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The Modern Pathologist: Lab Data Deliverer, Interpreter, and Diagnostician

Daniel J. Brat, MD, PhD

A well known jab directed at the pathologist’s role in patient management goes something like this: “the pathologist knows all of the answers regarding a patient’s disease with absolute certitude… it’s just a day too late!” Although this always gets a chuckle from clinicians, it has always seemed a bit dated and is also focused on only a small sliver of the pathologist’s place in today’s health care environment. Certainly, the pathologist remains responsible for hospital-based and forensic autopsies, which still have critical functions in hospital quality practice, education, and the medico-legal arena. The larger role of the modern pathologist, however, is within the laboratory setting, providing expertise and testing of patient biospecimens, either by establishing a pathological diagnosis directly or by providing laboratory data and consultation that assists in patient management.

Most clinicians would agree that a definitive and accurate diagnosis is critical to proper patient care, as it represents a decision node and inflection point between patient presentation and the treatment plan. For this purpose, clinicians will frequently rely heavily on results from anatomic and clinical laboratory-based tests, performed under the watchful eye of pathologists. Just as the bank robber Willie Sutton quipped that he robbed banks because that is where the money was, most pathologist were attracted to their diagnostic discipline because that is where the data are. It has been estimated that laboratory results account for 70%–90% of data within a patient’s electronic medical record. It has also been suggested that nearly 70% of all medical decisions depend on results from laboratory tests. The current issue of the Journal of Neuro-Ophthalmology includes a number of articles that highlight the importance of the pathologist in clinical practice, demonstrating their role in establishing a tissue-based diagnosis, providing laboratory test results that aid in patient management, and establishing an infrastructure for clinically relevant research that advances our understanding and treatment of disease.

The report by Traynis et al (1) shows the importance of a surgical neuropathologist in establishing the diagnosis of a cerebral hemispheric lesion that extended to involve the optic chiasm and nerve of an 18-year-old man. Magnetic resonance imaging (MRI) showed widespread bilateral bright lesions on T2 images that did not enhance, consistent with an infiltrative disease process. Definitive therapy required a tissue-based diagnosis because treatment of those lesions within the differential diagnosis varies considerably. The biopsy revealed the features of an anaplastic astrocytoma, WHO grade III, with a pattern of brain involvement on MRI consistent with gliomatosis cerebri. The histological section displayed neoplastic cells with astrocytic differentiation invading individually through the brain neuropil. The presence of mitoses and the lack of features associated with a higher grade (necrosis or vascular hyperplasia) led to the diagnosis rendered. Further laboratory testing for purposes of patient prognosis include assessment of isocitrate dehydrogenase 1 (IDH1) mutational status and a MIB-1 proliferation index. With the diagnosis established, the multidisciplinary team had a solid framework from which to initiate the next stage of patient care, which included neurosurgical resection, radiation therapy, and chemotherapy. This case points out a source of quiet pride among anatomic pathologists: most clinicians believe themselves to be credible, or even expert radiologists in their area of expertise, capable of interpreting MRIs and other imaging studies. However, most clinicians do not have similar confidence or skills in the more esoteric realm of pathological diagnosis and rely on their pathology colleagues to interpret histological findings within biopsied material.

The series of 3 patients reported by Parker et al (2) demonstrates how the pathologist assists with the diagnosis of a rapidly developing neurodegenerative disease involving the visual cortex. All 3 patients
had initial symptoms ranging from a visual field defect to cortical blindness, in combination with significant cognitive decline and psychiatric symptoms. The unifying hallmark of the diseases was the rapid pace of clinical deterioration. To establish a presumptive diagnosis of Heidenhain variant of Creutzfeldt-Jakob disease (HvCJD), the authors used the best available diagnostic tools: the clinical exam, diffusion-weighted imaging, electroencephalography, and testing of cerebrospinal fluid (CSF) for the proteins 14-3-3 and neuron-specific enolase (NSE). Although none of these tests is capable of establishing a definitive diagnosis by itself, the cumulative results provided sufficient evidence to make medical decisions based on the expected rapid clinical course of HvCJD. Definitive tissue-based diagnosis during life would require a brain biopsy, a practice that has lost favor for rapidly progressing dementias because of concerns that prions may contaminate surgical instruments. Laboratory results that were helpful included elevated CSF levels of 14-3-3 and NSE, which are shed into the CSF in destructive neurodegenerative diseases and support the diagnosis of HvCJD. Patients with HvCJD unfortunately die within a very short time frame, as there is no effective treatment. Postmortem examination of tissue sections demonstrated the characteristic severe spongiform encephalopathy extensively involving the brain, whereas Western blotting and immunohistochemistry for the causative prion protein PrPSc confirmed the diagnosis of HvCJD. Postmortem laboratory testing of the PRNP gene may be warranted to determine the presence of a genotype predisposing to disease and also associated with disease progression (homozygosity for the 129M allele). In the United States, most molecular testing, disease tracking, research, and education on prion diseases is being performed by a team of investigators led by neuropathologists at the National Prion Research Center at Case Western Reserve University, a center that has been central to advancing the understanding of the disease, and its variants, genetics, transmission, detection, and clinical course. Thus, these 3 cases of a rare, yet devastating, neurodegenerative disease demonstrate the full range of the pathologist in the clinical labs, in establishing a diagnosis postmortem using ancillary testing, and in research and education.

Tsang et al (3) report a highly unusual case proved to be a diagnostic and patient management challenge. Despite extensive clinical and laboratory work-up, the ultimate underlying pathological insult was not uncovered until postmortem exam, emphasizing the important educational role of the pathologist, not only for the clinicians directly involved with patient management but also for the larger medical community through investigation and publication. The patient was a 29-year-old man who presented with flu-like symptoms, headaches, and retinopathy and was diagnosed with acute multifocal placoid pigment epitheliopathy based on fundoscopy and fluorescein angiography. Disease progression was unusually rapid, leading to new onset seizures and multiple cerebral infarcts within 2 weeks. Because this syndrome can be associated with multiple infectious and autoimmune etiologies including adenovirus, measles, mycobacteria, arthritis, and vasculitis, the clinical labs were extensively used to rule in or rule out specific diseases. Laboratory results were either negative or nonspecific for all infectious agents tested (human immunodeficiency virus, syphilis, toxoplasma, Borrelia, tuberculosis, Cryptococcus, bacteria, and neurotropic viruses) and autoimmune markers (ANCA, rheumatoid factor, angiotensin-converting enzyme, complement, and oligoclonal bands). The patient’s clinical course deteriorated rapidly with multiple cerebral infarcts and brain swelling leading to death within 2 weeks. A postmortem examination of the brain confirmed the neuroimaging findings of multiple cerebral infarctions of variable ages, consistent with a progressively evolving disease process. Sections of leptomeningeal vessels showed a striking giant cell arteritis involving large caliber vessels, establishing the cause of the underlying vasculopathy involving the brain that led to the fatal ischemic events. The precise relation of the vasculitis presented in this case to classic CNS angiitis is not entirely clear because the latter typically shows more transmural inflammation that is destructive of vascular walls. Nonetheless, publication of such reports is critical to the medical community because they inform clinicians of potential pathophysiologic mechanisms underlying specific clinical syndromes, which may influence future patient management.

Granted, the reviews provided here are from the perspective of a pathologist, which almost certainly focus more on laboratory testing, interpretation, and diagnosis. These 3 articles demonstrate the role of the pathologist in patient management, education and research. Establishing accurate tissue-based diagnosis remains the central mission of anatomic pathology, whereas the clinical labs generate important results that guide clinical decisions. Laboratory-based testing will only increase and become more complex with new genomic and proteomic platforms quickly emerging, making the role of pathologists in data delivery and interpretation even more critical.

REFERENCES

The Journal of Neuro-Ophthalmology: Looking Ahead

Lanning B. Kline, MD, Editor-in-Chief

The North American Neuro-Ophthalmology Society (NANOS) Board of Directors has asked, and I have agreed, to serve a second (and final) 4-year term as Editor-in-Chief of the Journal of Neuro-Ophthalmology (JNO). The Journal has experienced significant growth during my first 4-year term. Let me summarize some of the highlights:

- Submissions have increased approximately 40%.
- The time from submission to first decision averages 26 days (under 30 days is very quick in biomedical publishing).
- Forty percent of submissions come from North America and 60% from international contributors.
- Approximately 200 of our colleagues assist with the peer review process each year.
- The time from manuscript acceptance until publication averages 8–10 weeks.
- Our impact factor has increased 60% since 2010 to 1.628, our highest-ever score.

Despite our success, we have added, and plan to continue to add, a variety of improvements to ensure that the JNO publishes material of the highest quality, while providing, simultaneously, an enriched author experience. We have enhanced our online site with podcasts that feature contributing authors and created virtual issues on topics such as nonarteritic anterior ischemic optic neuropathy and idiopathic intracranial hypertension. A section has been created entitled “Worldwide Neuro-Ophthalmology” featuring clinical and educational activities in neuro-ophthalmology that take place internationally. The journal now is available through an iPad app, allowing access to the latest publications in neuro-ophthalmology with a touch of a finger!

I have altered the JNO editorial board somewhat. I am pleased to welcome the following new members: Janet Rucker, Greg Van Stavern, Byron Lam, Patrick Yu-Wai-Man, and Nitza Goldenberg-Cohen. Discussions are underway regarding increasing publication of the journal from quarterly to 6 times per year. In addition, consideration is being given to transition to a fully online journal, with an option for the subscriber to receive the print version as well. We are also considering publishing theme-based supplements, providing an in-depth publication on a specific neuro-ophthalmic disorder or evolving technology.

I am honored to serve as the Editor-in-Chief of the JNO. Any success that we have had rests with the editorial board, our managing editor, Jason Roberts, and, most importantly, members of NANOS and the international neuro-ophthalmic community for submitting high-quality manuscripts. I look forward to your continued support as the future of the JNO never looked brighter!
The Heidenhain Variant of Creutzfeldt-Jakob Disease—A Case Series

Sarah E. Parker, MD, Meena Gujrati, MD, John H. Pula, MD, Sarah N. Zallek, MD, Jorge C. Kattah, MD

Background: To study the neuro-ophthalmologic characteristics of patients with the visual variant of Creutzfeldt-Jakob disease (CJD) predominantly affecting the occipital and parietal lobes, known as the Heidenhain variant (HvCJD). The initial symptoms and findings may overlap with other posterior cerebral degenerative disorders. We reviewed our experience with HvCJD including clinical course and results of neuroimaging, electroencephalography (EEG), and cerebrospinal fluid (CSF) studies. Neuropathological postmortem findings were reviewed when available to confirm the clinical impression.

Methods: Retrospective study of HvCJD patients examined in the past 15 years at a single tertiary referral university hospital. Rapid rate of visual and neurological deterioration and abnormal diffusion-weighted imaging (DWI) were characteristic for HvCJD.

