exploring contralateral hemispace, anticipatory saccades, and saccades to remembered targets (20–22). Antisaccades are a special case requiring inhibition of a reflexive saccade and reprogramming of an internally driven saccade to the opposite hemifield involving widespread activation of cortex (23–25).

Lesions of the SEFs do not affect the dynamics of bottom-up reflexive saccades but seem more involved with temporal sequencing of combinations of movements. Imaging studies demonstrate activation during voluntarily generated and memory-guided saccades as well as with antisaccades (26).

FIG. 1. Neural regions involved in the control of saccadic eye movement. CN, caudate nucleus; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye field; GPi, globus pallidus externa; GPe, globus pallidus interna; INC, interstitial nucleus of Cajal; IPL, inferior parietal lobule; LGN, lateral geniculate nucleus; LIP, lateral intraparietal sulcus; NRT, nucleus reticularis tegmenti pontis; PEF, parietal eye field; PPC, posterior parietal cortex; PPRF, paramedian pontine reticular formation; Pre-SMA, prefrontal supplementary motor area; riMLF, rostral interstitial nucleus of the median longitudinal fasciculus; RIP, nucleus raphe interpositus; SEF, supplementary eye field; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticularis; STN, subthalamic nucleus; TPJ, temporoparietal junction (inferior parietal lobe, IPL/superior temporal gyrus, STG).
Ocular motor testing of cognitive function

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Ocular Motor Paradigms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Visually/symbolically cued saccades, gap-overlap task</td>
</tr>
<tr>
<td>Memory</td>
<td>Memory-guided saccades, memory-guided sequences of saccades</td>
</tr>
<tr>
<td>Executive function</td>
<td>Antisaccades</td>
</tr>
</tbody>
</table>

Visually/symbolically cued saccades, participants fixate a central target and are presented with a cue indicating the possible location of an upcoming target. A target then appears, which is either congruent or incongruent with the preceding cue and the subsequent saccade is then evaluated. Gap-overlap task, participants fixate a central target that is extinguished either before or after the presentation of a peripheral target. They make a saccade to the peripheral target on presentation. Memory-guided saccades, participants fixate a central target while a peripheral target flashes briefly. After a variable delay, the central target extinguishes and participants make a saccade to the remembered previously illuminated target position. Memory-guided sequences, targets are present on the screen. Participants must then memorize the sequence in which they illuminate and subsequently make saccades sequentially to those targets on cue. Antisaccades, participants fixate a central target. A peripheral target appears and they make a saccade of equal amplitude in the opposite direction.

State-of-the-Art Review

TABLE 1. Common tests of neuropsychological function

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Symbol Digit Modalities Test, Paced Auditory Serial Addition Test</td>
</tr>
<tr>
<td>Memory</td>
<td>Digit span, brief visuospatial memory test</td>
</tr>
<tr>
<td>Executive function</td>
<td>Stroop, Wisconsin card sorting task</td>
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</tbody>
</table>

Symbol Digit Modalities Test, a simple substitution task. Using a reference key, the participant has 90 seconds to pair specific numbers with given geometric figures. Paced Auditory Serial Addition Test, participants are given a number every 3 seconds and are asked to add the number they just heard with the number they heard before. Digit Span, participants are presented with a series of digits (e.g., '8, 3, 4') and must immediately repeat them back. If they do this successfully, they are given a longer list (e.g., '9, 2, 4, 0'). The length of the longest list a person can remember is that person's digit span. Brief Visuospatial Memory Test, participants view a number of geometric patterns on the stimulus page for 10 seconds and are then asked to draw as many of the figures as possible in their correct location on a page in the response booklet. Stroop, the written color name differs from the color ink it is printed in, and the participant must either say the written word or name the ink color. Wisconsin Card Sorting Task, stimulus cards are matched by color design or quantity. The participant is not told how to match the cards; however, he or she is told whether a particular match is right or wrong. During the course of the test, the matching rules are changed and the time taken for the participant to learn the new rules, and the mistakes made during this learning process are analyzed to arrive at a score.

Executive function Antisaccades

Memory Memory-guided saccades, memory-guided sequences of saccades

Attention Visually/symbolically cued saccades, gap-overlap task

Cognitive Domain Ocular Motor Paradigms

NEUROPSYCHOLOGICAL ASSESSMENT

Neuropsychological evaluation measures activity in widespread cerebral circuitry not readily assessed with standard clinical examination techniques or neuroimaging studies. Methods of evaluation primarily document deficits in planning, working memory, attention, problem solving, mental flexibility, multitasking, initiation, and monitoring of actions.

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</tbody>
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Testing is complex and involves cognitive functions without directly relating them to output functions (Table 1). For example, deficits in Parkinson disease may span the full spectrum from mild executive dysfunction and memory failure to overt dementia associated with severely impaired thought processes and manipulation of acquired knowledge (2,29–31). The severity of cognitive impairment correlates with more advanced motor dysfunction and particularly with postural instability of gait (31). Cognitive dysfunction has been widely recognized as an independent entity in Parkinson disease (32) that correlates over time with progression of motor dysfunction. There remains uncertainty whether this correlation is an epiphenomenon or plays a distinct role in the generation of motor deficits (33,34).

Huntington disease shares some characteristics with Parkinson disease, being a degenerative disorder with widespread basal ganglia pathology, but differs in that there is also extensive cortical degeneration. Cognitive dysfunction includes impaired attention (35), language (36) and memory disturbances (37) and reduced perceptual processing speed and memory. Cognitive abnormality has been associated with structural abnormality. For example, impairment of executive function correlates with atrophy of the striatum and insula on magnetic resonance imaging (MRI) (38). Neuropsychological profiling has been used to identify patients at an early stage (39) and investigated as a means of...
monitoring the development of disease (40). Unfortunately, such deficits can be seen in lesonial disease as well and, as such, the value of a profile may not be so much in diagnosis but in establishing a profile in time for subsequent evaluation of progression.

Cognitive deficits occur early in the course of clinically definite MS, at which time there may be minimal evidence of impairment as measured by the routinely used Kurtzke Expanded Disability Scale Score (EDSS) (41–43). In larger studies, cognitive deficits have been recognized in 45%–60% of patients across the spectrum of disease and have been shown to progress with the course of the disease, predicting decline in clinical performance and correlating, to some degree, with MRI changes (44–47).

Much attention has been paid to neuropsychological impairment in traumatic brain injury, particularly with the development of the Ruff Neurobehavioral Inventory (48). Differences in self-perception of deficit have been demonstrated between those patients with mild injury and those with moderate to severe injury (49). Patients with milder traumatic brain damage typically demonstrate more attentional deficits, while more severely injured patients show difficulties with memory and learning. Studies have shown that conventional MRI of the brain does not define the widespread nature of white matter and cortical pathology for patients with moderate to severe injury, although such pathology is demonstrated by fractional anisotropy and diffusivity studies (50).

**COGNITION AND THE OCULAR MOTOR SYSTEM**

Movement of the eyes requires resolution of the potential conflict between top-down cognitive activity and bottom-up reflexive responses. This is the conflict between voluntary scanning of the environment and a response to a visual or auditory stimulus attracting attention. In a well-functioning system, information projects from visual cortex to association cortex, with subsequent parallel and serial projections to premotor and motor cortex. There are also numerous reciprocal cortical–basal ganglia connections. The final common output is a product of synaptic function at multiple levels, producing a balance of information resulting in excitation or inhibition of neuronal activity. In pathologic states, abnormalities at different levels may produce characteristic, and possibly pathognomonic, patterns of dysfunction. With multilesion disease, there may be an accumulation of deficits with increasing burden of disease.

Investigation and evaluation of the cognitive processing involved in the generation of ocular motor responses permit correlation of motor dysfunction with cognitive deficits (Table 2). In particular, abnormalities of attention, including inhibition, working memory and executive function, may not merely be epiphenomena but may actually cause ocular motor abnormalities (Fig. 2) (51–56). Such motor deficits may include delayed, slow, or hypometric saccades, as seen in Parkinson disease, or hyperactive saccadic function seen in Huntington disease. These changes may not only characterize disease processes, particularly those with well-defined systems pathology, but also document staging of disease.

**OCULAR MOTOR COGNITIVE FINDINGS IN NEUROLOGIC DISEASE**

A comprehensive literature review of all neuropathologic states with abnormal eye movement is beyond the scope of this review. As stated above, we will restrict the discussion to...
Parkinson disease and Huntington disease as system degenerations, MS, and traumatic brain injury (Table 3).

**Parkinson Disease**

Abnormalities of eye movement have long been recognized in Parkinson disease (57,58). There is general agreement that patients with Parkinson disease tend to make a series of hypometric saccades to achieve targets (51,59) (Table 3). There is some dispute as to whether latencies are always normal or abnormal and whether saccadic velocities are slowed (59–64).

Ocular motor abnormalities in patients with Parkinson disease include slowed movement initiation, impaired executive function manifested as impaired generation of voluntary movements, and suppression of inappropriate reflexive movements (51,55,56,65–67). Abnormalities of remembered saccades previously have been attributed to a need for a visual target to make accurate saccades (68), implying visual feedback as a requirement for accurate performance right up until the time of saccade generation. This suggests that working memory is profoundly impaired. Investigation of memory-guided saccades (67), and the temporal effects of providing visual cue to direct attention before making a saccade, demonstrates a complex abnormality of attention and working memory (56).

Purely self-paced saccades, wherein 2 targets remain illuminated and participants saccade between them, are normal. These probably utilize direct frontocortical pathways bypassing the basal ganglia (69). However, studies of visually guided eye movements have shown complex effects of cues (valid cues truly indicating direction of target movement and invalid being misleading) and distractor stimuli on both saccades and smooth pursuit (52,65–67,70). For example, during presentation of smooth pursuit stimuli, we have shown differential effects of distractors in the hemifield ipsilateral to target movement versus those in the contralateral hemifield (67). Also, spatially invalid cues have a substantial effect on saccade latency compared with valid cues (56).

Variation of ocular motor deficits seen in patients with Parkinson disease is explicable if one assumes that not all dopaminergic neurons in the substantia nigra pars compacta deteriorate at the same rate and not all patients are tested at the same stage of the disease. With progression of the disease, more characteristic eye movement abnormalities to specific tasks may develop.

There are complex relationships between how well an object of regard is recognized within its visual environment including spatial characteristics of the target and competing targets (distractors) and the task the subject is being asked to perform. For example, in early Parkinson disease there is difficulty in performing antisaccades (Fig. 2). An antisaccade requires suppression of a reflexive saccadic response to a newly appearing object of regard and internal generation of a saccade in the opposite direction and of the same distance from central fixation, in the absence of a target (51).

**Huntington Disease**

Huntington disease, commonly thought of as a basal ganglia disorder, has more complex pathology, with substantial cortical pathology becoming evident as the disease progresses. The hallmark ocular motor abnormalities are difficulty in initiating saccades accompanied by saccadic intrusions (fixation instability) (71–74) and an increased tendency to make inappropriate saccades in response to targets and instructions (Table 3). Increased errors (either anticipatory or in response to a nontarget stimulus), increased latency, and greater variability of responses have been identified in antisaccade and memory-guided protocols (75). Complex spatial (55) and temporal (56) effects of cuing have been demonstrated in Huntington disease. This may be an effect of the basal ganglia pathology as seen in Parkinson disease, although there is a different ocular motor abnormality in each disorder. Patients with Parkinson disease demonstrate increased inhibitory output from the basal ganglia and patients with Huntington disease show just the opposite—facilitation of saccades (56,65). This may be the

### Table 3. Summary of eye movement findings in Parkinson disease, Huntington disease, and multiple sclerosis

<table>
<thead>
<tr>
<th>Process</th>
<th>Clinical Features</th>
<th>Clinical Eye Movements</th>
<th>Pathological Eye Movements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson disease</td>
<td>Bradykinesia, rigidity; tremor, impaired multitasking, cognitive impairment</td>
<td>Hypometric and multistep saccades, long latencies, slowed saccades, variability, saccadic smooth pursuit</td>
<td>Antisaccade errors, impaired memory-guided saccades, impaired endogenous cuing of saccades, impaired suppression of distractor stimuli</td>
</tr>
<tr>
<td>Huntington disease</td>
<td>Chorea, bradykinesia, dementia</td>
<td>Intrusive saccades to irrelevant stimuli, impaired fixation, slowed saccades, impaired smooth pursuit</td>
<td>Antisaccade errors, prolonged saccade latencies, impaired memory-guided saccades, impaired endogenous cuing; abnormal trajectory responses to distractor stimuli</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Multiple motor and sensory deficits, cognitive impairment</td>
<td>Internuclear ophthalmoplegia, spontaneous nystagmus, impaired smooth pursuit</td>
<td>Antisaccade errors, impaired memory-guided saccades</td>
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*Note: Data from (56,65,67,71–74).*

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*State-of-the-Art Review*  

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**TABLE 3. Summary of eye movement findings in Parkinson disease, Huntington disease, and multiple sclerosis**

**Process** | **Clinical Features** | **Clinical Eye Movements** | **Pathological Eye Movements**
---|---|---|---
Parkinson disease | Bradykinesia, rigidity; tremor, impaired multitasking, cognitive impairment | Hypometric and multistep saccades, long latencies, slowed saccades, variability, saccadic smooth pursuit | Antisaccade errors, impaired memory-guided saccades, impaired endogenous cuing of saccades, impaired suppression of distractor stimuli
Huntington disease | Chorea, bradykinesia, dementia | Intrusive saccades to irrelevant stimuli, impaired fixation, slowed saccades, impaired smooth pursuit | Antisaccade errors, prolonged saccade latencies, impaired memory-guided saccades, impaired endogenous cuing; abnormal trajectory responses to distractor stimuli
Multiple sclerosis | Multiple motor and sensory deficits, cognitive impairment | Internuclear ophthalmoplegia, spontaneous nystagmus, impaired smooth pursuit | Antisaccade errors, impaired memory-guided saccades

*Note: Data from (56,65,67,71–74).*
result of the differing effects these disorders have on inhibitory and facilitatory pathways through the basal ganglia.