Results: Three patients displayed abnormalities in DWI, EEG, and CSF and had rapid clinical progression, leading to a clinical diagnosis of HvCJD. None underwent diagnostic cerebral biopsy. In 2 patients, the diagnosis of sporadic CJD was confirmed by postmortem neuropathologic, immunohistochemical, and genetic studies.

Conclusions: The gold standard for establishing the diagnosis of HvCJD is based on the characteristic histopathologic findings and molecular confirmation. Concern with potential iatrogenic CJD, related to surgical instrumentation or operating room prion contamination, has limited the availability of confirmatory brain biopsy. Our case series illustrates how the combination of clinical neuroimaging and EEG studies and 14:3:3 protein and other neuronal protein marker levels can lead to the diagnosis of HvCJD. Immuno- histochemical analysis and genetic testing at a specialized prion research center will assist in identifying the sporadic variant and genetic forms of CJD.

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Introduction

Posterior cortical degeneration (PCD) is the final common outcome from myriad etiologies with differing pathophysiologic mechanisms. Although several different histological subtypes have been identified, the essential feature of PCD is neuronal degeneration centered in the occipital, posterior temporal, and parietal lobes. The initial clinical manifestations of PCD suggest topographic localization but do not provide etiologic specificity.

The Heidenhain variant of Creutzfeldt-Jakob disease (HvCJD) is characterized by occipital and posterior parieto-temporal cortex neuronal loss induced by the mutant prion protein PrPSc. HvCJD is one cause of PCD, which is typically difficult to diagnose, rapidly progressive and accounts for approximately one-third of all Creutzfeldt-Jakob disease (CJD) cases (1–9).

METHODS

Three patients with HvCJD evaluated at the University of Illinois between 1998 and 2012 were included in our study. The institutional review board determined that this project did not meet the definition of human subject research according to federal regulations, given that all 3 patients died before the initiation of this retrospective investigation.

Concern about instrument and/or surgical suite contamination as possible sources of iatrogenic CJD (10) obstructed acquisition of a diagnostic brain biopsy at our institution. We pursued alternative diagnostic options. Elevation of the 14:3:3
and other neuronal proteins as a CJD marker could lead to a misdiagnosis of HvCJD in PCD patients with or without associated dementia. We applied diagnostic criteria proposed by Kropp et al (6) that are endorsed by the World Health Organization and the American Academy of Neurology 14:3:3 protein evidence-based guideline (2). These criteria include disease duration less than 2 years and a compatible aggregate of clinical magnetic resonance imaging (MRI), serial electroencephalography (EEG) data, and elevated cerebrospinal fluid (CSF) 14:3:3 and/or other neuronal proteins (2–5).

Postmortem tissue examination with immunohistochemical staining and genetic testing confirmed sporadic CJD in 2 of our patients.

Case Reports

All patients were referred to our Neuro-Ophthalmology Unit with visual disturbances. One patient was transferred from an outside facility with progressive cortical blindness and advanced encephalopathy. The other 2 patients presented at an earlier stage of disease: 1 with an isolated visual field defect and 1 with a visual field defect, dyschromatopsia, and visual hallucinations. These latter 2 patients developed rapid neurological deterioration occurring over the ensuing 4 weeks.

Case 1

A 73-year-old Caucasian cattle farmer with diabetes mellitus, hypertension, and essential tremor noted episodic painless diplopia and blurry vision. He had previously received panretinal photocoagulation for diabetic retinopathy in both eyes. At that time, his symptoms were believed due to the diabetic complications of retinopathy and ocular motor paresis. Three weeks later, he reported “progressive fading vision” and that he “could not talk right.” Computed tomography and MRI of the brain were reported to be normal. Over the next 2 weeks, his visual loss progressed. He could not visually recognize objects or people, although he could recognize them by touch or hearing their voices.

We initially evaluated the patient 2 months after the onset of symptoms. At that time, he could not perform any activities of daily living. His visual acuity could not be assessed. Pupils reacted sluggishly to light and optokinetic response was absent. Ophthalmoscopic examination showed bilateral optic disc pallor and evidence of panretinal photocoagulation. He had no family history of dementia or medical procedures that would have placed him at risk for iatrogenic CJD. During his hospitalization, the patient slept most of the time, with weak arousals, and developed startle myoclonus.

MRI of the brain showed ribbon-like gyriform hyperintensities in the occipital lobes due to restricted diffusion. No abnormalities were noted in the basal ganglia. He had 2 EEGs: the first showed diffuse slowing and intermittent generalized spike and wave complexes. Three days later, a second EEG showed generalized triphasic wave complexes at a 1 Hz frequency (Fig. 1). Laboratory testing showed low serum thiamine and vitamin B12 levels. CSF 14:3:3 and neuron-specific enolase levels were increased. Following an advanced directive, his family elected to withdraw care. Ten weeks after the onset of visual symptoms, he expired. Examination before death in the hospital revealed a mute, akinetic cortically blind patient.

Autopsy performed by the National Prion Disease Pathology Surveillance Center at Case Western Reserve University showed spongiform encephalopathy. Immunoblot revealed abnormal protease-resistant prion protein (PrPSc), known as PrP 27-30, confirming the diagnosis of sporadic CJD. Genetic testing showed homozygosity for methionine in codon 129.

Case 2

A 74-year-old Caucasian woman with chronic bronchitis and bilateral hearing loss secondary to otosclerosis complained of blurred vision and difficulty with balance. Visual acuity was 20/25 in each eye with reduced color vision bilaterally. Pupillary reactions and eye movement were normal, and the fundi were unremarkable. Automated visual field testing demonstrated a left homonymous hemianopia (Fig. 2). Neurological examination including vestibular testing was normal.

EEG showed focal slowing in the right parietal region, and brain MRI revealed increased signal in the cortical gyri of the right tempo-parietal junction. No abnormalities were noted in the cerebellum or basal ganglia.

Two weeks later, neuropsychometric testing showed deficits involving multiple cognitive domains. The patient had short- and long-term memory loss and impairment of orientation, attention, and concentration. She had decreased ability to learn new information, impaired verbal comprehension and arithmetic skills, and decreased left sensory perception. She had bilateral visual field defects, difficulty with left hand-eye coordination, spasm of fixation, and optic ataxia. One week later, she was still able to walk without assistance but progressive difficulty with her vision rendered her unable to get around her home or feed herself without assistance. On examination, she was cortically blind.

Six weeks after initial evaluation, the patient was admitted to hospital because she was unable to care for herself. She was in a mute akinetic state with reactive pupils but without response to visual threat. There was left beat nystagmus in primary gaze alternating with periods of left gaze deviation that could be overcome with head turn (See Supplemental Digital Content, Video, http://links.lww.com/WNO/A73).

A few days later, she developed startle and spontaneous myoclonus. EEG showed 1-Hz periodic sharp wave discharges preceding the myoclonus, characteristic of CJD. MRI revealed right temporo-parietal gyriform hyperintensity on T2 and fluid-attenuated inversion recovery image (FLAIR) sequences, CSF demonstrated elevated protein of 75 mg/dL (normal: 35–45 mg/dL) but no other abnormalities. The 14:3:3 protein was not tested. She was discharged home with hospice care and died about 12 weeks after the onset of her first visual symptoms. An autopsy was not performed.
Case 3
A 77-year-old Caucasian woman, retired surgical nurse, with hypertension, diabetes mellitus, congestive heart failure, atrial fibrillation, ulcerative colitis, and osteoporosis reported a 2-week history of multicolored visual hallucinations and intermittent distortion of images. Visual acuity was 20/60, right eye, and 20/100, left eye. Pupils reacted normally to light and accommodation. She could not read the Ishihara color plates but was able to name individual colors. A right homonymous hemianopia was detected by confrontation technique but the patient could not perform formal visual field testing. Ophthalmoscopic and biomicroscopic examinations were normal.

There was diffuse slowing of background activity on EEG and a visual evoked potential testing showed prolonged P100 latencies. There was an area of increased gyriform signal in the left striate cortex on brain MRI without abnormalities in the basal ganglia or cerebellum (Fig. 3). Single-photon emission computed tomography (SPECT) scan showed decreased perfusion in the left posterior parietal-occipital region.

Within 2 weeks of presentation, the patient developed visual agnosia, prosopagnosia, impaired short-term memory, speech problems, confusion, and mild right-sided clumsiness. On admission, the Folstein Mini Mental Status Examination score was 4/30 (normal: 30/30). She was still able to recite the Lord’s Prayer with no mistakes. She had a 2-fold increase in CSF 14:3:3, and neuronal-specific enolase level was also increased (82.5 ng/mL; normal: <35 ng/mL). A follow-up examination 7 weeks after initial presentation demonstrated startle myoclonus. She was unresponsive but arousable and had a right hemiparesis and right Babinski sign. She died approximately 8 weeks after the onset of her visual symptoms.

Autopsy showed spongiform encephalopathy, neuronal loss, and gliosis, affecting primarily the occipital cortex and cerebellum (Fig. 4). These findings were consistent with the diagnosis of CJD. Western blot prion (PrP) gene and immunohistochemical examination of the brain confirmed the diagnosis of sporadic CJD with homozygosity for methionine in codon 129. Given her occupation history as a surgical nurse for 50 years, there was an investigation into the possibility of an iatrogenic mechanism, but no exposure link to a CJD source was identified.
DISCUSSION

In 1998, Benson et al (11) described PCD as an unusual neurodegenerative disorder involving the posterior parietal and occipital lobes. Neuropathologic findings in PCD include senile plaques and neurofibrillary tangles, typical for Alzheimer disease in the majority of cases (7–9). Less frequently, subcortical gliosis as a variant of Pick disease and spongiform changes, neuronal loss and gliosis due to prion infection were reported (9). However, epidemiologic data are lacking. Clinical findings in PCD and HvCJD include combinations of visual field defects, cortical blindness, dyschromatopsia, visual agnosia, alexia, prosopagnosia, palinopsia, optical anosognosia, Balint and Gersmann syndrome (12–16).

Between 1998 and 2012, we evaluated 10 patients with PCD; 3 had sporadic HvCJD who were followed until their death. We are uncertain about the etiology in the remaining 7 patients who developed either a slowly progressive...
dementia (evolving over several years) and are still alive or were lost to follow-up.

The largest published series of the HvCJD included 34 pathologically confirmed cases over a 51-month period (6). This study from the University of Göttingen in Germany is the geographic base of the “German National Creutzfeldt-Jakob Disease Surveillance Study.” Clinical findings were available in 25 cases and consisted of a combination of visual loss and higher visual deficits as found in previous studies. The rate of neurological deterioration was faster in the HvCJD group compared with other CJD variants and did not correlate with location or extent of neuropathologic findings. Homozygosis for methionine in codon 129, identified in 2 of our patients, was noted as a possible genetic indicator of an aggressive clinical course.

We evaluated our patients by applying the diagnostic criteria used by Kropp et al (6) and endorsed by the World Health Organization (Table 1). Neuroimaging findings showed subtle increased intensity in the parieto-occipital region on T2 and FLAIR images only in case 2. Yet all 3 patients had striking visual deficits on examination. Therefore, HvCJD should be considered in any patient with visual field loss and a normal MRI or when imaging abnormalities fail to explain the clinical findings (15). Our imaging protocol included diffusion-weighted imaging (DWI) sequences (12,16). Restricted diffusion involving the gyri of the parieto-occipital cortex was observed in 2 of our cases (Fig. 3). The third patient (Case 2) was evaluated before the incorporation of DWI sequences in the MRI protocol at our institution. DWI was the most helpful ancillary test supporting the diagnosis of HvCJD, and to our knowledge, other PCD variants usually are not associated with DWI changes.

Initial EEG results showed nonspecific focal or generalized slowing, but follow-up EEG showed periodic sharp waves (Fig. 2) characteristic of CJD in later stages, correlating with the presence of myoclonus. SPECT scanning confirmed occipital hypoperfusion in one of our cases and should be part of PCD evaluation. SPECT largely has been replaced by PET that demonstrates focal cerebral hypometabolism in PCD (13,17).

An important characteristic observation suggesting HvCJD in our patients was rapid clinical deterioration. The initial HvCJD diagnosis in Case 1 was supported by progressive neurological deterioration over 10 weeks after the onset of visual symptoms. Our other 2 patients were evaluated at an earlier stage of disease and were scheduled for additional testing over several days. Both patients failed to keep their 2-week follow-up appointments, and contact with their families revealed that they experienced rapid neurological deterioration with inability to perform activities of daily living. This prompted us to perform house calls to complete neurological evaluation and discussion with the family.

Markers of massive neuronal loss (14:3:3 protein and neuronal-specific enolase) were elevated in 2 of our cases. These markers are deemed highly specific and sensitive (1). Their value must be interpreted with caution in individual cases, as increased neuronal protein levels (false positives) may be found in other rapidly progressive dementias and potential PCD mimics including autoimmune and paraneoplastic encephalitis, nonconvulsive status epilepticus, intraocular lymphoma, and vasculitis (2,5).

Although characteristic histopathology of CJD remains the gold standard in establishing the diagnosis, the risk of instrument or surgical suite prion contamination during brain biopsy has limited the availability of brain biopsy (10). Until a specific serum or CSF prion marker is available, the premortem diagnosis of HvCJD in a patient with PCD continues to rely on close clinical monitoring, neuroimaging testing, serial EEG, and elevated CSF markers (18,19). We

### TABLE 1. Diagnostic criteria for Heidenhain variant of Creutzfeldt-Jakob disease

<table>
<thead>
<tr>
<th>Definite</th>
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<tbody>
<tr>
<td>Pathologic evidence of spongiform degeneration, gliosis, neuronal loss in posterior, temporal, parietal, and occipital lobes</td>
</tr>
<tr>
<td>Probable</td>
</tr>
<tr>
<td>Visual impairment: blurred vision, visual field defect, cortical blindness</td>
</tr>
<tr>
<td>Rapidly progressive dementia (&lt;2 years)</td>
</tr>
<tr>
<td>Myoclonus</td>
</tr>
<tr>
<td>Cerebellar, pyramidal, or extrapyramidal tract signs</td>
</tr>
<tr>
<td>Akinetic mutism</td>
</tr>
<tr>
<td>EEG with periodic sharp wave complexes</td>
</tr>
<tr>
<td>MRI: increased cortical signal in parieto-occipital region (DWI)</td>
</tr>
<tr>
<td>Elevation of neuronal destruction markers in CSF</td>
</tr>
<tr>
<td>Possible</td>
</tr>
<tr>
<td>Same criteria as “probable” without EEG findings</td>
</tr>
</tbody>
</table>

Adapted from Kropp et al. (6)

EEG, electroencephalogram; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; CSF, cerebrospinal fluid.
strongly recommend that specimens be sent to the National Prion Research Center at Case Western Reserve University in Cleveland, OH, and similar prion research centers for confirmatory, cerebral histopathology, immunohistochemical staining of abnormal protease-resistant prion protein, and genetic testing. This testing protocol establishes the diagnosis of sporadic, variant, and genetic forms of CJD and hopefully will prevent delay in establishing the correct diagnosis (20).

In vitro, anti-prion agents have been found effective in controlling prion growth and progression. Unfortunately, these agents have failed to cure or slow CJD infection in humans (21–23).

ACKNOWLEDGMENTS

The National Prion Disease Pathology Surveillance Center at Case Western Reserve University, Cleveland, OH, performed histopathologic, genetic, and immunologic studies in 2 of our patients.

REFERENCES

Fatal Ischemic Stroke Complicating Acute Multifocal Placoid Pigment Epitheliopathy: Histopathological Findings

Benjamin K.-T. Tsang, MBBS, BPharm, Devinder S. Chauhan, MBBS, MD, FRCOphth, FRANZCO, Rebecca Haward, MBBS, Ida Whiteman, MBBS, Judith Frayne, MBBS, FRACP, Catriona McLean, BSc, MBBS, FRCPA, MD

Abstract: A previously healthy 29-year-old man was admitted to a tertiary referral center with acute left hemiparesis followed shortly by de novo convulsive status epilepticus. This was in the context of a 2-month history of flu-like symptoms, severe headaches, and retinopathy recently diagnosed as acute multifocal placoid pigment epitheliopathy. Neuroimaging demonstrated bilateral, multiple territory cerebral infarction. Despite intravenous methylprednisolone and craniotomy for the management of raised intracranial pressure, the patient deteriorated and died 14 days later. At autopsy, multiple infarcts of varying ages within a 10-day period were seen in association with a segmental giant cell vasculopathy of meningeal arteries.

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Acute multifocal placoid pigment epitheliopathy (AMPPE) is a chorioretinal disorder characterized by creamy round exudates seen on funduscopy with bilateral involvement in approximately 75% of cases (1–3). Typical lesions are found primarily in the posterior pole at the level of the retinal pigment epithelium (RPE) and choriocapillaris (1,4,5). Symptoms include acute or subacute binocular visual blurring, metamorphopsia, and scotomas (1,6). Fluorescein angiography characteristically shows a pattern of early hypofluorescence and late hyperfluorescence, which is considered to indicate lobular obstruction of the choriocapillaris caused by vascular inflammation (7). Spectral domain optical coherence tomography (SD-OCT; Cirrus, Carl Zeiss Meditec, Dublin, CA) findings in acute AMPPE lesions include elevated perifoveal retinal thickness, hyperreflectance of the outer retinal layers with photoreceptor disorganization and, rarely, intraretinal cysts or loculations (4,8). A retrospective study at the Mayo Clinic estimated the incidence to be 0.15 cases per 100,000 persons per year (3). There is no sex predilection, but AMPPE has a striking preponderance for young adults, with a mean age of onset of 26.5 years (1).

The pathophysiology of AMPPE is not well elucidated, despite being associated with a number of infectious and autoimmune conditions. The primary lesion in AMPPE appears to occur in the small choroidal arterioles whereby choriocapillaris ischemia may induce increased vascular permeability (4). Secondary ischemic changes produce disruption of the RPE, resulting in placoid lesions. Alternate mechanisms include choriocapillaris occlusion, with case reports of association with anticardiolipin antibodies (9). Complaints of a “viral” prodrome with fever, malaise, upper respiratory symptoms, myalgias, or arthralgias have been reported in about 40% of cases (2,6). Associated infectious agents include adenovirus (10), measles (11), and mycobacterium (12). Some patients have developed AMPPE in the context of recent vaccination (13) and antibiotic administration (2). In a small but significant minority of patients, evidence of a systemic vasculitis exists including erythema nodosa (2,9,14). Other systemic autoimmune or collagen vascular diseases associated with AMPPE include sarcoidosis (14,15), psoriatic arthritis (3), perinuclear antinuclear...
cytoplasmic antibody (ANCA)–positive systemic vasculitis (16), and central nervous system (CNS) vasculitis (17).

Neurological involvement associated with AMPPE includes headaches (6,9,18), strokes (6,7,17,19), cerebral venous sinus thrombosis (20), seizures (5,6), and CNS vasculitis (6,17,21). These neurological complications tend to occur early in the clinical course and are usually self-limited (18). We report a case of AMPPE complicated by multiple territory strokes and death with autopsy correlation.

CASE REPORT

A healthy 29-year-old man was referred to a retinal specialist by his local optometrist with a 10-day history of right central vision loss. This was preceded by a 1-month history of flu-like symptoms including fever and night sweats. He had a history of stable asthma but no ophthalmological or neurological disease and a familial history of glaucoma. At presentation, the patient’s visual acuity was 20/80, right eye, and 20/20, left eye. Pupillary responses and intraocular pressure measurements were normal. Slit-lamp examination of both eyes showed 1+ anterior chamber cells and funduscopy showed 1+ vitreous cells and widespread multiple pale subretinal lesions bilaterally (Fig. 1). On fluorescein angiography, there was early blockage of the lesions (Fig. 2A) with late hyperfluorescence (Fig. 2B). Indocyanine green angiography showed persistent hypofluorescence of the lesions (Fig. 3). Figure 4 demonstrates the findings on SD-OCT.

FIG. 1. Funduscopy reveals bilateral multifocal areas of choroiditis with a large number of placoid lesions involving the fovea in the right eye and the parafoveal region in the left eye.

FIG. 2. Fluorescein angiography demonstrates lesion hypofluorescence in the early phase (A) and hyperfluorescence in the late phase (B).
These clinical findings were thought to be typical of bilateral AMPPE and no treatment was prescribed.

One week later, the patient returned complaining of frequent severe bilateral headaches on waking associated with photophobia, phonophobia, and nausea. On funduscopy, the lesions were less active but a small new temporal hemorrhage was noted in the left eye. The patient saw a neurologist 2 weeks later and computed tomography (CT) brain imaging was normal. Five weeks after initial presentation, the patient had visual acuity of 20/25, right eye, and 20/20, left eye, with fewer vitreous cells.

Approximately 3 weeks later, the patient developed sudden onset dizziness and a left hemisensory disturbance, closely followed by acute left hemiparesis and convulsive status epilepticus. He was intubated under general anesthesia and transferred to our institution. On examination, pupil responses were normal, and the patient had extensor responses to peripheral pain and bilaterally sustained clonus in the lower limbs. His reflexes were symmetrically pathologically brisk with extensor plantar responses. Retinal appearance on funduscopy showed no evidence of worsening ocular disease.