Functional MRI studies performed during saccades to targets and antisaccades define characteristic patterns of activity in normal subjects. This includes fronto-parieto-subcortical network of FEFs, SEFs, DLPFC, ventrolateral prefrontal cortex, posterior parietal cortex, supramarginal gyrus, striatum, thalamus, and cerebellum (25). This widespread activity also occurs in patients with Huntington disease, but with progression of disease and an increase in antisaccade errors, there is loss of activity in pre-supplementary and dorsal anterior cingulate regions (76). In these patients, particularly with antisaccade error, activity is more widespread, indicating compensatory activation of cortex not normally involved in error monitoring (76).

**Multiple Sclerosis**

Early diagnosis of MS is important because therapy with immune modulating agents improves long-term outcomes. With growing awareness that cognitive dysfunction is a “silent” process in patients with MS, detection of impaired cognitively mediated ocular motor may provide one method of establishing early diagnosis.

Examination of antisaccade performance has been shown to be a sensitive marker of cerebral cognitive dysfunction in patients with early disease (77,78) (Table 3). Over a 2-year period, during which there was no change in EDSS, an increase in saccade latency and error rate has been shown to correlate with worsening in scores on Paced Auditory Serial Addition Test, considered the reference task for the cognitive evaluation of MS patients. Interestingly, impaired antisaccade performance also has been found in patients with a clinically isolated syndrome, suggestive of more widespread CNS dysfunction.

In MS patients, visually guided saccades, in the presence of randomly presented distractor stimuli, shows abnormal function (79). MS patients also are less accurate and make more errors with memory-guided saccades (80), suggesting impaired working memory. These findings probably reflect abnormality in the extensive circuitry required for the inhibitory function of attentional control as well as working memory and programming of saccades. Such circuitry involves long range projections between parietal cortex and prefrontal cortex and corticobasal connections (Fig. 1).

**Traumatic Brain Injury**

In moderate traumatic brain injury, where conventional MRI studies are normal, more detailed imaging of axon bundles using fractional anisotropy and diffusivity demonstrate widespread disruption of white matter tracts. The use of eye movement paradigms to assess cognitive processes of working memory and attentional control could provide an opportunity to evaluate deficits in patients at an early stage and may be a fertile area for future research (81). It remains possible that early introduction of cognitive retraining programs may enhance recovery in patients with mild and moderate traumatic brain injury.

**SUMMARY**

Tests of cognition provide evidence of more widespread pathology in a number of processes that affect the brain, including degenerative diseases, autoimmune disorders and, potentially, trauma. The assessment of such tests is rightly within the domain of neuro-ophthalmology. It is a small step to extend evaluation from the eye to the brainstem and on to cognitive cerebral function. We measure individual eye movements and parameters of eye movements. We document abnormalities of eye movements unique to brainstem dysfunction. Evaluation of cognitive processes, dependent on cerebral hemispheric circuitry, would seem a logical next step in terms of understanding central nervous system dysfunction.

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Progressive Facial Palsy With Ipsilateral Fasciculation and Sensory Neuropathy

John S. Elston, MD, Vanessa Venning, MD, Tom Parks, MD, Ruth Asher, MD

Dr Elston:

A 69-year-old woman presented with an 18-month history of progressive facial asymmetry, the right eye appearing more prominent than the left. She also complained of tearing of the right eye and inability to close the eye tightly. She had noted recurrent focal superficial red skin lesions on the right brow that initially blistered and then healed over 2–3 weeks. She described similar lesions occurring on her hands and lower legs over the past 2 years that resolved after local steroid cream treatment prescribed by her primary care physician. The patient denied any disturbance in her vision, headaches, or other neurologic symptoms. Hearing was normal. Her medical history was unremarkable, and she was taking no current medication. She had smoked 15–20 cigarettes a day for 50 years. She had lived and worked in Lombok, Indonesia, for 8 years, returning to live in the United Kingdom 3 years before presentation.

On examination, the patient’s best-corrected visual acuity was 20/20 bilaterally with normal visual fields. Extraocular movements were full, and the patient was orthophoric. There was no proptosis. The anterior and posterior segments of each eye were normal. There were foci of erythema and blistering on the right brow (Fig. 1A). Right facial weakness was evident and involved the orbicularis oculi disproportionately (Fig. 1B). Left facial nerve function was normal. After forceful bilateral eye closure, mid-facial fasciculations lasting 5–10 seconds were seen on the right side. Trigeminal sensory function was reduced in the first and second divisions on the right, including corneal sensation; motor function was normal. Bell phenomenon was preserved, and all other cranial nerve function was intact.

Routine hematologic and biochemical studies, including liver function tests, revealed no abnormalities. Serum immunoglobulins were normal as were inflammatory markers, including eosinophil sedimentation rate and C-reactive protein. The antinuclear antibody test and an autoantibody screening were negative. Varicella zoster virus–specific IgM antibody was negative as were both Lyme and treponemal serologies. Chest radiography was normal. MRI revealed no abnormalities other than age-related involutional changes and T2 hyperintensities consistent with microvascular disease in the deep white matter of both cerebral hemispheres. The orbits were normal. There was no space-occupying or inflammatory lesion in the pons, and both facial nerves and trigeminal nerves had normal imaging characteristics.

The patient’s clinical signs gradually progressed. The right facial palsy increased, and she developed a right lower lid entropion. She also developed numbness in the distal lower limbs and increased frequency and persistence of the skin lesions. Neurological examination showed reduced sensation to temperature and touch below the knees and an anesthetic patch on the left palm. Knee flexion and extension were weak. The patient was referred for a dermatological assessment.

Drs Venning and Parks:

Dermatological examination revealed that the facial skin was shiny and thickened. A single eroded lesion was present on the nose on the right, the previous brow lesions having healed. Asymptomatic waxy infiltrated plaques were noted over the lower thighs and shins. These findings are nonspecific, and the differential diagnosis covers a range of pathologies, including many granulomatous disorders and skin infiltrations. Cutaneous sarcoidosis can cause nasal skin lesions and facial palsy. Primary dermatological and hematological malignancies, including mycosis fungoides, can present with atypical plaque-like lesions. Infections causing thickened plaques include tuberculosis (lupus vulgaris), nontuberculous mycobacterial infection, syphilis, cutaneous leishmaniasis, and leprosy. Multibacillary (MB) leprosy may cause plaques and papules that differ from the hypopigmented macules of paucibacillary disease.

As it was not possible to make a definitive diagnosis based on the clinical findings, a skin biopsy was obtained from a typical lesion on the patient’s right shin (Fig. 2).
**Dr Asher:**

Histological sections from the specimen showed a diffuse infiltrate of macrophages filling the reticular dermis (Fig. 3A). The papillary dermis was spared. Although the infiltrate was composed mainly of macrophages, some of which displayed foamy cytoplasm and small scattered aggregates of lymphocytes, and plasma cells were also present. Small cutaneous nerves (Fig. 3B) were surrounded by macrophages and plasma cells indicating perineuritis and endoneuritis. Wade-Fite (modified Ziehl–Neelsen) staining revealed large numbers of acid-fast bacilli within macrophages (Fig. 3C), small cutaneous nerves, and endothelial cells. The features described are characteristic of MB leprosy.

**Dr Elston:**

**Pathological Diagnosis: Mutibacillary Leprosy**

The patient was treated with multidrug therapy for MB leprosy according to World Health Organization (WHO) guidelines, consisting of 600 mg of rifampicin once a month, 300 mg of clofazimine once a month, and 100 mg of dapsone once daily along with 30 mg of prednisone once daily. Within 6 weeks, she reported general malaise, back pain, and hoarseness of the voice; her skin lesions had worsened with diffuse dermal infiltration. The peripheral neuropathy also progressed, and at 12 weeks, her shins and forearm skin were marked from local trauma. There was also increased mucosal involvement. Her right lower lid entropion and lagophthalmos worsened with corneal exposure keratopathy for which she was scheduled for surgery. Before this could take place and 5 months after treatment had started, she developed an intractable cough and was diagnosed with lung cancer. She declined further treatment and died 3 months later.

**DISCUSSION**

A unifying diagnosis for the combination of slowly progressive facial palsy with muscle fasciculation, ipsilateral trigeminal sensory neuropathy (V1 and V2), and recurrent skin blistering in an otherwise healthy Caucasian woman covers a wide spectrum of potential pathologies.

The facial neuropathy with fasciculations suggested either intrinsic pontine pathology (tumor or inflammation) or chronic peripheral axonal compromise with ephaptic transmission due to, for example, schwannoma of the facial nerve. Sarcoidosis can present with facial palsy and involve other cranial nerves and the skin. Infections presenting with facial palsy, including Lyme borreliosis (which can also cause recurrent or migrating skin lesions and trigeminal neuropathy), as well as HIV and varicella infection, were considered. On a world-wide basis, leprosy is the most common infective cause of facial palsy.

Trigeminal sensory neuropathy can be the presenting sign of an autoimmune connective tissue disease (1), such as...
primary Sjögren syndrome, which can also cause cranial motor neuropathy. Perineural skull base lesions can also cause this clinical picture.

The morphology and characteristics of the skin lesions were not diagnostic. Herpes zoster ophthalmicus was considered in this case, but the lesions were recurrent and occurred elsewhere on the body. A skin biopsy was required to make the correct diagnosis of MB leprosy.

Leprosy is a chronic granulomatous disease caused by infection with *Mycobacterium leprae*. The infection is spread by respiratory droplets, but only a small proportion of infections (approximately 10%) lead to clinical disease with genetic determinants of cell-mediated immunity conferring protection on the majority. Clinical disease as classified by the WHO has a wide spectrum from the paucibacillary variant, characterized by high cellular immunity and low bacterial load to MB disease (as in our case), where cellular immunity is low and bacterial load is high. The spectrum of disease is also likely to be determined by host genetic heterogeneity. The incubation period is usually between 3 and 5 years (2).

The majority of new cases of leprosy occur in global areas of high endemicity. Since the start of the WHO leprosy elimination program in 1995, the global prevalence and annual incidence of leprosy has progressively declined. The remaining pockets of high endemicity are in parts of India, Burma, and Nepal. In endemic areas, awareness of the clinical presentation with peripheral neuropathy (90% of cases) and skin changes is high. Thus, the disease is recognized early and can be treated successfully in most cases. Ophthalmic complications (Table 1) are well recognized but rarely the presenting feature; however, 2.8% of patients with MB leprosy are visually impaired at presentation, and 11% have potentially blinding pathology (3). In addition, patients with MB leprosy who have completed treatment remain at risk of the development of new ocular complications, such as corneal opacity, that may be sufficiently severe as to be sight threatening (4).