Complete blood count showed only mild neutrophilia. Serum biochemistry, inflammatory markers, coagulation profile, and urinalysis were unremarkable. Tests for tuberculosis and serology for HIV, syphilis, toxoplasma, and borrelia were negative. Serum antinuclear antibodies, ANCA, rheumatoid factor, angiotensin-converting enzyme, and complement levels were unremarkable. Lumbar puncture revealed an opening pressure greater than 30 cm H₂O, and cerebrospinal fluid (CSF) revealed a lymphocyte count of 17×10⁶/L (normal, <5×10⁶/L) and a mildly elevated

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**FIG. 3.** Angiography using indocyanine green shows persistent hypofluorescence of the fundus lesions in the early (A) and late (B) phase, indicative of choriocapillaris infarction.

**FIG. 4.** Spectral domain optical coherence tomography (Cirrus, Carl Zeiss) demonstrates the loss of the photoreceptor inner segment/outer segment junction line and increased choroidal signal due to disturbance of the retinal pigment epithelium. A. Right eye. B. Left eye.
protein level of 0.53 g/L (normal, <0.45 g/L) without evidence of oligoclonal bands. Latex agglutination studies for cryptococcus, gram stain, and polymerase chain reaction of neurotropic viruses were negative.

Brain CT and magnetic resonance imaging (MRI) revealed extensive, acute bilateral infarctions in both anterior and posterior circulation (Fig. 5). Computed tomographic angiography and magnetic resonance angiography demonstrated intracranial vessels that were diffusely reduced in caliber without focal irregularities or stenoses. CT venography indicated no filling defects. Transesophageal echocardiography excluded the presence of a vegetation, intracardiac thrombus, or shunt. The patient underwent bilateral decompressive craniectomy for cerebral edema. With attempts to terminate general anesthesia, seizures occurred despite multiple anticonvulsant medications. Interictal electroencephalogram showed diffuse, bilateral, moderate amplitude theta to delta range slowing. The patient was given intravenous methylprednisolone, but his condition deteriorated and died 2 weeks later.

At autopsy, external examination of the circle of Willis showed a normal vascular anatomy with no evidence of atherosclerosis or thrombotic occlusion of major vessels. There was extensive softening and swelling on the external surface of the brain in both the left and right parietal and frontal regions. Focal areas of subarachnoid hemorrhage were noted. On serial cross sectioning, there was extensive softening and loss of the gray white definition in the distribution of the left and right anterior, middle, and posterior cerebral arteries with swelling of the white matter and displacement of cerebral cortex superiorly within the craniectomy site with mass effect (Fig. 6). The ventricles

**FIG. 5.** Multiple axial diffusion-weighted images of the brain show hyperintense areas involving all lobes of both cerebral hemispheres and bilateral cerebellar hemispheres consistent with acute multiterritory infarctions.
appeared compressed. Sectioning through the cerebellum and brainstem were unremarkable.

Microscopic examination of arteries of the meninges revealed partial or total occlusion with a segmental giant cell vasculopathy with focal intimal expansion by reactive myofibroblasts in association with histiocytes and giant cells, some of which were multinucleated (Fig. 7). The giant cells appeared to be predominantly within the intima rather than showing active destruction and association with the internal elastic lamina. The vessel wall did not show fibrinoid necrosis or was there extensive inflammation of the media and adventitia. Intracortical vessels were not involved. Cortical sections showed features of acute infarction of varying ages within a 10-day period.

DISCUSSION

As seen in our patient with AMPPE, stroke usually occurs within months of the onset of ocular disease (6). An estimated 50% of AMPPE patients have headaches with or without neck stiffness (6,18). Possibly, severe headaches are the earliest indication of cerebral inflammation and can predate the onset of more severe neurologic involvement by several weeks to months (6,8,19,21,22).

The topography of reported strokes with minimal sequelae are usually within small to medium vascular territories such as the posterior circulation (7), basal ganglia, caudate nuclei (19), and corpus callosum (19). Extensive and multiple territory strokes resulting in death, as seen in our patient, are rare (5,8,22,23). To judge if a patient is in danger of severe neurologic complications, the severity of the ophthalmological disease has not been a reliable marker (18). In some patients, cerebral vasculitis may cause ischemic complications in the CNS. In these cases, there may be elevated erythrocyte sedimentation rate (22) and CSF pleocytosis (6,17,21). Biopsy of the dura mater has shown lymphocytic infiltrates (18). There have been only 2 previous autopsy reports describing giant cells within the medium-sized arteries of the leptomeninges (5,23). These reports documented fragmentation of the internal elastic lamina and giant cells within the intima “at the level of the internal elastic lamina,” associated with prominent and focal myofibroblastic proliferation (5,23). Inflammation within the media also was noted, along with focal fibrinoid necrosis. The intimal location of the giant cells and the focal intimal myofibroblastic proliferation were seen in our case, but we found the internal elastic lamina to be intact without inflammation of the media or evidence of fibrinoid necrosis. Further cases are required to determine whether the distribution of vessel involvement and pathology of giant cell vasculopathy seen in AMPPE represents a separate type of a giant cell vasculopathy compared with that of giant cell arteritis.

The differential diagnosis of systemic illnesses leading to uveoretinal meningoencephalitis includes Vogt–Koyanagi–Harada disease, sarcoidosis, Behçet disease, systemic lupus erythematosus, Crohn disease, metastatic malignancy, primary intraocular lymphoma, and systemic infection (histoplasmosis, toxoplasmosis, cytomegalovirus, syphilis).

Although management of patients with stroke or cerebral vasculitis associated with AMPPE is a topic of much debate, current treatment usually includes aggressive immunosuppression with steroids or steroid sparing agents (5–7,17,21).
However, strokes (18) and even death (8,22) have been reported during rapid tapering of immunosuppressive therapy.

REFERENCES

Bilateral Optic Nerve Involvement in Immunoglobulin G4–Related Ophthalmic Disease

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Background: To describe a presumptive case of immunoglobulin G4–related ophthalmic disease (IgG4-ROD) with bilateral optic nerve involvement and to review the clinical features of this entity.

Methods: Case report.

Results: A 62-year-old man presented with bilateral blurred vision. He had a history of sinus surgery, and a biopsy specimen showed dense infiltration of IgG4-positive plasma cells. His visual acuity was 20/25, right eye, and 20/125, left eye. Serologies demonstrated elevated serum levels of IgG and IgG4, and computed tomography showed masses surrounding both optic nerves at the orbital apices and bilaterally enlarged infraorbital nerves. The patient underwent 2 cycles of intravenous pulse steroid therapy followed by a taper of oral steroids. Three months later, vision was 20/20 in each eye and, while the serum level of IgG was within normal limits, the IgG4 level remained elevated.

Conclusion: IgG4-ROD may involve the optic nerves resulting in vision loss. Although steroid administration is the primary treatment for this entity, slow tapering is essential to avoid relapse.

CASE REPORT

A 62-year-old man reported a 1-year history of blurred vision in both eyes. Ten months previously he had undergone surgery for maxillary and ethmoidal sinusitis. Histopathological examination of the excised paranasal polyps disclosed infiltration of lymphocytes, plasma cells, and eosinophils (Fig. 1A). Although fibrosis was present, it was not in a storiform pattern with obliterative phlebitis. There was no histopathological evidence of sarcoidosis, Castleman disease, Wegener granulomatosis, or malignancy. Immunostaining for IgG and IgG4 demonstrated intensely stained IgG4-positive plasma cells, with the IgG4/IgG plasma cell ratio >40% and >10 IgG4 plasma cells per high-power field (Fig. 1B). Vision initially improved after surgery but soon worsened again. His medical history was otherwise unremarkable.

At our initial evaluation of the patient, visual acuity was 20/20, right eye, and 20/125, left eye. Pupils reacted normally without a relative afferent pupillary defect. Ocular motility was intact, and Hertel exophthalmometry measurements were 16.5 mm bilaterally (base, 100 mm). Slit-lamp and funduscopic examinations were unremarkable. Kinetic perimetry showed bilaterally enlarged blind spots and pericentral scotomas in the left eye. There was no facial numbness.

Hematological studies revealed elevated serum levels of: IgG 3,550.3 mg/dL (normal: 870.0–1,700.0 mg/dL), IgG4 1,850.0 mg/dL (normal: <135 mg/dL), and IgE 1,400 IU/mL (normal: <170 IU/mL). The IgG4/IgG ratio was 52.1% (normal: <6%). Results of other blood tests that were within normal limits included anti-myeloperoxidase and anti-proteinase 3, antineutrophil cytoplasmic antibodies, rheumatoid factor, angiotensin-converting enzyme, soluble...
interleukin-2 receptor, β2-microglobulin, C-reactive protein, and β-D-glucan. Antinuclear antibody titer was 1:80 (normal: <1:40). Computed tomography demonstrated masses surrounding the optic nerve at the orbital apices (Fig. 2A) and enlarged infraorbital nerves bilaterally (Fig. 2B). There was soft tissue swelling in the maxillary, ethmoidal, and frontal sinuses. The patient underwent 2 cycles of pulse steroid therapy each consisting of 10 mg/kg/d of intravenous methylprednisolone for 3 days. After the first cycle, his vision improved to 20/20 in each eye. Kinetic perimetry was normal after the second cycle of pulse steroids, with a decline in the serum levels of IgG (2071.0 mg/dL) and IgG4 (973 mg/dL).

The patient was treated with 30 mg of oral prednisolone daily for 2 weeks and the dose was gradually reduced by 5 mg every 2 weeks. One month after starting oral medication, there was a significant reduction in the size of the lesions on magnetic resonance imaging (Fig. 3). Three months after completion of steroid therapy, visual function was stable and Hertel exophthalmometry measurements decreased to 13.0 mm, right eye, and 14.0 mm, left eye (base, 100 mm). Serum IgG returned to within normal limits (1,343.1 mg/dL), although IgG4 (382.0 mg/dL) and the IgG4/IgG ratio (28.4%) remained elevated.

**DISCUSSION**

According to the proposed diagnostic criteria, our patient had “possible” IgG4-ROD (4) (Table 1). He had masses at the apex of each orbit with optic nerve involvement and elevated serum level of IgG4. We were unable to biopsy the tumor masses, given their proximity to the optic nerves. However, histopathological findings of the nasal polyps, elevation of serum IgE, involvement of the infraorbital nerves, and improvement of symptoms immediately after steroid administration are supportive of the diagnosis (1,4,6). Histopathological findings of the nasal polyps showed dense infiltration
of IgG4-positive plasma cells and eosinophils with a ratio of IgG4+ cells/IgG+ cells >40% and >10 IgG4+ cells/high-power field. Although fibrosis in a storiform pattern and obliterative phlebitis, which are the major histopathological features of IgG4-related disease, were not demonstrated, these findings occasionally are lacking (9).

Often the functions of the involved orbital structure, such as lacrimal gland, extraocular muscle, or trigeminal nerve, are relatively maintained in cases of IgG4-ROD (1,2,10,11). Yet our patient had optic nerve involvement with severe visual impairment in the left eye. In cases with severe vision loss, IgG4-ROD lesions always involve the orbital apex (8). The optic neuropathy leading to vision impairment may be due to a compressive or inflammatory process or both.

Reports of involvement of a variety of orbital structures have been described in IgG4-ROD with optic nerve involvement. The infraorbital nerves were affected in our patient and other cases as well (2,3). Other reported sites include lacrimal gland (3,7), extraocular muscles, and supraorbital nerve (3). One case showed panorbital inflammation, including the extraocular muscles (8). All reported IgG4-ROD cases with optic nerve involvement affect single or multiple additional orbital structures (2,3,7), which may be a typical feature of IgG4-ROD cases with optic nerve involvement.

Systemic involvement has been described in 3 patients with IgG4-ROD and optic nerve involvement. Lesions were detected in the pancreas and inguinal lymph nodes (7), and salivary gland lesion and skin (3). Our patient had bilateral sinusitis with nasal polyps. This indicates that systemic evaluation is warranted in patients with IgG4-ROD.

Steroid administration is the primary treatment for IgG4-ROD. Yet the optimal dose and length of treatment have yet to be established. Treatment of IgG4-ROD often consists of oral prednisolone at a dose of 30–40 mg/d (12). Pulse steroid therapy followed by oral steroid administration has been used for IgG4-ROD with optic nerve involvement (3,11). Both regimens are initially effective, but recurrence often occurs after short-term administration (1–3). Gradual tapering of steroid treatment is an essential step to avoid relapse. Rituximab has shown promise in the treatment of IgG4-related diseases (13), but there are no reports of its use in IgG4-ROD with optic nerve involvement.

**TABLE 1.** Proposed comprehensive diagnostic criteria for IgG4-related disease

1. Clinical examination reveals characteristic diffuse/localized swelling or masses in single or multiple organs.
2. Hematological examination shows elevated serum IgG4 concentration (>135 mg/dL).
3. Histopathological examination demonstrates:
   (a) Marked lymphocytic and plasmacytic infiltration and fibrosis.
   (b) Infiltration of IgG4+ plasma cells: ratio of IgG4+ cells/IgG4 cells >40% and >10 IgG4+ plasma cells/HPF.

**Definite disease:** 1 + 2 + 3
**Probable disease:** 1 + 3
**Possible disease:** 1 + 2

It is important by histopathological examination differentiating IgG4-related disease of each organ from neoplasm (e.g., carcinoma, lymphoma) and other inflammatory conditions

Modified from Umehara et al (4).
HPF, high-power field.
Modified with permission from Umehara H, Okazaki K, et al. Mod Rheumatol 2012.
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Recovery of Ocular Motor Cranial Nerve Palsy After Herpes Zoster Ophthalmicus

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Objective: To report the course of ocular motor cranial nerve palsy due to herpes zoster.

Methods: A retrospective chart review identified patients with ocular motor cranial nerve palsy occurring at the time of herpes zoster ophthalmicus. Patients were seen by a single neuro-ophthalmologist from 1994 to 2012.

Results: Twenty-one patients were identified; 3 were excluded because of incomplete follow-up. Nine (50%) had complete recovery and 8 (44%) had partial recovery but no diplopia in primary gaze (mean time = 10 weeks). One patient with complete ophthalmoplegia had persistent diplopia in primary position for recovery.

Conclusion: Ophthalmoplegia secondary to herpes zoster ophthalmicus has good long-term prognosis for recovery.

Infection with herpes zoster, commonly known as shingles, is caused by varicella zoster virus (VZV) in individuals who have already been exposed to the virus, either wild type or via vaccination (1). The initial VZV infection usually occurs in childhood, and once it resolves, the virus is not eliminated and remains in the body and can cause zoster later in life. There are reports of at least 1 million cases of herpes zoster annually in the United States (1–5).

Herpes zoster ophthalmicus (HZO) refers to the involvement of the ophthalmic division of the fifth cranial nerve (6). Patients acutely develop a rash that evolves through papular, vesiculobullous, pustular, and crusting stages over days to weeks. The mean time from onset of HZO to ophthalmoplegia was 8.6 days with range 1–15 days. All patients were already on oral antivirals (acyclovir or valacyclovir) at the time of referral. Seven patients were also treated with a short course of oral prednisone.

RESULTS

We found 21 patients of which 3 were excluded because they were only seen on initial visit. The mean age of the patients was 75 years (range: 41–91 years). Mean interval between the onset of HZO and ophthalmoplegia was 8.6 days with range 1–15 days. All patients were already on oral antivirals (acyclovir or valacyclovir) at the time of referral. Seven patients were also treated with a short course of oral prednisone.

The mean time period for follow-up to resolution was 10 weeks (range: 2 weeks to 8 months). Sixth nerve involvement (6 patients) was most common followed by third (5 patients) and fourth (3 patients) nerve palsies. Four patients had multiple ocular motor cranial nerve involvement; third
and sixth in 2 patients, third and fourth in 1 patient, and 1 patient had complete ophthalmoplegia due to involvement of all 3 ocular motor cranial nerves.

Nine patients (50%) recovered completely (Table 1). Eight patients (44%) had incomplete recovery but had resolution of diplopia in primary gaze. The one patient with complete ophthalmoplegia had mild improvement but persistent diplopia in primary gaze for 6 months after which he was lost to follow-up.

**DISCUSSION**

There are reports of ocular motor cranial nerve palsies in 5%–31% of the cases of HZO (6–8). Multiple mechanisms have been postulated for the involvement of ocular motor cranial nerves after HZO. Wyss (9) proposed that thrombophlebitis is responsible for extraocular muscle paresis. Edgerton (10) postulated that contiguous inflammation in the cavernous sinus or the superior orbital fissure from the trigeminal to ocular motor cranial motor nerves is responsible. Kreibig (11) believed the cause to be myositis as well as perineuritis and perivasculitis. Naumann et al (12) evaluated the histopathology of 21 enucleated eyes affected by herpes zoster after HZO and proposed that occlusive vasculitis is responsible for the ocular motor cranial nerve palsy.

In 1948, Edgerton (8) reviewed 40 cases of unilateral ophthalmoplegia in the setting of HZO. He included a number of his own patients, 4 of which had ophthalmoplegia. Three of these 4 patients recovered completely in 2 weeks to 12 months. Archambault et al (13) described 6 cases of ophthalmoplegia after HZO. The third nerve was involved in 4 patients, fourth nerve in 5, and sixth nerve in 3 cases. Five patients (83%) recovered from diplopia over 3 weeks to 12 months. Chang-Godich et al (14) reported 3 cases of complete ophthalmoplegia associated with HZO and reviewed 13 additional cases of complete ophthalmoplegia reported from 1968 to 1997. Recovery was documented in 9 of these patients ranging from 1 to 18 months. Cases of isolated sixth (15–17) and fourth (18) nerve palsies also have been described.

Our series of patients with ophthalmoplegia associated with HZO appears to be the largest from a single institution. Only 1 patient with complete ophthalmoplegia had persistent diplopia in primary gaze at a 6-month follow-up. It is possible that our follow-up duration was too short to witness recovery in this patient because patients reported by Chang-Godich et al (14) required up to 18 months to recover. It is also possible that our patients with incomplete recovery (diplopia in eccentric gaze) could have recovered completely over a longer period of time. Nevertheless, our report shows that patients with ophthalmoplegia after HZO have a good prognosis with almost all recovering from diplopia at least in primary gaze.

**REFERENCES**


Retinal Nerve Fiber Layer Thickness, Brain Atrophy, and Disability in Multiple Sclerosis Patients

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Objective: To study the relationship between retinal nerve fiber layer (RNFL) thickness and brain atrophy using magnetic resonance imaging (MRI) with bicaudate ratio (BCR) in patients with multiple sclerosis (MS) with different levels of disease severity. We also assessed whether RNFL thickness correlated with Expanded Disability Status Scale (EDSS) score.

Methods: The participants consisted of 88 patients with MS and 59 age- and sex-matched healthy control subjects. Eleven patients had clinically isolated syndrome (CIS), 68 patients had relapsing-remitting MS (RR-MS), and 9 patients had secondary progressive MS. Patients and controls were evaluated using optical coherence tomography (OCT, Cirrus) and scanning laser polarimetry with variable corneal compensation (GDx VCC). Patients underwent the same brain MRI scanning protocol. Disability was evaluated according to the EDSS. The BCR was calculated by dividing the minimum intercaudate distance by brain width along the same level.

Results: The BCR was higher in patients with MS (0.12 ± 0.03) than in controls (0.08 ± 0.009) (P < 0.001). OCT average RNFL thickness in patients with MS was significantly lower (84.51 ± 14.27 μm) than in control subjects (98.44 ± 6.83 μm). BCR was correlated with OCT average RNFL thickness (r = −0.48, P = 0.002) in patients with MS without optic neuritis. Significant correlations were found between average RNFL thickness and EDSS (r = −0.43, P = 0.003). Additionally, there were correlations between BCR with GDx parameters in patients with MS without optic neuritis.

Conclusions: This study shows that RNFL thickness correlates with BCR and with MS subtypes. Additionally, our study indicates that OCT is better suited for MS assessment than GDx. We conclude that the damage of retinal axons appears related to brain damage in patients with MS.

MUltiple sclerosis (MS) is a degenerative disorder of the central nervous system characterized by areas of demyelination and axonal injury. Even at early stages, brain atrophy can be detected histopathologically and with magnetic resonance imaging (MRI). Although MS historically has been considered a white matter disease, many studies have demonstrated prominent changes in gray matter as well (1).

The prechiasmal anterior visual pathways provide an attractive model for assessing the relationships between inflammation, demyelination, and neurodegeneration in MS. Axons emanating from retinal ganglion cells first display the morphologic characteristics of nonmyelinated (gray matter) fibers within the retinal nerve fiber layer (RNFL), and then become myelinated within the optic nerve, where they form a white matter tract (2). Several studies have established the presence of RNFL atrophy and reduction in macular thickness in patients with MS (3–6). Optical coherence tomography (OCT) and scanning laser polarimetry are proven techniques to measure RNFL thickness and provide a method to measure visual pathway axonal injury.

MRI is well suited to assess alteration in brain structure, including brain atrophy, in patients with MS (7). Brain
atrophy may occur early in the course of MS and may be associated with disability. The bicaudate ratio (BCR) is a method using MRI for estimating brain atrophy in normal aging (8,9) and in patients with MS (10). The BCR is calculated by dividing the minimum intercaudate distance by brain width along the same level, and reflects subcortical atrophy. It has been shown that BCR is correlated with gray and white matter atrophy in patients with MS (11) and used to monitor progression in patients with MS (12).

The aim of our study was to investigate the relationship between RNFL thickness and brain atrophy in patients with MS using the BCR. We also studied whether RNFL thickness correlated with the Expanded Disability Status Scale (EDSS) (13).