In the United Kingdom, a small and declining number of cases of leprosy are identified annually, the majority occurring in immigrants from endemic areas, especially India. In a UK study of 28 patients with leprosy referred for treatment to the London Hospital for Tropical Diseases (5), most presented with a peripheral “glove and stocking” sensory neuropathy or an ulnar neuropathy with or without skin lesions. There was an average delay of 3.1 years between onset of symptoms and diagnosis. Of the 28 patients, 3 were Caucasian British who had acquired the disease while working abroad in endemic areas between 8 and 40 years.

Leprosy has not previously been described presenting with progressive facial weakness and fasciculation and ipsilateral trigeminal sensory neuropathy in a UK Caucasian. Moreover, muscle fasciculation, although previously noted in leprosy, is a very rare feature. It was recognized at presentation that this case was unusual, particularly taken with the unexplained cutaneous features, but the diagnosis of leprosy was not considered initially, and the importance of the patient’s history of time spent in Indonesia not appreciated until disease progression occurred and a dermatological opinion was obtained.

The key to the diagnosis of exotic infections is an awareness of the current ubiquity of overseas travel and work, the potential importance of which may not be appreciated by the patient or the physician. With a multisystem presentation, the active involvement of colleagues from other disciplines is important. Leprosy is readily diagnosed by skin biopsy, and this is a standard dermatological procedure when a clinical diagnosis cannot be made.

### TABLE 1. Ophthalmological complications of leprosy

<table>
<thead>
<tr>
<th>Complication</th>
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<tbody>
<tr>
<td>Lagophthalmos</td>
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<tr>
<td>Lid malposition—entropion and ectropion</td>
</tr>
<tr>
<td>Trichiasis</td>
</tr>
<tr>
<td>Nasolacrimal duct obstruction</td>
</tr>
<tr>
<td>Corneal anesthesia</td>
</tr>
<tr>
<td>Corneal ulcer/opacity</td>
</tr>
<tr>
<td>Loss of brow hair and lashes</td>
</tr>
<tr>
<td>Uveitis</td>
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<tr>
<td>Cataract</td>
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Early diagnosis and treatment of leprosy lead to an improved clinical outcome. It also militates against the spread of this disease in the country of residence.

REFERENCES
Point Counter-Point

Sohan Singh Hayreh, MD, MS, PhD, DSc, FRCS, FRCOphth (Hon), Valérie Biousse, MD

Treatment of Acute Visual Loss in Giant Cell Arteritis: Should We Prescribe High-Dose Intravenous Steroids or Just Oral Steroids?

A 76 year-old Caucasian woman presents to her ophthalmologist with acute visual loss in her right eye. She has a medical history of hypertension well-controlled with one medication, diet-controlled borderline diabetes mellitus, hysterectomy, and cholecystectomy. She takes one aspirin 81 mg per day. She is mildly overweight and denies smoking or drinking alcohol. She had cataract extractions in both eyes 10 years previously, and she only wears reading glasses.

One day ago, she noticed a “shadow” in her right eye while vision seemed normal in the left eye. Her ophthalmologist documented visual acuities of hand motion in the right eye and 20/25 in the left eye. Color vision was normal in the left eye. There was a large right relative afferent pupillary defect. Fundus examination showed diffuse, pallid right optic disc edema with attenuated arteries and a few cotton wool spots in the peripapillary area. In the left eye, the optic nerve was normal with a cup-to-disc ratio of 0.3, with mild retinal arterial attenuation and a few macular drusen. Suspicious that the patient may have arteritic ischemic optic neuropathy (AION), the ophthalmologist obtained an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), which came back “very high” the following morning. The patient denied headache, scalp tenderness, jaw claudication or diplopia, but mentioned an episode of blurry vision in the right eye 2 days before permanent visual loss. The diagnosis of arteritic-AION secondary to giant cell arteritis (GCA) was considered very likely. Aware of your expertise in GCA, the ophthalmologist calls the following morning asking whether the patient should be sent to the local hospital for high-dose intravenous (IV) methylprednisolone or rather begin treatment with oral prednisone 1 mg/kg per day. What do you recommend and why?

IV corticosteroids are not more effective than oral corticosteroids to treat patients with acute visual loss secondary to GCA.

Oral steroids should be given to GCA patients with acute visual loss: Sohan Singh Hayreh, MD, MS, PhD, DSc, FRCS, FRCOphth (Hon)

First of all, I would like to comment on the management of the narrated case, by the referring ophthalmologist. It is stated: “he obtained ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein), which came back “very high” the following morning.” Having dealt with giant cell arteritis (GCA) cases for more than 40 years, I am very concerned about this statement for the following 2 reasons.

1. The ophthalmologist described ESR and CRP as “very high.” When a referring physician tells me that the ESR and/or CRP are “normal”, “high,” or “very high”, I always ask for the exact values, because these descriptive terms are subjective and meaningless in the management of a case of GCA.

2. The ophthalmologist reported that ESR and CRP came back “very high” the “following morning.” Kears (1) rightly stressed that GCA “ranks as the prime medical emergency in ophthalmology, there being no other disease in which the prevention of blindness depends so much on prompt recognition and early treatment.” To wait for the ESR and CRP results until “the following morning” is unacceptable, in my opinion. I do not let my patients leave the clinic until I have the results, which I get within 1–1½ hours—CRP much earlier than ESR. If those tests indicate the possibility of GCA, then I immediately start the patient on high-dose corticosteroid therapy to prevent visual loss or further visual loss. This is an emergency and there is NO safe period between diagnosis and start of corticosteroid therapy to prevent visual loss.

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Role of IV vs oral corticosteroid therapy in prevention of visual loss due to GCA

The primary concern in the management of GCA is visual loss. I have reviewed the conflicting literature on this subject (2). The use of IV vs oral corticosteroids in the management of GCA has been reported, but these studies are mostly based on only a few patients (3–8). In addition, progressive visual loss has been described in GCA, despite corticosteroid therapy (IV or oral) (6,7,9).

I investigated the question whether IV megadose corticosteroid therapy was more effective than oral therapy in the prevention of visual loss (2). A total of 144 consecutive patients fulfilled the criteria for the study. All patients had temporal artery biopsy positive for GCA. At their first visit, 53 patients had no visual loss, whereas 91 had a variable degree of visual loss in one or both eyes. Initially, 96 patients were treated by high-dose (80–120 mg) oral prednisone only and 48 with IV megadose of corticosteroid therapy; the treatment regimen for IV therapy was usually 150 mg dexamethasone every 8 hours for 1–3 days, followed by high-dose oral prednisone. During the initial stages of the study, because of the prevalent impression that IV therapy was better than the oral therapy, IV treatment was generally given to patients with visual loss and also to some patients without visual loss. Later on, with greater experience, my criteria for initial IV therapy became: 1) history of amaurosis fugax but no visual loss; 2) complete or marked loss of vision (judged by both visual acuity and visual fields) in one eye; and 3) early signs of involvement of the second eye. Tapering of the oral corticosteroid therapy was done very gradually, guided only by the levels of ESR and CRP (10).

The results of this study showed that 13% of those on IV corticosteroid therapy had visual deterioration compared with 3% on oral corticosteroid therapy. This indicated that IV megadose corticosteroid therapy was no more effective than oral therapy in preventing visual deterioration.

The following GCA case with positive temporal artery biopsy is an instructive example. A 78-year-old Caucasian man noticed blurred vision in the left eye when he awoke one morning, which progressively worsened during the day (Day 1). That day his ophthalmologist recorded visual acuity of hand motions in the left eye and normal acuity in the right eye. On the second day (Day 2) he was seen in my clinic, with visual acuity of hand motions in a temporal island of visual field in the left eye and 20/20 in the right eye. Fundus examination revealed chalky white left optic disc swelling (classic finding of arteritic AION (11)), and a normal right fundus. He was admitted to hospital and immediately started on IV dexamethasone 150 mg every 8 hours. Beginning on Day 3, he was switched to 120 mg oral prednisone daily. Vision in both eyes was stable until Day 6 (while still in hospital), when he awoke with visual acuity of counting fingers at 2½ feet in the right eye and light perception in the left eye. The right optic disc now had chalky white swelling. IV dexamethasone 150 mg was again started immediately and repeated every 6 hours 4 times that day. The following morning (Day 7), his visual acuity was hand motions in the right eye and no light perception in the left eye. So, despite IV megadose corticosteroid therapy, the patient suffered progressive visual loss in both eyes. For that reason, I felt that IV corticosteroid therapy was not helping him, so he was switched to 120 mg prednisone orally. On Day 8, visual acuity in the right eye was bare light perception and in the left it no light perception. On Day 9, it was no light perception in both eyes and remained unchanged on follow-up. Despite intensive IV and oral corticosteroid therapy, there was relentless visual deterioration in both eyes.

Role of IV vs oral corticosteroid therapy in visual improvement in visual loss due to GCA

A review of the literature reveals disagreement on the effect of IV vs oral corticosteroid therapy on visual improvement in GCA. The majority of the reported patients with visual loss due to GCA in these studies initially were started on IV corticosteroids, followed by oral therapy. Some authors (3,12,13) claimed that IV corticosteroid therapy improved vision (based on only a total of 4 anecdotal cases). These 3 reports (3,12,13) require comment. In 2 cases (12,13), improved visual acuity without concomitant improvement in visual fields probably represented the patients’ learning to fixate eccentrically (see below). The report by Matzkin et al (3) illustrates another problem with visual improvement during corticosteroid therapy in GCA. These authors reported visual improvement with megadose IV methylprednisolone in 2 eyes diagnosed with “central retinal artery occlusion.” My review of these cases offers a different interpretation. One of the 2 eyes had a cilioretinal arterial occlusion and NOT central retinal artery occlusion. Our natural history study of 61 eyes with cilioretinal arterial occlusion showed marked spontaneous improvement in visual acuity (14). Similarly, our natural history study of 260 eyes with central retinal artery occlusion showed evidence of spontaneous improvement in visual acuity (15). It seems that the improvement in visual acuity claimed by Matzkin et al (3) in 2 cases simply represented natural history rather than the effect of the megadose IV methylprednisolone. Clearkin (16,17), on review of reports in the literature that have claimed visual improvement with IV megadose corticosteroid therapy, rightly pointed out that these claims were not justified and concluded that oral therapy is safer and just as efficacious. I agree with these conclusions. Liu et al (5) retrospectively reviewed the records of 41 GCA patients with visual loss. IV methylprednisolone was given to 25 patients, while the rest received oral prednisone alone. These authors reported that in the 41 patients with visual loss, there was visual improvement in 39% after IV treatment vs 28% on oral therapy. They claimed that
Visual loss due to giant cell arteritis had a 34% chance for some improvement in visual function after corticosteroid treatment; however, this is not supported by other prospective studies (see below).

In view of this controversy, we investigated the usefulness of IV vs oral systemic corticosteroid therapy in visual improvement in 84 consecutive patients with visual loss due to biopsy-proven GCA (18). The regimen of IV and oral corticosteroid therapy was the same as described above. Visual loss was due to arteritic AION (91%), central retinal artery occlusion (10.5%), cilioretinal artery occlusion (10%), and/or posterior ischemic optic neuropathy (4%) alone or in various combinations. Visual improvement was seen in 7% of 41 patients treated initially with IV corticosteroids vs 5% of 43 patients treated with oral corticosteroids (P = 0.672). This study did not support IV megadose corticosteroid therapy as being more effective than oral therapy in leading to visual improvement. Comparison of patients with visual improvement in both visual acuity and fields vs those with no improvement suggested a shorter (P = 0.065) interval between onset of visual loss and start of therapy in the improved patients. The data suggested early diagnosis and immediate start of corticosteroid therapy give a better chance of visual improvement. Overall, only 4% of eyes with visual loss due to GCA improved, judging from improvement in both visual acuity and central visual field (by kinetic perimetry and Amsler grid). Similarly, Danesh-Meyer et al (9), in a series of 34 consecutive biopsy-proven GCA patients, found that only 5% had improvement in both visual acuity and visual field. These 2 studies contradict the finding of Liu et al (5) that 34% of patients had improvement in visual function after corticosteroid treatment.

It is important to stress that reported “improvement in visual acuity” does not always reflect genuine visual improvement, as shown by my various studies (14,15,18–20) and by others (9). Genuine visual improvement involves improvement in both visual acuity and central visual field. Improvement in visual acuity alone, without corresponding improvement in the central visual field, usually represents the patient’s learning to see better by eccentric fixation. My studies (2,18) in GCA patients demonstrated no difference in effectiveness between IV vs high-dose oral corticosteroid therapy in the prevention or improvement of visual loss (2,18). Based on my studies, my current recommendations for corticosteroid therapy in GCA are as follows (10).

For all patients, with or without vision loss, I initially begin with a dose of at least 80 mg oral prednisone daily, except in the following 3 situations. 1) A history of amaurosis fugax but no visual loss; amaurosis fugax is an ominous sign of impending visual loss. 2) Complete or marked (judged by both visual acuity and visual field—particularly the latter) loss of vision in one eye. 3) Early signs of involvement of the second eye. In these conditions, it is essential to act urgently to achieve high levels of corticosteroid concentration in the circulation as soon as possible. Oral corticosteroid therapy takes some time to achieve high levels in the circulation. Therefore, in these patients, I initially give one megadose of IV corticosteroid (as an outpatient) and immediately start the patient on at least 80 mg oral prednisone daily. What I have learned from my experience in dealing with GCA patients over the past 4 decades is that it is most important to play the game according to the situation at hand, and not believe “one size fits all patients.”

I think it is relevant to point out that about a year ago I was diagnosed with GCA, without any loss of vision. My ESR was >140 mm/hour (my normal value usually about 10 mm/hour) and CRP was 17.1 mg/dL (normal value <0.5 mg/dL) with a positive temporal artery biopsy. I wanted to be treated the way I had treated my patients because if the treatment is appropriate for them, it is also appropriate for me. I asked my treating physician to start me immediately on 80 mg oral prednisone daily. With this treatment my ESR dropped to 8 mm/hour and CRP to <0.5 mg within 3 weeks. I experienced no visual problems. Since then, I have been slowly tapering my prednisone, guided exclusively by the levels of ESR and CRP (10).

In light of all this information, my recommendation for the management of the patient in question is as follows. The patient had “hand motion” vision in the involved eye. Therefore, this patient falls in one of my 3 “emergency” situations, discussed above, that is, complete or marked loss of vision in one eye. One has to try to reduce the risk of visual loss in the fellow eye. Therefore, as stated above, I would initially give her one megadose of IV corticosteroids and immediately start her on 80 mg prednisone daily. I would regulate the tapering of her therapy based only on the levels of ESR and CRP (10).

**IV steroids should be given to GCA patients with acute visual loss: Valérie Bioussé, MD**

Visual loss is the most feared complication of GCA and was noted in 30%–60% of patients with GCA before the era of corticosteroid treatment (21). Despite the widespread use of corticosteroids in the modern era, devastating visual loss may still occur in 14%–20% of patients (21–24).

GCA encompasses a broad spectrum of clinical subtypes: cranial arteritis with severe ischemic complications, such as visual loss and cerebral ischemia; large vessel arteritis causing subclavian and axillary artery stenosis, and arteritis leading to aortic dissection, aneurysm, and aortic rupture; and
a systemic inflammatory syndrome with nonstenosing vasculitis; and “isolated” polymyalgia rheumatica (PMR) with myalgias, fatigue, anorexia, and subclinical systemic vasculitis (22–24). Few studies have evaluated treatment protocols by individual GCA subtype. Instead, studies examining treatment protocols for GCA are influenced by the patient populations from which they draw. Those performed by ophthalmologists and researchers in tertiary care centers have generally recommended more aggressive treatment measures, sustained for longer periods of time, than population-based studies and those by rheumatologists (10–25). Rheumatologists, for example, may use low-dose oral prednisone to treat isolated PMR, while neuro-ophthalmologists often use high-dose IV methylprednisolone to treat patients with acute visual loss or brain ischemia (22).

The treatable nature of GCA and the devastating visual consequences of a delayed diagnosis make identification and treatment of this disorder a true medical emergency (26,27). However, delays in recognition and management of GCA still occur. In a recent study (28) of 65 GCA patients in the United Kingdom, mean time from symptom onset to diagnosis (and therefore, to treatment) was 35 days! This delay likely explains the high rate of irreversible visual complications in many series. Even a short delay of 24 hours in treatment seen in the case presented above is unacceptable and the timing of steroid therapy is probably more important than the dose or route of administration. Once a patient has lost vision in one eye, the risk of GCA-related visual loss in the fellow eye is highest within hours to days (10). Delaying steroid treatment by 24 hours not only reduces the chances of visual improvement but also places the patient at risk for fellow eye involvement, which occurs in more than 50% of cases. Although the visual outcome of arteritic AION is poor, immediate treatment with steroids might result in some visual improvement, and rarely, even complete visual recovery (5,21).

There is universal agreement that corticosteroids are the mainstay of treatment for GCA and should be initiated immediately and aggressively, with the goal of suppressing inflammation and disease activity, preventing further visual loss in the involved eye, preventing visual loss in the fellow eye, and possibly restoring vision (26,27). The initial starting dose, method of delivery, and duration of therapy are still matters of debate but depend largely upon the patient’s potential for visual loss (26,27).

What does the literature tell us?

Oral prednisone is the first-line therapy for GCA in most cases. The initial starting dose used to control GCA varies widely in the literature, from 20 mg per day in a mixed population of patients with either GCA or PMR, but with strictly constitutional signs and symptoms (29), to more than 100 mg per day in a high-risk neuro-ophthalmic population with recent or impending visual loss (10). Selection bias during enrollment influences the conclusions of these studies; rheumatologic reports often combine GCA with PMR and neuro-ophthalmic reports often enroll patients with severe visual loss and occult GCA. Although no consensus exists for initial dose of prednisone, the majority of patients respond to a dose of 1 mg/kg per day (22–24). Higher doses of 80–100 mg per day often are given to patients with visual or neurological symptoms (10,30).

IV pulse methylprednisolone is frequent induction therapy when vision is at risk. Four studies have examined IV steroid therapy in GCA, 2 of which were prospective randomized controlled trials (Table 1). The study by Chevalet et al (31) showed no benefit for a single induction dose of IV methylprednisolone (250 mg) in reducing cumulative steroid dose at 1 year. Mazlumzadeh et al (32) found that a 3-day course of induction IV methylprednisolone at a much higher dose of 15 mg/kg per day allowed more rapid weaning from oral prednisone than placebo and also reduced the cumulative steroid dose at Week 78. Interestingly, the benefits of pulse steroid therapy in this study only became obvious later in the course of the disease. Chan et al (33) evaluated IV steroids in exclusively high-risk patients—those with biopsy-proven GCA and recent or impending visual loss—and found improvement of visual acuity in significantly more patients treated with induction IV steroids compared with oral steroids alone. A study by Hayreh et al (18) did not show any obvious benefit of high-dose IV steroids, but the patients were not randomized and the group of patients treated with IV steroids tended to have greater vision loss at presentation as were those reported by Gonzales-Gay et al (21).

After the initiation of corticosteroid treatment, no matter what the route, systemic symptoms of GCA disappear rapidly and dramatically over hours to days in nearly all patients (22–24,26,27). Improvement of visual loss is much less frequent, occurring in only 4%–34% of affected eyes (Table 2). Visual improvement, when it occurs, is mild, with persistent and often severe visual field defects (5,9,21,34–36). There does not seem to be any major difference in terms of visual outcome based on whether patients receive induction IV bolus steroids initially or whether they are treated with oral steroids alone. However, when treatment is initiated within 24 hours of visual loss, 58% of patients have visual improvement compared with the 6% of patients who improve after a delay in treatment (21). This trend toward better visual outcomes when steroids are commenced early after visual loss has been documented in other studies (18) (Table 2). While published case reports also suggest occasional dramatic improvement of visual function in rare patients receiving high-dose IV methylprednisolone (3,13,16,21), it is impossible to draw conclusions from isolated cases.

Despite treatment with high-dose corticosteroids, both oral and IV, bilateral visual loss or worsening of unilateral vision loss may sometimes occur, usually within the first 5 days of treatment (2,6,37). While there are reports of
<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>N</th>
<th>Population</th>
<th>Intervention</th>
<th>Primary Endpoint</th>
<th>Outcome</th>
</tr>
</thead>
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<tr>
<td>Chevalet et al (31)</td>
<td>3-armed RCT</td>
<td>164</td>
<td>GCA without ocular or cerebrovascular involvement</td>
<td>Pulse of 240 mg IV methylprednisolone followed by 0.7 mg/kg oral prednisone</td>
<td>Cumulative steroid dose at 1 year</td>
<td>No benefit with IV vs oral steroids</td>
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<td>Pulse of 240 mg IV methylprednisolone followed by 0.5 mg/kg oral prednisone</td>
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<td></td>
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<td></td>
<td>Oral prednisone 0.7 mg/kg</td>
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<tr>
<td>Chan et al (33)</td>
<td>Retrospective</td>
<td>73</td>
<td>Vision loss from biopsy-proven GCA</td>
<td>High-dose IV methylprednisolone (≥1,000 mg/d for 3 d), followed by oral prednisolone at 75 mg/d</td>
<td>Significant improvement in visual acuity on Snellen chart</td>
<td>Benefit for IV vs oral steroids (40% vs 13%; P = 0.01)</td>
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<td></td>
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<td></td>
<td></td>
<td>Oral prednisolone alone at ~75 mg/d</td>
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<tr>
<td>Hayreh et al</td>
<td>Longitudinal observational</td>
<td>145</td>
<td>Biopsy-proven GCA (96 with visual loss; 49 without visual loss)</td>
<td>&quot;Megadose&quot; IV dexamethasone (up to 450 mg/d for 1–3 d), followed by oral prednisolone at 80–120 mg/d</td>
<td>Visual outcome; cumulative steroid dose</td>
<td>No benefit with IV vs oral steroids</td>
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<td></td>
<td></td>
<td>Oral prednisone alone 80–120 mg/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazlumzadeh et al (32)</td>
<td>2-armed RCT</td>
<td>27</td>
<td>GCA without ocular or cerebrovascular involvement</td>
<td>Oral prednisone 40 mg/d followed by a systematic taper at Week 4, plus an &quot;induction&quot; dose of IV methylprednisolone 15 mg/kg/d for 3 d (about 1,000 mg/d) and placebo</td>
<td>Prednisone dose of no more than 5 mg/d at 36 wk</td>
<td>Benefit for IV vs oral steroids (71% vs 15%; P = 0.003)</td>
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GCA, giant cell arteritis; IV, intravenous; RCT, randomized controlled trial.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>N (All With Permanent Visual Loss)</th>
<th>Steroid Regimen</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al (5)</td>
<td>Retrospective</td>
<td>41 patients (63 eyes)</td>
<td>25 patients received IV methylprednisolone followed by oral prednisone; 20 patients received 60–100 mg oral prednisone alone</td>
<td>34% of patients with visual loss had visual improvement with IV or oral corticosteroids. More benefit was seen in the patients who received IV treatment. More fellow eye involvement while receiving oral steroids than IV steroids</td>
</tr>
<tr>
<td>Gonzales-Gay et al (21)</td>
<td>Retrospective</td>
<td>34 patients</td>
<td>10 with severe visual loss received 1 g IV methylprednisolone × 3 d, followed by oral prednisone; 24 patients received 45–80 mg oral prednisone alone</td>
<td>Early treatment (within 24 hours) was the only predictor of recovery of VA. No significant difference between IV and PO treatment (but all patients treated with IV steroids had severe visual loss)</td>
</tr>
<tr>
<td>Kupersmith et al (35)</td>
<td>Prospective</td>
<td>7 patients (9 eyes)</td>
<td>3 patients received 1g IV methylprednisolone with oral prednisone; 6 patients received 40–200 mg oral prednisone</td>
<td>44% of eyes had improved VA within 1 month of starting treatment with steroids</td>
</tr>
<tr>
<td>Hayreh et al (18)</td>
<td>Retrospective</td>
<td>84 patients (114 eyes)</td>
<td>41 patients received “Megadose” IV dexamethasone (up to 450 mg/d for 1–3 d) followed by oral prednisone at 80–120 mg/d; 43 patients received oral prednisone alone 80–120 mg/d</td>
<td>4% of eyes had improvement of both VA and central VF on treatment. A trend toward improvement was seen with immediate treatment. No difference in outcomes between IV and oral steroids</td>
</tr>
<tr>
<td>Foroozan et al (36)</td>
<td>Retrospective</td>
<td>32 patients (39 eyes)</td>
<td>All patients received 1 g IV methylprednisolone for 3 d followed by oral prednisone 1 mg/kg/d</td>
<td>13% of patients had improvement of VA with treatment (time from onset of symptoms not specified), but none showed significant improvement in VF</td>
</tr>
<tr>
<td>Danesh-Meyer et al (9)</td>
<td>Prospective</td>
<td>34 patients</td>
<td>All patients received 1 g IV methylprednisolone for 3 d followed by oral prednisone 1–3 mg/kg/d</td>
<td>Patients received treatment within 10 d after onset of visual loss (mean 2 d). 15% of patients had improvement of VA of 2 or more lines</td>
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IV, intravenous; VA, visual acuity; VF, visual field.
GCA patients progressively losing vision while on oral steroids, and then stabilizing with high-dose pulse IV methylprednisolone. Hayreh and Zimmerman (2) reported a higher incidence of visual deterioration in patients receiving high-dose IV methylprednisolone (in 6 of 48 patients) than in those treated with oral steroids (in 3 of 97 patients). However, Hayreh emphasized that high-dose IV steroids are often prescribed to those patients with severe unilateral or bilateral visual loss at the time of diagnosis, hence suggesting a bias toward treating more severe forms of GCA with IV steroids (2,10).