PATIENTS AND METHODS

Patients

This case–control study consisted of 88 patients (62 women and 26 men; mean age 39.19 ± 9.62 years and 39.85 ± 8.00 years, respectively) referred to the Ophthalmology Service from neurology of the Complexo Hospitalario Universitario de Santiago de Compostela between January 2010 and May 2011. The study received approval of the local ethics committee. Eleven patients presented with clinically isolated syndrome (CIS), 68 patients had relapsing-remitting MS (RR-MS), and 9 patients had secondary progressive MS (SP-MS). MS was diagnosed according to Poser criteria (14). For the RR-MS subtype, we further subdivided the patients into benign MS and nonbenign MS. Patients with benign MS had a score on the EDSS of ≥3.0 at least 10 years after the onset of disease (15). A history of optic neuritis (ON) episodes was determined for eyes of patients with MS by self-report and physician report, and was confirmed by medical record review. We included patients with ON, but only if the episode occurred more than 6 months preceding enrollment in this study. A total of 43 patients had a history of ON, which was bilateral in 10 cases and unilateral in 33 cases. Fifty-nine age- and sex-matched healthy controls with no history of ocular or neurological disease were recruited. All had visual acuity of 20/20 in each eye.

Patients with comorbid ocular conditions not related to MS or other causes of optic atrophy, such as glaucoma, ischemic optic neuropathy, or compressive optic neuropathy also were excluded. Patients with acute optic neuritis (within the 6 months before the study) were also excluded. None of the patients with MS had any other major medical illness or pre-existing medical conditions known to be associated with brain pathology.

OCT was performed on both eyes using a Cirrus HD-OCT (Model 4000, Carl Zeiss, Meditec, Inc, Dublin, CA). The RNFL measurements were made using the Optic Disc Cube 200 × 200 protocol (200 horizontal scan lines, each composed of 200 A-scans) to generate a 6-mm square grid. Good-quality OCT scans were defined by a signal strength of 7 or greater (maximum, 10) and uniform brightness across the scan circumference. All scans were carried out by the same technician. The average thickness of the RNFL was used for statistical analysis.

The GDx VCC (Laser Diagnostic Technologies, San Diego, CA) confocal scanning laser ophthalmoscope also was used to determine RNFL thickness. Circular scans (3.2 mm in diameter) centered on the optic disk were obtained. Pupils were dilated when image acquisition was impaired by small pupil size. Scan quality was considered adequate when the quality number was 7 or greater. The nerve fiber index (NFI) and temporal–superior–nasal–inferior–temporal (TSNIT) average RNFL thickness obtained with the GDx were used for statistical analysis. The NFI provides a single number (range, 1–100) representing the overall integrity of the RNFL. High NFI values indicate thinner RNFL. NFI values of ≤30 are considered normal.

Patients underwent the same brain MRI scanning protocol at baseline using a 1.5T MRI scanner (Magneton Vision; Siemens, Erlangen, Germany). BCR was measured from a FLAIR axial image where the heads of the caudate nuclei were most visible and closest to each other (Fig. 1). We did not have access to the MRI in 5 patients with MS, and the BCR was not assessed in those cases.
Disability was evaluated according to the EDSS score, which range from 0 to 10 with higher scores indicating more severe disability. Physical disability was assessed by a single experienced neurologist blinded to the MRI findings by using the EDSS within 1 week of the MRI. Disease duration was defined from the time of the first manifestation of disease until trial enrollment.

Statistical Analysis

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS). Descriptive statistics and plots were created to determine whether the continuous variables (RNFL, NFI, TSNIT, and BCR) were normally distributed. All variables fit a normal distribution, except for NFI, which was skewed to the right. In this case, a logNFI was used for statistical purposes, because this transformation fit a normal distribution. The variable EDSS score is an ordinal variable.

For statistical comparisons of the variables studied among different groups, generalized estimating equation (GEE) regression models were used to account for within-patient and inter-eye correlations (16). The GEE regression model allows adjustment for patient age and gender.

The partial Pearson product–moment correlation test and the partial Spearman Rank correlation tests were used to study the correlation between variables RNFL, NFI, TSNIT, BCR, and EDSS. Because no statistical differences were found between values from both eyes of each subject, the average was used instead. The correlation between pairs was obtained after controlling for age and gender. Correlation was considered to be significant for $P < 0.05$.

RESULTS

RNFL of MS Eyes vs Control Eyes

We compared the RNFL measured with OCT and GDx between eyes of patients with MS and controls. Table 1 shows the average RNFL thickness, the logNFI, and the TSNIT average of both groups. There were significant differences (GEE, $P < 0.001$) between both groups for all 3 measurements. MS eyes had a significantly thinner RNFL than control eyes.

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<tr>
<th>TABLE 1. Comparisons of OCT average RNFL thickness, logNFI, and TSNIT average between MS eyes and control eyes</th>
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<tr>
<td><strong>MS Eyes</strong></td>
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<tr>
<td>OCT: average RNFL thickness, $\mu$m</td>
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<tr>
<td>GDx: logNFI</td>
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<tr>
<td>GDx: TSNIT average, $\mu$m</td>
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<td>Number of eyes</td>
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Values are mean and SD.

GEE, generalized estimating equation; MS, multiple sclerosis; NFI, nerve fiber index; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; TSNIT, temporal-superior-nasal-inferior-temporal average RNFL thickness.

RNFL and MS Subtypes

To assess the relationship between RNFL and each MS subtype, we looked for statistical differences of RNFL thickness obtained with both OCT and GDx among the 3 MS subtypes (CIS, RR-MS, and SP-MS). There was a significant progressive reduction in OCT average RNFL thickness from CIS to SP-MS types (GEE, $P = 0.008$) (See Supplemental Digital Content, Table E1, http://links.lww.com/wno/a86). Differences were not found for logNFI or TSNIT.

We classified the RR-MS subtype into benign and nonbenign. There were significant differences (GEE, $P < 0.05$) between both groups (See Supplemental Digital Content, Table E2, http://links.lww.com/wno/a86). All measurements showed that patients with nonbenign RR-MS had significantly thinner layers than patients with benign RR-MS.

BNFL of Eyes Without ON and Eyes With ON

We compared RNFL thickness between eyes with ON ($n = 123$) and eyes without ON ($n = 53$). Eyes with a history of ON showed significantly thinner RNFL than eyes with no history of ON (average RNFL, logNFI, and TSNIT) (See Supplemental Digital Content, Table E3, http://links.lww.com/wno/a86).

BCR and MS

To assess the effect of MS on brain atrophy, we compared the BCR of patients with MS and controls. Additionally, we compared the BCR in patients with RR-MS judged to be benign vs nonbenign MS. Mean BCR was significantly higher reflecting more brain atrophy in patients with MS $(0.12 \pm 0.03)$ than in controls $(0.08 \pm 0.009)$ (GEE, $P < 0.001$) (Table 2). There was no statistical differences between BCR in patients with nonbenign RR-MS and patients with benign RR-MS (GEE, $P = 0.103$).

EDSS and MS

We compared the EDSS score among the 3 MS subtypes, and between benign and nonbenign RR-MS. All comparisons showed significant differences (GEE, $P < 0.001$) (See Supplemental Digital Content, Table E4, http://links.lww.com/wno/a86). MS subtypes showed a progressive impairment of the EDSS score from CIS (median 1.0) to...
TABLE 2. Comparisons of BCR between patients with MS and control subjects, and patients with benign and nonbenign RR-MS

<table>
<thead>
<tr>
<th></th>
<th>Patients With MS</th>
<th>Controls</th>
<th>GEE P</th>
<th>Patients With Nonbenign RR-MS</th>
<th>Patients With Benign RR-MS</th>
<th>GEE P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR</td>
<td>0.12 (0.03)</td>
<td>0.08 (0.009)</td>
<td>&lt;0.001</td>
<td>0.14 (0.37)</td>
<td>0.12 (0.02)</td>
<td>0.103</td>
</tr>
<tr>
<td>Patients</td>
<td>83</td>
<td>59</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean and SD.
BCR, bicaudate ratio; GEE, generalized estimating equation; MS, multiple sclerosis; RR-MS, relapsing-remitting multiple sclerosis.

SP-MS (median 4.5). Patients with nonbenign MS had a higher EDSS score (median 4.5) than patients with benign MS (median 1.5) (GEE, P < 0.001). No statistical differences of EDSS score were found between patients with MS without ON and those with ON.

Relationship Among OCT, GDx, EDSS, BCR, and Duration of Disease

To detect any possible relationship among the parameters measured, correlations among OCT RNFL thickness, logNFI, TSNIT, EDSS, BCR, and disease duration were calculated using the partial correlation test (Pearson product moment or the Spearman Rank). Only patients without history of ON were included in this analysis because this condition may alter RNFL thickness. We used the average between both eyes for each patient. Because each patient had RNFL measurements for the left and right eyes, we compared the group of eyes with thinner RNFL with the contralateral group of eyes. There was no significant difference (P = 0.11) between the OCT RNFL thickness in the group of eyes with thicker RNFL (92.36 ± 10.6 μm) and the group of eyes with thinner RNFL (88.76 ± 10.87 μm). A total of 40 patients were included in this analysis.

Significant correlations were found between OCT average RNFL thickness and BCR, EDSS score, and disease duration (Table 3). GDx logNFI was significantly correlated with BCR. TSNIT correlated with BCR. EDSS score showed a significant correlation with BCR. BCR correlated with EDSS score and disease duration. Specific data are given in Supplemental Digital Content, Figure E1, http://links.lww.com/wno/a87.

DISCUSSION

In this study, we investigated the use of OCT and GDx to assess several parameters related to the RNFL thickness in patients with MS and looked for a correlation of those parameters with cerebral atrophy and disability score. We found that the brain atrophy index BCR was higher in patients with MS than in controls and that it correlated with average RNFL thickness, logNFI, and TSNIT. A significant correlation also was found between the average RNFL thickness and EDSS.

In our study, eyes of patients with MS had significantly thinner RNFL than eyes of control subjects. The amount of reduction in the RNFL thickness appeared related to the subtype of MS (See Supplemental Digital Content, Table E1, http://links.lww.com/wno/a86). Additionally, within the RR-MS patient group, we found that patients with nonbenign MS had thinner RNFL than benign patients with MS (See Supplemental Digital Content, Table E2, http://links.lww.com/wno/a86). These findings suggest that the severity of the RR-MS may be because of an increased loss of axons within the central nervous system.

Substantial reduction in RNFL thickness after a clinical episode of acute has been reported previously (17). In agreement with these reports, all measurements in our study showed significantly thinner RNFL in eyes with history of ON than eyes with no history of ON (see Supplemental Digital Content, Table E3, http://links.lww.com/wno/a86).

As shown in Table 2, our results for brain atrophy, as assessed by the BCR, are consistent with other studies using various MRI methods for evaluation of brain atrophy (18).