I always recommend IV steroids for patients with acute visual loss and presumed GCA for the following reasons:

1. It is essential to administer steroids as soon as possible when GCA is suspected. Usually, I send the patient directly from my office to the Emergency Department (ED) where IV methylprednisolone can be started immediately. This is much more efficient than sending an anxious and sick patient home with a prescription for oral prednisone. It also guarantees immediate patient compliance with treatment. The GCA population is by definition older, often with numerous comorbidities, and have difficulties with transportation. These factors, which may lead to delay in treatment, are mitigated by referral to the ED. When a patient is seen a few days after visual loss and is already on oral prednisone or does not have any visual symptoms, outpatient oral steroids are appropriate.

2. Recommending IV steroids allows me to admit the patient to the hospital for at least 48 hours. Comorbidities such as hypertension, heart disease, and diabetes mellitus increase the risk of life-threatening complications of steroids. A short admission to hospital ensures that IV steroids are well tolerated, and any other medical conditions are properly managed. It facilitates obtaining all necessary tests, such as temporal artery biopsy, brain and orbital imaging in some cases, evaluation of vascular risk factors and osteoporosis, and patient education regarding long-term steroid use and prevention of complications. The patient is usually discharged from hospital after 3 days of IV methylprednisolone with a prescription for oral prednisone and adjunctive treatments to prevent osteoporosis and other complications of long-term steroid treatment, recommendations from a nutritionist, and follow-up appointments.

3. Most medications act faster and have a more potent effect when administrated IV rather than taken orally. This is why IV therapy is chosen over oral prednisolone in a variety of clinical settings including organ transplant rejection, severe systemic lupus erythematosus, acute glomerulonephritis, and other autoimmune and systemic vasculitides (38,39).

Corticosteroids mediate their function in part by binding to glucocorticoid receptors present in the cell cytoplasm. After binding, the glucocorticoid receptors are translocated to the nucleus and modulate gene expression, resulting in the up- or downregulation of specific genes affecting the expression of several cytokines and/or adhesion molecules. In addition, glucocorticoid receptors regulate the inflammatory response through interference with numerous transcription factors. These properties of glucocorticoid receptors are known as “nongenomic effects” and can be seen as early as 30 minutes after drug administration, as opposed to “nongenomic effects,” which are detected in seconds to minutes (39). While a dose of 30–100 mg oral prednisolone results in 100% glucocorticoid receptor saturation, administration of IV pulse methylprednisolone at doses greater than 250 mg may enhance clinical effects by additional nongenomic mechanisms. In addition, IV pulse methylprednisolone has a longer duration of action than oral prednisolone and may have greater anti-inflammatory and immunosuppressive effects (39). This is clearly desirable in the initial treatment of ischemic complications of GCA including visual loss. IV pulses of methylprednisolone are generally greater than 10 mg/kg (frequently a dose of 1,000 mg is used) and given daily for 3 days (oral prednisone equivalent: 1,250 mg). This dose was adapted

### TABLE 3. British Society of Ophthalmology guidelines regarding the initial dose and route of steroids to treat GCA (adapted from Dashgupta (27))

<table>
<thead>
<tr>
<th>Condition</th>
<th>Steroids Administration</th>
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<tbody>
<tr>
<td>Uncomplicated GCA (no jaw claudication or visual disturbance)</td>
<td>40–60 mg oral prednisone daily (not less than 0.75 mg/kg daily)</td>
</tr>
<tr>
<td>Evolving visual loss (recent onset visual symptoms over 6–12 h or transient visual loss)</td>
<td>Intravenous methylprednisolone 500–1,000 mg daily for 3 d before oral steroids</td>
</tr>
<tr>
<td>Established visual loss</td>
<td>At least 60 mg prednisone daily, to protect the contralateral eye</td>
</tr>
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Patients should also receive bone protection with weekly bisphosphonate and calcium/vitamin D supplementation. Proton pump inhibitors for gastrointestinal protection should be considered, especially if low-dose aspirin is also prescribed. The symptoms of GCA should respond rapidly to high-dose glucocorticosteroid treatment, followed by resolution of the inflammatory response. Failure to do so should raise the question of an alternative diagnosis. The initial dose of steroids should be continued for 3–4 weeks and reduced in the absence of any clinical symptoms or any laboratory abnormalities suggestive of ongoing active disease. The steroid tapering should be gradual, provided there is no relapse.

GCA, giant cell arteritis.

from treating graft rejection in renal transplant recipients with supporting evidence from animal experiments (38,39). It has been suggested that 500 mg per day may be as effective as 1 g per day for severe systemic lupus erythematosus (40) and such a dose also might be considered for GCA, particularly in patients with hypertension, heart disease, or diabetes mellitus.

4. IV high-dose pulse methylprednisolone seems to be as well tolerated as oral prednisone. It does increase the risk of osteoporotic fractures and avascular necrosis, but its use may lead to a reduction of total steroid dose, exposing the patient to fewer long-term side-effects of steroid therapy (32).

In conclusion, symptoms of GCA are exquisitely sensitive to corticosteroid therapy. Administering high-dose steroids as quickly as possible after the onset of visual loss is essential to suppress inflammation, prevent further visual loss, prevent visual loss in the fellow eye, and possibly restore vision. IV pulse methylprednisolone at a dose of 500–1,000 mg per day is a relatively easy and safe way to treat GCA patients and should be recommended in patients with acute visual loss. This statement is in accordance with the guidelines from the British Society of Ophthalmology and the British Society of Rheumatology (Table 3) (26,27).

Rebuttal: Sohan Singh Hayreh, MD, MS, PhD, DSc, FRCS, FRCOphth (Hon)

I conducted studies on various aspects of GCA for approximately 40 years as a part of the prospective studies on ocular vascular occlusive disorders funded by the National Institutes of Health. Thus, the comment by Dr Biousse that my studies were retrospective is not correct.

One has to be extremely careful in accepting claims of visual improvement with IV corticosteroid therapy vs oral therapy based simply on visual acuity improvement. My various studies on visual outcome (14,15,18–20) consistently have shown that unless there is a corresponding improvement in central visual field, better visual acuity alone simply represents a patient learning to see better by eccentric fixation.

In light of this important fact, I find the information in Dr Biousse’s table 2 misleading. Gonzales-Gay et al (21) in their retrospective chart review were able to obtain detailed data on both therapy and visual acuity outcome in only 29 patients with visual loss—10 patients treated with IV pulse methylprednisolone and 19 with oral prednisone. There was no difference in the visual acuity outcome between the 2 groups (P = 0.26). They found that those who were treated within 24 hours had better chance of visual improvement but the therapeutic regimen did not influence the visual outcome (odds ratio, 0.6; 95% confidence interval, 0.1–40.8). In the studies by Kupersmith et al (35) and Foroozan et al (36), there was no visual field improvement corresponding to improved visual acuity improvement. The study by Kupersmith et al (35) had multiple other problems as discussed elsewhere (41). In the prospective study by Danesh-Meyer et al (9), only 5% of GCA patients had improvement in both visual acuity and visual field when treated with IV corticosteroid therapy. Similarly, in our prospective (not retrospective) study (18), only 4% showed improvement in both visual acuity and visual field. Dr Biousse commented that our study (18) did not show any obvious benefit of high-dose IV steroids because the group of patients treated with IV steroids tended to have worse visual loss at presentation. This is contradicted by the fact that visual improvement in our study (84 patients, 114 eyes) (18) and in that of Danesh-Meyer et al. (34 patients, 40 eyes) (9) was similar, that is, 4% and 5%, respectively. The report of visual improvement in 34% of GCA patients by Liu et al (5) was based only on visual acuity. Cornblath and Eggenberger (6) found that results of high-dose IV methylprednisolone treatment of patients with visual loss from GCA were similar to the results of treatment with oral corticosteroid therapy. Salvarani et al (42) found no evidence that IV methylprednisolone was better than oral therapy.

As regards Table 1, Chan et al (33) conducted a retrospective study and noted visual improvement based only on visual acuity and the authors stated: “intravenous steroids may offer a greater prospect of improvement compared with oral steroids.” Yet, they concluded: “A prospective trial comparing intravenous with oral steroid is needed to validate these finding.” The study by Mazlumzadeh et al (32) (rheumatologists) needs to be put in perspective in relation to visual outcome and relapses of GCA. In that study, 14 patients received a 3-day course of IV methylprednisolone plus oral prednisone and 13 received only oral prednisone. The oral prednisone dose was 40 mg daily initially. Then the dose was reduced successively every 2 weeks to daily 30, 25, 20, then by 2.5 to 10 mg, and thereafter by 1 mg every 2 weeks. No information regarding visual acuity was included. My studies show that this treatment regimen was totally inadequate to prevent visual loss in GCA. It is not surprising that in the oral group there were 37 relapses, which also can put a GCA patient at risk for visual loss. There were no relapses at all in my studies. There is not a single large comprehensive study that has shown significantly better visual improvement with IV corticosteroid therapy compared with adequate oral corticosteroid therapy.

Dr Biousse has cited much rheumatologic literature about the management of GCA. As I have stressed previously (10), rheumatologists and ophthalmologists have different perspectives on GCA (22,42). Rheumatologists...
deal essentially with patients with rheumatologic manifestations, while ophthalmologists see GCA patients with visual loss or patients with occult GCA (43) who may lose vision without any rheumatologic or systemic symptoms. For the ophthalmologist, GCA is a blinding disease with tragic consequences; for the rheumatologist it is a disease with mainly systemic complaints, with less severe medical consequences. Salvarani et al (rheumatologists) (22,42) have given a “cookbook” regimen of corticosteroid therapy in GCA, which may be adequate to manage rheumatologic symptoms but is inadequate to prevent visual loss. Similarly, Mazlumzadeh et al (32) (rheumatologists), as discussed above, recommended a course of corticosteroid therapy that is inadequate to prevent visual loss, as is evident from multiple relapses in their patients. My studies have shown that a “one-size-fits all” regimen is totally inadequate to prevent visual loss. There is marked interindividual variation in the dose and duration of corticosteroid therapy required to control GCA and prevent visual loss. Rheumatologists advocate corticosteroid therapy to be guided by systemic symptoms, which is not effective to prevent visual loss (41). Levels of ESR and CRP are the only reliable methods to regulate treatment in GCA. Rheumatologists believe that GCA burns itself out in approximately 2 years and there is no need to continue corticosteroid therapy. I have seen patients whose rheumatologists stopped corticosteroid therapy, who then lost vision.

Finally, Dr. Biousse proposes admitting a patient to hospital for “a 3-day course of induction intravenous methylprednisolone,” as also was done by Mazlumzadeh et al (32), Danesh-Meyer et al (9), and advocated by the British Society of Ophthalmology (26). But there is no scientific study showing that such an inpatient “3-day course” is superior to outpatient management; therefore, to hospitalize patients for 3 days is not justified in my experience. Dr. Biousse also stated that that hospitalization enabled brain and orbital imaging in some cases and the evaluation of vascular risk factors and osteoporosis. In my experience, neurological and orbital findings are extremely rare in GCA and I see no justification for admitting a patient for evaluation of vascular risk factors and osteoporosis. I have not admitted a GCA patient to the hospital in approximately 30 years. In the University of Iowa Hospitals and Clinics, the cost of 3-day hospitalization and IV medication is approximately $15,000. As I have discussed, when IV corticosteroid therapy is indicated, giving one IV dose as an outpatient costs approximately $500. In my opinion, not only is hospitalization an unnecessary inconvenience and possibly traumatic to the patient; it is a totally unnecessary medical expense.

Rebuttal: Valérie Biousse, MD

I completely agree with Dr Hayreh regarding the unacceptable delay in treating the patient under discussion. Most troubling is that the ophthalmologist waited until the next day to check the results of the ESR and CRP and not initiate steroid therapy immediately. A 24-hour delay in treatment is still within the window of time for “acute visual loss,” and the patient is at very high risk for worsening vision in the involved eye and for loss of vision in the fellow eye. This is why, despite Dr Hayreh’s statement, I still would not hesitate to recommend immediate administration of pulse IV methylprednisolone (500 or 1,000 mg) and admission to hospital for close observation and further testing as detailed above. I am pleasantly surprised to see that Dr Hayreh recommends giving one initial bolus of IV methylprednisolone in this setting to acutely achieve higher levels of corticosteroids. However, unlike Dr Hayreh, I would then keep the patient in the hospital for 2 more days and repeat the bolus of IV methylprednisolone so that the patient receives 1,000 mg of methylprednisolone per day for 3 days before being discharged on 1 mg/kg per day of oral prednisone.

Although I am glad that Dr Hayreh did not experience any visual symptoms himself, his last comment is irrelevant to this case and this pro-con discussion; I would have managed Dr Hayreh similarly, with oral prednisone as an outpatient.

This Point-Counter-Point discussion confirms that despite voicing different opinions regarding the management of GCA patients with acute visual loss, Dr Hayreh and I agree that patients with acute visual loss should be treated emergently with at least one bolus of high-dose IV steroids, not just oral steroids.

REFERENCES


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To determine whether oral zinc supplementation might affect the efficacy and duration of botulinum toxin treatments.

Methods: In a double-blind, placebo-controlled, crossover pilot study, we examined the efficacy of 3 botulinum toxin preparations (onabotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB) following oral supplementation with zinc citrate 50 mg and phytase 3,000 PU, zinc gluconate 10 mg, or lactulose placebo in individuals treated for cosmetic facial rhytids, benign essential blepharospasm, and hemifacial spasm.

Results: In 77 patients, 92% of subjects supplemented with zinc 50 mg and phytase experienced an average increase in toxin effect duration of nearly 30%, and 84% of participants reported a subjective increase in toxin effect, whereas no significant increase in duration or effect was reported by patients following supplementation with lactulose placebo or 10 mg of zinc gluconate. The dramatic impact of the zinc/phytase supplementation on some patients’ lives clinically unmasked the study and prompted an early termination.

Conclusions: This study suggests a potentially meaningful role for zinc and/or phytase supplementation in increasing the degree and duration of botulinum toxin effect in the treatment of cosmetic facial rhytids, benign essential blepharospasm, and hemifacial spasm.

Botulinum toxin requires the presence of zinc to block neuromuscular function. Phytates are dietary compounds that block zinc absorption in the gut. Phytases are enzymes that degrade phytates and improve zinc absorption. Patients with optic neuritis who attended the Ann Neurol participating in the pilot study, we examined the ef

It would really be nice if a simple dietary supplement could increase the effect and duration of action of botulinum toxin. Although this study would suggest this is the case, the problems you have identified, the early termination because of apparent benefit and the conflict of interest of the senior author, limit the credibility of the report. I wonder whether the benefit of the combined zinc and phytase treatment was more related to a higher zinc dose (50 mg vs 10 mg) than the effect of the phytase. The improvement could have been based on the difference in zinc dose rather than the phytase.

—Michael S. Lee, MD

The senior author of this article notes that he has a patent pending for a zinc/phytase combination, which could result in some bias. The zinc/phytase combination pill comes in a pack of 10 with the trade name of Zytaze (Ocusoft, Inc, Richmond, TX) and requires a prescription. It is quite a bit more expensive than taking zinc alone.

—Mark L. Moster, MD


Objectives: Based on findings in animal models of autoimmune optic nerve inflammation, we have assessed the safety and efficacy of erythropoietin in patients presenting with a first episode of optic neuritis.

Methods: Patients with optic neuritis who attended the University Hospitals of Homburg/Saar, Göttingen, or Hamburg (Germany) were included in this double-blind, placebo-controlled, phase II study (ClinicalTrials.gov, NCT00355095). They were randomly assigned to groups receiving either 33,000 IU recombinant human erythropoietin i.v. daily for 3 days, or placebo, as an add-on therapy to methylprednisolone. The primary outcome parameter was change in retinal nerve fibre layer (RNFL) thickness after 16 weeks. Secondary outcome parameters included optic nerve atrophy as assessed by magnetic resonance imaging, changes in visual acuity, visual field, and visual evoked potentials (VEPs).
**Results:** Forty patients were assigned into either treatment group (21/19 erythropoietin/placebo). Safety monitoring revealed no relevant issues. Thirty-seven patients (20/17 erythropoietin/placebo) were analysed for the primary endpoint according to the intention-to-treat protocol. RNFL thinning was less apparent after erythropoietin treatment. Thickness of the RNFL decreased by a median of 7.5 μm by week 16 (mean ± STD: 10.55 ± 17.54 μm) compared to a median of 16.0 μm (22.65 ± 29.18 μm) in the placebo group (P = 0.0357). Decrease in retrobulbar diameter of the optic nerve was smaller in the erythropoietin group (P = 0.0112). VEP latencies at week 16 were shorter in erythropoietin-treated patients than in the placebo group (P = 0.0011). Testing of visual functions revealed trends towards an improved outcome after erythropoietin treatment. **Interpretation:** These results give the first indications that erythropoietin might be neuroprotective in optic neuritis.

This is an exciting Phase II trial of erythropoietin as a neuroprotective agent in acute optic neuritis. When erythropoietin was added to pulsed methylprednisolone and compared with placebo, there was less retinal nerve fiber layer (RNFL) thinning on Stratus optical coherence tomography (OCT), less delay in visual evoked potentials peak latency, and less atrophy of optic nerve on magnetic resonance image at 16 weeks. No serious adverse events were noted. Not surprisingly, visual function was not significantly different between placebo and erythropoietin groups, likely because patients had good visual recovery. However, low-contrast visual acuity was not tested and would have more chance at demonstrating a difference. Even if visual function was not affected in this study of acute optic neuritis, preservation of RNFL and therefore future “reserve” in the optic nerve is worthwhile and promising.

—Mark L. Moster, MD

Optic neuritis is a difficult disorder to study because of the natural history of near normalization of acuity and field. I agree, however, that the structural benefit on OCT is promising. I certainly like the idea of trying erythropoietin for optic neuropathies for the following reasons:

1. It is recognized as neuroprotective in multiple animal studies.
2. It is FDA approved for use in humans.
3. It is relatively safe.

I look forward to future studies involving erythropoietin for optic neuropathies.

—Michael S. Lee, MD

**Objective:** To assess prospectively the accuracy and precision of a method for noninvasive intracranial pressure (ICP) measurement compared with invasive gold standard CSF pressure measurement.

**Methods:** Included were 62 neurologic patients (37 idiopathic intracranial hypertension, 20 multiple sclerosis, 1 Guillain-Barré syndrome, 1 polyneuropathy, and 3 hydrocephalus). The average age was 40 +/- 12 years. All patients had lumbar puncture indicated as a diagnostic procedure. ICP was measured using a two-depth high-resolution trans-cranial Doppler insonation of the ophthalmic artery (OA). The OA is being used as a natural pair of scales, in which the intracranial segment of the OA is compressed by ICP and the extracranial segment of the OA is compressed by extracranial pressure (Pe) applied to the orbit. The blood flow parameters in both OA segments are approximately the same in the scales balance case when Pe = ICP. All patients had simultaneous recording of noninvasive ICP values and invasive gold standard CSF pressure values.

**Results:** Analysis of the 72 simultaneous paired recordings of noninvasive ICP and the gold standard CSF pressure showed good accuracy for the noninvasive method as indicated by the low mean systematic error (0.12 mm Hg; confidence level [CL] 0.98). The method also showed high precision as indicated by the low SD of the paired recordings (2.19 mm Hg; CL 0.98). The method does not need calibration.

**Conclusion:** The proposed noninvasive ICP measurement method is precise and accurate compared with gold standard CSF pressure measured via lumbar puncture.

Here is the logic used in this study. The blood flow velocity of the intracranial segment of the ophthalmic artery is modulated by the intracranial pressure (ICP). A controlled pressure to the closed eyelid alters the blood flow velocity of the extracranial segment of the ophthalmic artery. When the blood flow parameters in both segments of the ophthalmic artery became equal, the external pressure should theoretically equal the ICP. Using a custom-made device, the authors used a transcranial Doppler to measure the blood flow in each segment. The external pressure device delivered the controlled pressure in steps of 4 mm Hg or 5.4 cm H2O (for reference, 1 mm Hg equals 1.36 cm H2O). The authors measured the opening pressure by lumbar puncture in the lateral decubitus position at the same time as the noninvasive method and compared the results. This is an interesting concept, which could be of great value, because it is noninvasive and takes less than 10 minutes to perform. It could certainly represent a screening test for possible papilledema, and if the noninvasive pressures were borderline, then one could proceed with lumbar puncture. However, there are some issues here. Both measurements in this study occurred simultaneously, which opens the risk of unmasking. The number of patients tested is small, and it is unclear if the results could be affected by any local or systemic disorders such as hypertension, glaucoma, ophthalmic artery stenosis, or occlusion and orbital disease.

—Michael S. Lee, MD

I agree with all of your concerns, Michael. The authors plan future studies conducted in the intensive care unit dealing with traumatic brain injury patients who have intraventricular ICP monitoring devices. This will provide data about whether the fluctuations in ICP can be picked up with this noninvasive technique and will study patients with markedly elevated ICP. Other factors that might affect the measurements, such as elevated intraocular pressure (IOP), also will have to be addressed in future studies. For instance, will this be valid with an IOP of 35 mm Hg? Nonetheless, this is an innovative study of what might become a valid noninvasive alternative for measuring ICP.

—Mark L. Moster, MD


Objective: Embolism from a proximal source to the retinal circulation could be a sign of embolism from the same source to the hemispheric circulation. We sought to determine the frequency of acute brain infarcts on diffusion-weighted imaging (DWI) in patients with monocular visual loss of presumed ischemic origin (MVL).

Methods: We retrospectively studied 129 consecutive patients with MVL secondary to retinal ischemia. All patients underwent DWI, comprehensive ophthalmologic and neurologic examination, and diagnostic evaluations for the underlying etiology. Statistical analyses explored univariable and multivariable predictors of DWI evidence of acute brain infarcts.

Results: DWI revealed concurrent acute brain infarct(s) in 31 of the 129 patients (24%). The probability of positive DWI was higher in embolic versus non-embolic MVL (28% vs. 8%, P = 0.04), in MVL characterized by permanent visual loss versus transient symptoms (33% vs. 18%, P = 0.04), and in MVL associated with concurrent hemispheric symptoms versus isolated MVL (53% vs. 20%, P < 0.01). Patients with positive DWI were more likely to harbor a major underlying etiology as compared to those with normal DWI (OR 3.7, 95% CI 1.5-9.4).

Interpretation: This study demonstrates that MVL does not always represent an isolated disease of the retina; approximately one out of every 4 patients with MVL demonstrates acute brain infarcts on DWI. Since patients with concurrent brain infarcts are more likely to exhibit a cardiac or vascular source of embolism, imaging evidence of brain injury in patients with MVL may be a useful marker to guide the timing and extent of the diagnostic examinations.

It is not surprising that patients with monocular visual loss can have simultaneous ipsilateral brain ischemia, as found 24% of the time. It is also not surprising that those with hemispheric symptoms had a higher frequency of stroke on diffusion-weighted imaging (53%) than those with isolated monocular visual loss (MVL) (20%). Many neuro-ophthalmologists do not obtain a magnetic resonance image (MRI) of the brain in cases of transient MVL or even retinal artery occlusion. The results of this study suggest that it may be important to consider MRI of the brain in patients with isolated MVL.

—Ideal L. Moster, MD


Objective: To describe first experiences with the integrin inhibitor natalizumab, given to patients with suspected relapsing-remitting multiple sclerosis (MS) who were later diagnosed with aquaporin 4-positive neuromyelitis optica (NMO).

Design: Retrospective case series.

Setting: Neurology departments at tertiary referral centers in Germany.

Patients: Patients with NMO who tested positive for antibodies to aquaporin 4.

Intervention: Treatment with natalizumab.

Main Outcome Measures: Relapses and accumulation of disability.