TABLE 3. Correlations between OCT average RNFL thickness, logNFI, TSNIT average, EDSS, and BCR and disease duration in patients with MS without optic neuritis

<table>
<thead>
<tr>
<th></th>
<th>BCR</th>
<th>EDSS Score</th>
<th>Disease Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCT average RNFL thickness, μm</td>
<td>-0.48 (P = 0.002)</td>
<td>-0.43 (P = 0.003)</td>
<td>-0.48 (P = 0.002)</td>
</tr>
<tr>
<td>GDx: logNFI</td>
<td>0.39 (P = 0.01)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>GDx: TSNIT average, μm</td>
<td>-0.34 (P = 0.03)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>EDSS score</td>
<td>0.33 (P = 0.04)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BCR</td>
<td></td>
<td>0.33 (P = 0.04)</td>
<td>0.40 (P = 0.01)</td>
</tr>
</tbody>
</table>

Values are correlation coefficient and P value (within brackets). Dashes indicate that there was no statistical significant correlation.
BCR, bicaudate ratio; EDSS, expanded disability scale score; MS, multiple sclerosis; NFI, nerve fiber index; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; TSNIT, temporal–superior–nasal–inferior–temporal average; RNFL index.
BCR was higher (more atrophy) in patients with MS (0.12 ± 0.03) than in control subjects (0.08 ± 0.009). Bermel et al (10) found similar results in MS (0.11 ± 0.02) compared to control subjects (0.09 ± 0.02).

BCR also correlated with average RNFL thickness ($r = -0.48$, $P = 0.002$; See Table 3 and Supplemental Digital Content, Figure E1A, http://links.lww.com/wno/a87) in patients with MS without ON, whereas this correlation was not present in patients with ON. Siger et al (19) also failed to find any correlation between average thickness RNFL and BCR in patients with MS with ON. This suggests that axonal loss in the retina resulting from ON occurs independently from brain lesions and atrophy.

Similarly, we observed that BCR correlates with TSNIT average ($r = -0.34$, $P = 0.03$; See Table 3 and Supplemental Digital Content, Figure E1E, http://links.lww.com/wno/a87) and also with logNFI ($r = 0.39$, $P = 0.01$; See Table 3 and Supplemental Digital Content, Figure E1D, http://links.lww.com/wno/a87), both being assessed with GDx. There are only a few studies assessing the relationship between GDx and brain MRI measurements. Frohman et al (20) found no correlation between normalized brain volume and TSNIT average RNFL thickness.

Several studies have observed a relationship between brain atrophy and EDSS or disease duration. We found that BCR was correlated with EDSS ($r = 0.33$, $P = 0.04$; See Table 3 and Supplemental Digital Content, Figure E1F, http://links.lww.com/wno/a87) and with disease duration ($r = 0.40$, $P = 0.01$; See Table 3 and Supplemental Digital Content, Figure E1G, http://links.lww.com/wno/a87). This is in agreement with Sanfilipo et al (11) who found that higher EDSS values were associated with higher BCR, but not with the findings reported by Bermel et al (10) who found no significant correlation between EDSS and BCR.

Disease duration and neurological disability are 2 clinical parameters linked with progressive axonal loss. In this study, we found that OCT average RNFL thickness showed a significant correlation with EDSS ($r = -0.43$, $P = 0.003$; See Table 3 and Supplemental Digital Content, Figure E1B, http://links.lww.com/wno/a87) and with disease duration ($r = -0.48$, $P = 0.002$; See Table 3 and Supplemental Digital Content, Figure E1C, http://links.lww.com/wno/a87). Patients with longer disease duration and higher disability had thinner RNFL. Correlation between RNFL thickness and EDSS has been reported in some studies (21,22), but not in others (23). We did not find a significant correlation between the GDx parameters (TSNIT average, logNFI) and EDSS or disease duration, as reported by Siepman et al (21).

OCT and GDx provide information on different aspects of RNFL structure. OCT provides thickness values similar to histology whereas GDx assesses birefringence of microtubules. Frohman et al (20) observed that MRI measurements and EDSS had a much stronger relationship with OCT RNFL than with GDx, and our results are in agreement with this observation. This suggests that OCT might better reflect the neurodegenerative process of MS compared to GDx.

REFERENCES


Papilledema Due to a Permanent Catheter for Renal Dialysis and an Arteriovenous Fistula: A “Two Hit” Hypothesis

Melissa A. Simon, MD, Ennis J. Duffis, MD, Michael A. Curi, MD, Roger E. Turbin, MD, Charles J. Prestigiacomo, MD, Larry P. Frohman, MD

Abstract: Elevated intracranial pressure in patients with chronic renal failure has several potential causes. Its rare occurrence secondary to the hemodynamic effects of hemodialysis is described and the findings support a multifactorial etiology (“two hits”).

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A variety of factors may lead to elevated intracranial pressure (ICP) in patients with chronic renal failure. Our patient had a permanent central catheter for hemodialysis and, after multiple procedures for dialysis access, presented with headaches and bilateral papilledema caused by elevated ICP. We propose a multifactorial etiology to explain our patient’s clinical findings.

CASE REPORT

A 65-year-old man complained of headaches, tinnitus, and slowly progressive blurring of vision for several months. He had end-stage renal disease and had undergone multiple angioplasties and revisions of arteriovenous fistulas (AVF) for dialysis. At the time of presentation, he had a permanent dialysis catheter in the right internal jugular vein (IJV). The patient was obese, with a history of hypertension, hypercholesterolemia, and seizures and had a pacemaker for episodes of bradycardia. Medications included sevelamer carbonate, benzonatate, enalapril, fexofenadine, isosorbide, hydralazine, amlodipine, nifedipine, and phenytoin.

A failed AVF placed in the left arm required ligation and led to placement of a permanent catheter in the right IJV and a new AVF was created in his right arm. Because the patient developed a steal syndrome affecting his right hand, the distal radial artery was treated with coil embolization. The right AVF continued to mature and the patient continued to rely on the central catheter for dialysis.

Three weeks later, visual acuity was 20/50 in each eye, with normal pupillary reactions, color vision, and ocular motility. Bilateral cataracts were present on slit-lamp examination. Confrontational visual fields were intact, and fundoscopically revealed bilateral optic disc edema. Neurological examination was normal.

Magnetic resonance imaging (MRI) studies could not be performed because of the patient’s pacemaker. Computed tomography (CT) of the brain without contrast (due to renal failure) showed only microvascular ischemic changes and mild pansinusitis. Opening pressure on lumbar puncture was 30 cm H2O with mild elevation of cerebrospinal fluid (CSF) protein of 51 mg/dL (normal, 15–45 mg/dL). CSF glucose and cell count were normal. Because of his renal failure, the patient could not be treated with acetazolamide.

Three days after the lumbar puncture, acuity was 20/30 bilaterally. Automated visual fields revealed enlargement of the blind spots and there was bilateral optic disc edema on funduscopia (Fig. 1).

An intracranial venogram demonstrated elevated intracranial venous pressures throughout the cerebral venous system with measurements ranging from 40 to 50 mm Hg. Although the venous system was patent, there was reduced opacification of the transverse sinuses and the IJVs. In addition, the transit times from the cerebral arterial through venous phases was increased.
Six days later, a fistulogram of the right dialysis shunt showed a patent AVF of the right forearm. A central venogram demonstrated a patent right subclavian vein and superior vena cava, the permanent catheter in the right IJV, and high-grade stenosis of the proximal right subclavian vein extending into the brachiocephalic vein (Fig. 2). Angioplasty of the right subclavian vein was performed and the right IJV catheter was removed. A repeat venogram immediately after these procedures demonstrated improved flow from the subclavian vein into the superior vena cava (Fig. 3).

The next day, the patient reported that his headaches had resolved, and 5 months later, visual acuity was 20/25 bilaterally, with normal visual fields and fundi. The patient noted resolution of headaches and tinnitus.

Over the following year, the patient experienced recurrent subclavian vein stenosis with right arm swelling. However, he had no recurrence of headaches or visual complaints.

**DISCUSSION**

There are 5 reported cases of patients with increased ICP linked to dialysis catheters or grafts, all with a combination of increased flow from the AVF and obstruction from venous stenosis or thrombosis (1–5). In 3 patients, papilledema resolved after ligation of the graft, 1 after balloon dilation to improve stenosis, and 1 patient’s symptoms did not resolve before her illness progressed to brain infarction.
and death (Table 1). All cases, including ours, are unified by similar etiologies: high venous flow in conjunction with venous obstruction. Retrograde venous flow from AVFs into the ipsilateral IJV led to impaired cerebral venous drainage. In addition, compromised venous outflow by an obstructed central vessel caused increased flow elsewhere in the cerebral venous network. Both factors led to elevated ICP.

Our patient had both an AVF-causing high flow and a central venous obstruction caused by ipsilateral permanent catheter and extended pacemaker wire. Our case is unique, in that the permanent catheter was still in place at the onset of elevated ICP. Because the symptoms improved dramatically after removal of the catheter and the AVF remained in place, the increased ICP cannot be explained solely by the AVF. Rather, the central catheter caused decreased venous return from the intracranial venous system, being partially obstructive in the IJV, the brachiocephalic vein, and superior vena cava. Increased venous flow from the arteriovenous graft combined with outflow obstruction resulted in elevated intracranial venous pressure.

Given the lack of reflux of dye into the jugular system after catheter removal (Fig. 3), we do not think that the fistula alone or the right subclavian stenosis alone caused our patient’s symptoms. Additionally, our patient developed right arm swelling and subclavian vein stenosis in the same location over a year after catheter removal, requiring repeat angioplasty. It is interesting that this did not lead to headache and papilledema. This suggests that the catheter was restricting outflow from the right IJV, either directly or by increasing IJV pressure with compromised superior vena cava outflow. Our patient’s condition was unusual because he had no alternative pathways for drainage; he had a chronic left innominate vein occlusion because of the pacemaker wire restricting outflow from the left side of the head and a fistula on the right with the subclavian stenosis. The result was high pressure in the right subclavian vein and restricted drainage of the external jugular vein, which could have provided an alternative drainage pathway. No vascular collaterals were apparent on his fistulogram.

Dialysis catheters have been associated with venous stenosis. Surratt et al (6) evaluated 43 patients for new fistula placement. In preoperative evaluation, 17 patients with previous or existing temporary dialysis catheters in the subclavian vein had moderate or severe subclavian vein stenosis. No stenoses were found in patients without a history of dialysis catheters in the subclavian vein. Wilkin et al (7) used ultrasound to evaluate the IJV of 143 patients with a history of dialysis catheter placement and found right IJV thrombosis in 25.9% of patients and 62% of these were occluded. Neither study assessed visual symptoms or headache related to stenosis or occlusion.