Results: We identified 5 patients (4 female; median age, 45 years) who were initially diagnosed with MS and treated with natalizumab before diagnosis of NMO was established. Natalizumab was given as escalation therapy after failure of first- or second-line immunomodulatory therapies for MS. During natalizumab therapy (median duration, 8 infusions; range, 2-11 infusions), all 5 patients displayed persisting disease activity; a total of 9 relapses occurred (median duration to relapse, 120 days; range, 45-230 days) after the start of treatment. Four patients had an accumulation of disability and 1 patient died 2 months after cessation of natalizumab treatment.

Conclusions: Our results suggest that natalizumab fails to control disease activity in patients with NMO. Neuromyelitis optica should be considered as a differential diagnosis in patients with suspected MS who are unresponsive to natalizumab therapy.

These 5 patients were initially misdiagnosed with multiple sclerosis (MS) and treated with natalizumab before...
the correct diagnosis of neuromyelitis optica (NMO). Despite receiving a median of 8 natalizumab treatments, 2 patients experienced 1 relapse, 2 patients had 2 relapses, and 1 patient had 3 relapses.

I would agree that anyone should rethink the diagnosis for any MS patient who fails natalizumab therapy. However, this is such a small group of patients that one cannot conclude that natalizumab fails to control disease activity in patients with NMO. There may be many more NMO patients misdiagnosed with MS whose disease is well controlled on natalizumab therapy. We need better data!

—Michael S. Lee, MD

This anecdotal series does not provide scientific evidence but is enough to raise some clinical concerns. The diagnosis of NMO really did exist in 3 patients who had known longitudinally extensive spinal lesions before initiation of natalizumab; it just seems to have been overlooked.

However, this report does add a few more cases to the literature demonstrating a poor therapeutic response and perhaps a worsening in NMO patients treated with conventional MS treatments. Because the outcomes in NMO patients without treatment are worse than with MS, I now send NMO antibody tests on all atypical, isolated optic neuritis patients.

—Mark L. Moster, MD


Objective: To report the safe and successful use of the carbonic anhydrase inhibitor acetazolamide for treatment of patients with episodic ataxia and periodic paralysis who had been denied treatment because of a history of severe allergic reactions to antibiotic sulfonamides.

Design: Case reports.

Setting: University of Rochester Medical Center, Rochester, New York.

Patients: A 61-year-old man with late-onset episodic ataxia, an 83-year-old woman with mutation-positive Andersen-Tawil syndrome, and a 21-year-old woman with mutation-positive episodic ataxia 2, all of whom had a history of severe skin rash with the use of sulfonamides for treatment of infection.

Results: The 3 patients had been considered for carbonic anhydrase inhibitor treatment but a pharmacist had refused to fill a prescription for acetazolamide for 1 patient and the other 2 patients were denied treatment because of the allergy history. All 3 patients were prescribed acetazolamide and had no adverse reaction. Two patients improved substantially and are continuing treatment. A review of the pharmacology literature suggests that cross-reactivity between antibiotic and nonantibiotic carbonic anhydrase inhibitors is unlikely. Moreover, a review of case reports does not suggest cross-reactivity. Previous reports in the ophthalmology literature also indicate that acetazolamide can be administered to patients with a history of antibiotic sulfonamide allergic reaction.

Conclusions: These 3 cases confirm that the carbonic anhydrase inhibitor acetazolamide can be given to patients with a history of allergic skin rash with antibiotic sulfonamide.

Nonantibiotic sulfonamides are used for treatment of diseases such as type 2 diabetes mellitus, hypertension, and ion channelopathies. However, patients who might benefit from these medications have often been prohibited from taking them owing to fear of cross-reactivity between antibiotic and nonantibiotic sulfonamides. In patients with severe allergic responses to sulfonamide antibiotics, the risk of severe reaction with other sulfa-containing drugs such as acetazolamide was thought to outweigh potential benefits. However, recent studies of the chemical structure and mechanisms of immune response to these drugs suggest that cross-reactivity is unlikely. Furthermore, there is little clinical evidence supporting allergic cross-reactivity, and several case studies have found them safe in patients allergic to sulfonamide antibiotics. The authors report the successful treatment of 3 patients with a reported sulfonamide allergy who had channelopathies meriting treatment with acetazolamide.

When treating patients with idiopathic intracranial hypertension (IIH), we are often limited when the patient has an allergy to sulfonamides. It usually restricts many of us from using acetazolamide, methazolamide, topiramate, and most diuretics. This report of 3 patients without allergic reaction to acetazolamide despite history of allergic skin reactions to sulfonamide antibiotics is encouraging.

The article reviews the literature and suggests that the reactions to the antibiotics may be specific to their structure as sulfonylarylamines and may not predict allergy to the carbonic anhydrase inhibitors. I will be more comfortable carefully trying acetazolamide in the future for IIH based on this and other reports.

—Mark L. Moster, MD

About a decade ago, Strom et al (1) reported that patients with sulfa antibiotic allergy experienced more allergic reactions to sulfa diuretics than controls without an allergy. However, the sulfa antibiotic allergic individuals were also more likely to be allergic to other medications as well. This suggests that patients with allergy to one medication (e.g., sulfa antibiotic) are more apt to have an allergy to any other medication. Therefore, I tell IIH patients with a sulfa antibiotic allergy that they are at higher risk of developing an allergy to sulfa diuretics, but it does not represent cross-reactivity. It is because they are just “more allergic” than patients with no known drug allergies.

—Michael S. Lee, MD

It is with great sadness to note the passing of John O. Susac, MD. He was a mentor and friend who passed away on February 23, 2012, at age 71, due to complications from lung cancer. He was several days shy of his 72nd birthday and never smoked.

John graduated valedictorian of Powhatan Point High School in Ohio and married his high school sweetheart, Lois. He earned academic scholarships to Ohio State University’s undergraduate and medical school programs and graduated cum laude from both. John also earned membership in the Phi Beta Kappa Society and was named to the Land Acre Medical Honor Society at the Ohio State Medical School. After graduating from medical school, he entered the Army, completing his internship and residency at Letterman Army Medical Center in San Francisco and spent time with William F. Hoyt at the University of California, San Francisco. He was Chief of Neurology at William Beaumont General Hospital in El Paso, Texas, and he completed a neuro-ophthalmology fellowship at the University of Miami, Bascom Palmer Eye Institute, with J. Lawton Smith. He was then appointed as Assistant Chief of Neurology and Neuro-Ophthalmology at Walter Reed Army Medical Center in Washington, DC, and served as Associate Professor of Neurology with Uniformed Services University of Health Sciences. During his career in the Army, he rose to the rank of Colonel. In 1978, John decided to forgo an academic university practice and joined Neurology and Neurosurgery Associates in Winter Haven, Florida. It was from this office that he conducted all of his future scholarly works.

In 1975, John saw a young woman with a previously unreported clinical triad of encephalopathy, branch retinal artery occlusions, and deafness. This patient was presented to him at a conference in Albany, New York. Shortly thereafter, John Selhorst referred a 40-year-old woman with an identical set of clinical findings. They published these cases in 1979 as microangiopathy of the brain and retina and since then there have been many additional patients reported.

In 1986, John presented a 26-year-old woman with this syndrome at the San Francisco Neuro-Ophthalmological Symposium, held in honor of William F. Hoyt. John relayed Dr. Hoyt’s response as “Well, this is just another case of Susac’s syndrome!” Robert Daroff, then Editor-in-Chief of Neurology, asked John to write a brief review for neurologists using the eponymous moniker, Susac syndrome. John often told me that his phone would ring at least once a week with a newly diagnosed case somewhere around the world from physicians asking for advice. He created the designation “Gass plaques” in honor of J. Donald Gass, MD, for the pseudoemboli found in the retinal arterioles of his patients with the syndrome. He also clarified the magnetic resonance imaging findings of this disorder.

John was passionate about the syndrome that he described and educated others about it. I remember clearly the day that he called me up and exclaimed “Let’s take the show on the road!” This led to international lectures in Portugal and Spain and he was instrumental for organizing a conference on his syndrome at Ohio State University. He had a tie designed with a large number of corpus callosums on them and of course the callosum had the distinctive “holes” that are found so commonly in the condition. The tie colors were of his alma mater and he would pass these out to people who had diagnosed cases of his syndrome.

John is survived by his wife, 2 daughters, 2 sons, 4 grandchildren, 1 brother, and 2 sisters. I believe that he will be best remembered for his brilliance, humility, and exuberance about life. Simmons Lessell once said, “He is a brilliant man,” and followed it by saying, “He hides it well.” Those who knew John understood his low-key manner. However, I will never forget an incident showing a more fiery side of his personality when he was being introduced to a gathering in Portugal. He walked around the partition, opened up his coat, and exclaimed “Heeeeeeeeeeeeere’s Johnny!” He will be sorely missed.

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Relief of Refractory Photo-Oculodynia With Botulinum Toxin

We read with great interest the recent comprehensive review of photophobia by Digre and Brennan (1). The complex underlying mechanisms continue to be elucidated and treatment can be challenging. We have treated a patient with refractory photo-oculodynia and her case exemplifies these challenges.

A 40-year-old woman lost left facial nerve function as a result of surgery for a vestibular schwannoma. She was assessed in the third postoperative week and found to have severe corneal epitheliopathy from exposure. A lateral tarsal pillar tarsorrhaphy was performed leading to improvement in the corneal appearance, but light sensitivity persisted. Over the next 6 months, sensitivity to light increased and the eye was increasingly painful. She was using hourly Lacrilube (Allergan, Inc) and patching overnight. Her anterior chamber was quiet and the cornea showed only a few punctate erosions. A medial tarsal pillar tarsorrhaphy was added, which improved her pain initially, but did not affect her light sensitivity. She began wearing dark glasses at all times, and FL41 filter was added 3 months later. She wore a baseball cap when outdoors. The patient described a constant aching pain that varied in intensity as well as distinct, intermittent sharp lancinating pains induced by light. At this point, her cornea did not show a single area of epithelial disruption. Patching improved her comfort level, so daily she would patch her eye closed at 6 pm.

Over the following 2 years, numerous lubricating agents, oral medications, including gabapentin, pregabalin, carbamazepine, and oxycodone, as well as acupuncture were tried without success. Botulinum toxin (58 units) was then injected subcutaneously over the frontalis, corrugator, procerus, lateral canthus, and temple. Her refractory symptoms responded to these injections with an improvement in both light sensitivity and pain that lasted 8 weeks. She has received further injections and continues to respond to the same dose.

Photo-oculodynia syndrome was first described by Fine and Digre in 1995 (2) to differentiate a category of idiopathic chronic eye pain accompanied by exquisite light hypersensitivity without signs of ocular inflammation. A history of ocular trauma, which may be minor, usually precedes the symptoms (2,3). Topical anesthesia and cyclopia provide no relief (3). Fine and Digre (2) showed improvement with cervical sympathetic ganglion block in 6 patients with chronic symptoms, supporting the classification of photo-oculodynia as a sympathetically mediated pain syndrome. Shoari and Katz (3) used botulinum toxin in 2 patients with photo-oculodynia syndrome with good results. Botulinum toxin has now been shown to be effective in 3 patients with refractory photo-oculodynia. Although the evidence is limited, we would advocate for a controlled trial of botulinum toxin in patients with photo-oculodynia.

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REFERENCES

A “Second Career”

In November 2011, Riri Sylvia Manor, MD, was awarded the Safran Medal (Fig. 1) and Prize for her resourceful efforts in bringing Romanian and Israeli cultural ties closer together. The award was given to Dr. Manor for her translation into Hebrew of a remarkable collection of poems by outstanding Romanian poets in the publication Moznaim.

Dr. Manor was born in Romania and, as a child during World War II, she frequently heard her parents speak of the Chief Rabbi of Romania, Dr. Alexandru Safran, and his remarkable efforts with the royal family to convince the authorities to spare the lives of hundreds of thousands of Romanian Jews.

After completion of medical school in Bucharest, Romania, and ophthalmology training in Israel, Dr. Manor completed a fellowship with William Hoyt, MD, in San Francisco, California. Returning to the Sackler School of Medicine in Tel Aviv, she established the first Neuro-Ophthalmology Unit in Israel at the Beilinson Hospital. In addition, she founded the Israeli Neuro-Ophthalmology Society, and throughout her career, she has made significant contributions to the neuro-ophthalmic literature.

But Dr. Manor also has a passion for poetry, and she continued to nurture this “second career” as well. Her writings became widely published, and one poem, “In Vain I Am a Doctor,” appeared in the Journal of Clinical Neuro-Ophthalmology in 1993.

With the rise of Communism in Eastern Europe, Rabbi Safran was forced to flee Romania in 1947 with his wife and 2 children. He became the Chief Rabbi of Geneva until his death in 2006. His son, Avinoam Safran, completed his medical school and ophthalmology training in Geneva, followed by a fellowship in neuro-ophthalmology with Joel Glaser, MD, in Miami, Florida. He ultimately became Chair of the Department of Ophthalmology at the University of Geneva School of Medicine.

And so Dr. Manor’s “second career” as a poet, and her achievements recognized with the Safran Medal and Prize, is significant on many levels. Her very survival was to a large extent the result of the humanitarian efforts of Rabbi Safran, and the medical career she pursued is one in which Rabbi Safran’s son excels. The Manor–Safran legacy is now linked in perpetuity.

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The First European Neuro-Ophthalmology Society (EUNOS) Update Course was hosted in Budapest by the Hungarian Ophthalmology Society and the Hungarian Society of Neurologists and Psychiatrists (http://eunosweb.org/HomeTop/UpdateMeetings.aspx). This was the first such course organized by EUNOS and was extremely successful, attracting 212 attendees from 32 countries. It was accredited by the European Accreditation Council for Continuing Medical Education and by the European Board of Ophthalmology.

Update Course President Gabriella Szatmáry and EUNOS President Christopher Kennard convened the meeting. Opening lectures dealt with the examination of the afferent, efferent, and autonomic visual systems and were given by Klara Landau, Caroline Tilikete, and Fion Bremner, respectively. Additional presentations included those by Marko Hawlina (Slovenia) on multimodal imaging of the eye and ischemic optic neuropathies and Shlomo Dotan (Israel) on idiopathic intracranial hypertension and compressive optic neuropathies. The second day included lectures on a variety of topics including neuro-ophthalmic emergencies by members of the Hungarian ophthalmology and neurology community. This was followed by a session on “Future Directions in Neuro-Ophthalmology” moderated by Christopher Kennard. The closing session focused on state-of-the-art diagnostic tests in neuro-ophthalmology. The prize for best poster went to Rita Rosa (Portugal).

In addition to the scientific program, there was a scenic tour of Budapest and a gala dinner held at one of the premier wineries in the region. At this dinner, Dr Katalin Korányi (Hungary) commemorated Prof László Remenár. Professor Remenár (1917–1998), an ophthalmologist with a special interest in neurological disorders and the “founding father” of Hungarian neuro-ophthalmology, established Hungary’s first ophthalmo-neurology department at The National Institute of Neurosurgery in Budapest (1953), which is now The National Institute of Neurosciences.

We hope to have more update courses in neuro-ophthalmology in the future. The next EUNOS meeting will take place in Oxford, England, April 10–13, 2013.

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The International Neuro-Ophthalmology Society (INOS) held its 19th meeting at the Grand Copthorne Waterfront Hotel, Singapore, on June 15–18, 2012. The meeting was held in conjunction with the 28th Singapore-Malaysia Joint Meeting in Ophthalmology. More than 400 people from 32 countries attended this truly international meeting that was organized by Kong Yong Goh, MBBS, FRCOphth, from the Tan Tock Seng Hospital, Singapore and Sharon Tow, MBBS, FRCS, from the Singapore National Eye Centre (Fig. 1).

The meeting began with a day of instruction courses delivered by 12 speakers from 6 countries. Agnes Wong, MD, PhD, presented “An Approach to the Patient With Nystagmus,” and this was followed by a symposium on unexplained visual loss organized by Graham Holder, MSc, PhD, and Neil Miller, MD. Walter Jay, MD, led a session entitled “Getting Your Manuscript Published.” Next was an interactive symposium on “The Patient With Transient Visual Loss,” chaired by Helen Danesh-Meyer, MD and Peter Savino, MD. A final course on “Dangerous Diplopia” was delivered by 7 speakers, chaired by Anthony Arnold, MD. Delegates were treated to a welcome reception that involved a trip by water taxi down the river from the conference hotel to the IndoChine restaurant at the Asian Civilisations Museum.

A plenary session began the formal part of the meeting the next day. Tien Yin Wong, MBBS, PhD, MPH, from the Singapore Eye Research Unit delivered the first lecture entitled “Can a Retinal Examination Provide Clues to a Person’s Risk of Stroke?” and this was followed by a lecture entitled “Differentiating Glaucoma from Non-glaucomatous Optic Neuropathies” delivered by Helen Danesh-Meyer, MD, from the University of Auckland, New Zealand.

On the second day of the meeting, Neil Miller, MD, delivered the third invited Singapore College of Ophthalmologists’ lecture entitled “Vascular Diseases in Neuro-Ophthalmology.” The rest of the meeting consisted of symposia on afferent neuro-ophthalmology, efferent neuro-ophthalmology, the pupil, systemic disease, diagnostic tests, pediatric neuro-ophthalmology, and visual restoration therapy. In all, 26 speakers delivered invited lectures and another 10 delivered free papers.

In addition, 131 posters were presented by authors from 21 countries. The prize for the best poster was awarded to S.P. Huang, MD (Taiwan) for “The Molecular Mechanism of Cytotoxic Effects of Ethambutol on Retinal Ganglion Cells,” and the prize for the best oral presentation was awarded to J.F. Cullen, MD (Singapore) for a talk entitled “Ischaemic optic neuropathy in South-East Asia: A different pattern of disease: 10 years’ observation.” Four runner-up prizes were awarded to T. Maekubo, MD (Japan), C. Yu-Wai-Man, MBBS (United Kingdom), M. Robert, MD, PhD (United Kingdom/France), and C.K.M. Chan, MBChir (Hong Kong).

INOS was an excellent meeting in all respects. In addition to being truly international, both scientific and educational standards of the meeting were extremely high and the hospitality extended to all attendees was outstanding. Kong Yong Goh and Sharon Tow can be extremely proud of their achievement.

The future of INOS was discussed by the International Organizing Committee. INOS was formed almost 40 years ago by a group of clinicians eager to disseminate neuro-ophthalmic...
knowledge and forge international links. Over the years, it has fulfilled these aims extremely well. However, the society does not have a formal structure and the meetings have been organized by the goodwill and hard work of our colleagues. This was felt to be unsustainable and there was much discussion about the future role of the society. At this point, there are no specific plans to hold another INOS meeting. There are currently a number of neuro-ophthalmology meetings held around the world such as North American Neuro-Ophthalmology Society (NANOS), European Neuro-Ophthalmology Society (EUNOS), and Asian Neuro-Ophthalmology Society (ASNOS), all of which have a strong international attendance. The committee will continue to review the potential role of INOS.

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Idiopathic Intracranial Hypertension

James Corbett, MD

In the past 18 years, the *Journal of Neuro-Ophthalmology* has published 83 articles that directly or indirectly deal with the clinical problem of idiopathic intracranial hypertension (IIH). In addition to individual case reports, small groups of patients, and reports of psychophysical tests, there is a superb review of unresolved “vexing” issues regarding papilledema (1), a discussion of disease definition and nomenclature (2), and 2 commentaries on surgical treatment of IIH (3,4). Various causes of visual loss are described, including subretinal hemorrhage (5,6), choroidal infarction (7,8), following liposuction (9), induced hyperopia and choroidal folds (10), and as a complication of hind brain herniation after lumboperitoneal shunt with resulting cortical blindness and simultanagnosia (11). Reports of progressive visual loss after optic nerve sheath fenestration (12–14), visual loss without papilledema (15) and IIH without papilledema (16,17) all deal with rare problems that may present to the neuro-ophthalmologist.

The clinical issue of “normal pressure IIH” (18,19) brings up a major diagnostic problem that faces the clinician who cares for these patients; there is no noninvasive way to measure cerebrospinal fluid (CSF) pressure longitudinally. In other words, were the “normal” pressures simply sampling error? The current intraventricular (20), intraparenchymal (21) or lumbar drain CSF pressure measurements are used only briefly in dire circumstances that surround severe visual loss and urgent surgical decision making. These invasive techniques are limited to answering surgical questions and cannot be routinely used to answer questions such as how high and how continuously high are the CSF pressure. While neuroimaging abnormalities detected with magnetic resonance imaging, magnetic resonance venography, and computed tomography are highly suggestive of IIH (22–24), these changes can also be seen in patients with cerebral venous sinus thrombosis (25). Orbital ultrasonic measurement of the optic nerve sheath is a relatively insensitive noninvasive technique indicating whether the CSF pressure is elevated (sheath dilated) or not (sheath not dilated), but cannot quantitate the level of intracranial pressure (ICP).

Two articles elucidated the relationship between IIH and obstructive sleep apnea (OSA) (26,27), and suggested that OSA is not a major risk factor for visual loss (27). Severity of visual loss in patients with IIH is unrelated to obesity (28) and it appears that severe obesity, by itself, does not predispose to a high incidence of papilledema (29).

A series of studies on vitamin A and case reports (30–33), as well as an authoritative review of vitamin A metabolism, and its potential relationship to obesity, vitamin A storage, and carrier proteins in CSF and serum (34), all provide tantalizing clues relating IIH to vitamin A and its congeners. More work needs to be done to see whether there is a causal relationship between vitamin A metabolism and IIH.

Epidemiologic and familial incidence studies (35,36) and a comparison of IIH in Israeli men and women (37) were reported. There were no clear differences between the Israeli IIH incidence study and earlier studies (36). In the male and female comparisons, women were statistically more likely to be obese than men. A report of “late-onset” IIH (patients were older than 45 years) found 5 of 14 were men (64% of the total), were obese, and a third were asymptomatic (38). Unfortunately this report was a mixture of symptomatic cases (4 of 14 patients had some identifiable cause of IIH) and idiopathic cases, which will make it difficult to compare their results with other studies of older patients. This report suggests that older patients are more likely to have an identifiable cause of increased ICP.

A multitude of unusual causes of “IIH-like” conditions are reported, and such reports emphasize the need to be compulsive using the modified Dandy Criteria to make the correct diagnosis of IIH.

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The author reports no conflicts of interest.

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The yearly reviews of IIH-related articles collected and summarized from other journals are worth reading (39–42). Many questions that are asked about the CSF pressure in IIH cannot be answered. What happens to the CSF pressure with change in posture, during ambulation, in recumbency, during Valsalva maneuvers, and what is the effect of various medications, when vision changes and pulsatile tinnitus occurs? All these questions could be answered with a noninvasive method to measure CSF pressure. IIH is a quintessential neuro-ophthalmologic problem waiting to be solved. It will take concerted planning and technical expertise to develop a noninvasive pressure monitoring device. New and not so new medications need to be studied to investigate their effectiveness. Drugs such as topiramate, octreotide, omeprazole, and others that have been used deserve to be studied. Continuous CSF pressure measurement would permit one to calculate CSF production rates as well as resistance to absorption and correlate the effects of sleep and exercise on CSF pressure. More work on the basic science of CSF production, absorption, and testing of the lymphatic drainage hypothesis may eventually allow us to understand the pathophysiology of IIH.

In 2009, a multicenter, double-blind, randomized placebo-controlled study (funded by National Institutes of Health) of the effect of weight and/or low sodium diet plus acetazolamide versus diet plus placebo in subjects with idiopathic IIH and mild visual loss was begun under the direction of Michael Wall and Mark Kupersmith (Neuro-Ophthalmology Research Disease Investigator Consortium). A group of 45 American and Canadian centers is recruiting 154 patients and an equal number of controls. The primary objective of the study is to determine the efficacy of weight reduction plus acetazolamide as compared with weight reduction and placebo in reducing or reversing visual loss. The secondary objectives are a genetic analysis (carried out by Edwin Stone, MD, PhD, at the University of Iowa Ophthalmology Laboratories) of subjects and controls for single-nucleotide polymorphisms within genes that encode molecules likely to be involved in the etiology of IIH. Vitamin A and other potential factors possibly related to the metabolism of IIH subjects will be studied by Bill Blamer, PhD, and Jennifer Libien, PhD, at NYU. Fundus photography is being studied by Steve Feldon at the University of Rochester, and the visual field scoring is being carried out under John Keltner’s watchful eye at UC Davis. Hormone levels related to gender and obesity will be studied using the results of the genetic testing. Carefully designed and carried out, this study holds the promise of producing some important answers to questions of the effectiveness of current standard treatment with acetazolamide and/or diet alone in the control of this condition. In addition, it is hoped that there will be new insights into the role of obesity and gender in the etiology and pathogenesis of this strange condition. Of particular interest will be the results of the dietary treatment as carried out by Dr. Xavier Pt-Sunyer, under the aegis of the New York Obesity Research Center.

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