The question remains whether more aggressive screening measures for papilledema should be instituted for patients with hemodialysis catheters or AVFs to detect possible elevated ICP. A cross-sectional observational case series of 44 patients with peripheral arteriovenous shunts found that none had optic disc edema or symptoms of elevated ICP: 1) the presence of a patent arteriovenous graft potentially increasing venous pressures and/or flow and 2) a thrombotic occlusion, as in the other reported cases, or

**FIG. 3.** Venogram after removal of catheter from the right internal jugular vein with improved flow from the right subclavian vein into the superior vena cava.
<table>
<thead>
<tr>
<th>Report</th>
<th>Summary of Findings</th>
<th>Proposed Mechanism of Increased ICP</th>
<th>Intervention and Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lal et al (1)</td>
<td>Patient with right AVF, right BCV thrombosis after repeat subclavian vein catheterizations, developed papilledema</td>
<td>Retrograde blood flow in the cerebral venous system</td>
<td>Arteriovenous graft ligation with resolution of elevated ICP</td>
</tr>
<tr>
<td>Molina et al (2)</td>
<td>Patient with both right and left BCV thrombosis after repeat subclavian and UV catheterizations developed ICP with bilateral papilledema after placement of right forearm Gore-tex graft</td>
<td>Intracranial venous outflow obstruction and retrograde flow</td>
<td>Graft was ligated with only partial resolution of elevated ICP</td>
</tr>
<tr>
<td>Chang et al (5)</td>
<td>Patient with left HD shunt and left BCV stenosis developed right optic disc edema, left-sided headache, left face and neck swelling</td>
<td>Retrograde flow in left IJV and cerebral venous system and outflow obstruction</td>
<td>Balloon dilation of left BCV, with improvement of stenosis and retrograde flow; resolution of symptoms and optic disc edema</td>
</tr>
<tr>
<td>Cuadra et al (3)</td>
<td>Patient with right brachial to IJV graft remaining after successful renal transplant and occlusion of the right axillary, subclavian, and IJVs with bilateral papilledema</td>
<td>Cerebral venous hypertension attributed to combination of internal jugular occlusion causing retrograde flow into cerebral and jugular circulation and functioning hemoaccess graft causing increased blow flow</td>
<td>Permanent graft occlusion with resolution of cerebral venous hypertension and papilledema</td>
</tr>
<tr>
<td>Cleper et al (4)</td>
<td>Patient with failed kidney transplants, occlusion of the left subclavian and left and right BCVs, calcified right subclavian stent, and stenosed SVC had left brachiobasilic AVF placed and developed facial edema, bilateral optic disc edema, and elevated opening pressure on lumbar puncture</td>
<td>Retrograde flow caused by high flow in left AVF contributed to impaired cerebral venous outflow and elevated ICP</td>
<td>Balloon dilation of SVC without resolution. Lumboperitoneal shunt with resolution of elevated ICP and disc edema. Patient then developed recurrent elevated intracranial pressure and superior sagittal sinus thrombosis and brain infarction. The AVF was closed, but patient ultimately expired.</td>
</tr>
</tbody>
</table>

AVF, arteriovenous fistula; BCV, brachiocephalic vein; ICP, intracranial pressure; IJV, internal jugular vein; HD, hemodialysis; SVC, superior vena cava.
occlusion from a permanent central catheter as a mechanism for compromising venous drainage from the jugular system.

REFERENCES

Optic Nerve Sheath Decompression: A Surgical Technique With Minimal Operative Complications

Annie Moreau, MD, Kenneth C. Lao, MD, Bradley K. Farris, MD

Background: The purpose of this study was to determine the safety and efficacy of optic nerve sheath decompression (ONSD) with a medial transconjunctival approach for a variety of indications in a larger population of patients than has previously been reported.

Methods: A retrospective chart review was performed on consecutive patients who underwent ONSD between January 1992 and December 2010. Before ONSD, all patients had documented evidence of progressive loss of visual acuity or visual field, or both. Postoperative follow-up visits were scheduled at 1 week, 1 month, and then every 3–6 months. Main outcome measures were visual acuity, visual fields, and surgical complications.

Results: Five hundred seventy-eight eyes of 331 patients underwent ONSD for progressive vision loss due to various indications, which included but were not limited to idiopathic intracranial hypertension (IIH), progressive nonarteritic ischemic optic neuropathy, and optic nerve drusen (OND). During a mean follow-up of 18.7 months (range, 1 week to 10 years), postoperative visual acuity remained stable or improved in 536 of 568 eyes (94.4%) and progressively worsened in 32 of 568 eyes (5.6%). Visual fields remained stable or improved in 257 of 268 eyes (95.9%) and progressive visual field loss occurred in 11 of 268 eyes (4.1%). There were no reported intraoperative complications. The most common postoperative complication was diplopia (6.0%).

Conclusions: To our knowledge, this review represents the largest series of patients who have undergone ONSD for any indication. Our data are consistent with current literature supporting ONSD as a safe and effective procedure for IIH. Other indications for ONSD, such as progressive visual field loss associated with OND, warrant further study. Regardless of the indication, complications following ONSD with the technique described in this report are infrequent.

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Optic nerve sheath decompression (ONSD), also known as optic nerve sheath fenestration, was first described by the French ophthalmologist De Wecker (1) in 1872 for the treatment of neuroretinitis, where it was thought to alleviate “strangulation of the nerve to remove pain and inconvenience.” ONSD has since become a well-established surgical procedure for papilledema associated with idiopathic intracranial hypertension (IIH).

The most devastating consequence of untreated IIH is visual loss. Visual field defects are detected in more than 90% of patients, and severe impairment of visual acuity has been reported in up to 10% of patients (2,3). ONSD has been demonstrated in multiple studies to be an effective and safe method of stabilizing progressive visual loss in IIH patients (4–9). After medical treatment strategies are exhausted or unable to be tolerated and there is progression of disease, ONSD is a mainstay of management to avoid further deterioration of acuity or visual field.

The majority of surgical complications following ONSD are typically transient and benign and include diplopia, anisocoria, and corneal dellen. Severe complications are infrequent but have been reported to include central retinal artery occlusion, intraoperative angle-closure glaucoma, and iatrogenic traumatic optic neuropathy. In 2 of the largest published series of ONSD, there were reported rates of permanent vision loss as a direct result of the surgery in less than 1% and 2% of patients, respectively (9,10). There were also concerns of adverse events associated with ONSD during the Ischemic Optic Neuropathy Decompression Trial (IONDT), which ceased recruitment early at the recommendation of the Data and Safety Monitoring Committee (11).
The purpose of our study was to determine the safety and results of ONSD with a medial transconjunctival approach in a larger population of patients than has previously been reported with IIH and various other causes of progressive visual loss.

METHODS

After obtaining University of Oklahoma Institutional Review Board approval, a retrospective chart review was performed in consecutive fashion on the preoperative and postoperative course of 578 eyes in 331 patients who underwent ONSD at the Dean A. McGee Eye Institute (Oklahoma City, OK) between January 1992 and December 2010. All patients received a full neuro-ophthalmologic examination, and all ONSDs were performed by the same surgeon (B.K.F.). When necessary to confirm the presence of buried optic nerve drusen, B-scan echography was performed, along with the 30° test to assess the amount of perineural fluid (12). Before ONSD, all patients had documented evidence of progressive loss of visual acuity or visual field, or both. Until 1998, all surgeries were unilateral, allowing 1–2 weeks of healing time between each eye. Starting in 1998, if bilateral ONSD was indicated, it was performed simultaneously.

A standard medial transconjunctival orbitotomy, initially described by Galbraith and Sullivan (13), was performed in all cases under general anesthesia. The medial rectus muscle was disinserted and reflected nasally with 6-0 synthetic polyester suture in typical fashion for eye muscle surgery. A traction suture was then placed through the insertion stump of the medial rectus in a baseball stitch fashion to facilitate abduction of the globe. The pupil was monitored at all times. A custom-made cupped orbital retractor was inserted along the medial scleral wall and used to retract the orbital fat and allow visualization of the optic nerve sheath (Fig. 1). Retraction and globe abduction were relaxed if any changes in pupil size were noted. Rhoton spatula dissectors (V. Mueller, part # NL 3785-006) were used to create adequate exposure of the optic nerve sheath and prevent damage of the posterior ciliary nerves and vessels. When adequate visualization was achieved, the dural sheath was elevated using cupped ENT forceps, and retinal scissors were used to excise a dural sheath window approximately 2 × 3 mm in size. Expulsion of cerebrospinal fluid was invariably observed with the initial incision into the dural sheath.

The goal was to create a decompression pocket in the medial intraconal space as shown in Figure 2. Rhoton spatula dissectors were then used to carefully dilate the dural window and lyse any arachnoid trabeculae. When feasible, an additional posterior radial incision was made in the dura. After removal of the traction suture, the medial rectus muscle was reattached to the globe at its original insertion site. In the postanesthesia care unit, visual acuity was assessed to confirm visual preservation in the operative eye.

Follow-up visits with the surgeon were scheduled at 1 week, 4 weeks, and every 3–6 months depending on the severity of the visual loss. Preoperative and postoperative visual acuities were reviewed in all patients. A change of greater than 2 lines on the Snellen acuity chart was used to define visual acuity improvement or worsening. Preoperative and postoperative results of visual field testing were reviewed. Visual fields were considered improved if the field expanded by at least 20° or a significant field defect (e.g., inferonasal defect) resolved. Any progression of the visual field defect was considered worsening. Preoperative and postoperative motility and alignment evaluation also were reviewed. All follow-up examinations included examination of the optic disc and documentation of its appearance.

RESULTS

Optic nerve sheath decompression was performed on 578 eyes in 331 patients. The most common indication for the procedure was progressive vision loss due to IIH (455 eyes...
from 236 patients), followed by progressive nonarteritic anterior ischemic optic neuropathy (pNAION; 47 eyes from 44 patients) and optic nerve drusen (OND; 13 eyes from 11 patients). The procedure was also performed on 63 eyes of 40 patients with a variety of other conditions (Table 1).

Four eyes from 3 patients had ONSD for progressive optic nerve head swelling with normal intracranial pressure and unknown etiology after extensive investigation.

Surgical complications were seen in 23 of 331 (6.9%) patients and are summarized in Table 2. The most common postoperative complication was an ocular motility disturbance causing diplopia. Esotropia was noted in 11 patients, with 5 requiring eye muscle surgery for persistent diplopia. Exotropia occurred in 4 patients, with 3 of them managed surgically. Three patients developed postoperative esophoria, and 2 patients were found to have an exophoria. Those patients not requiring strabismus surgery were managed with prism spectacles or had spontaneous resolution of symptoms.

Three patients experienced anterior segment complications. Corneal dellen secondary to postoperative conjunctival swelling occurred in 2 patients, and both resolved following aggressive lubrication. One patient was found to have a conjunctival pyogenic granuloma, which was successfully treated with topical antiinflammatory eye drops.

Follow-up ranged from 1 week to 10 years, with a mean of 18.7 months. Six patients were seen for the 1-week postoperative visit and subsequently co-managed by their ophthalmologist, limiting the availability of further postoperative data. Postoperative visual acuity was not available for 10 eyes. During follow-up, 536 of 568 eyes (94.4%) had stable or improved visual acuity (Table 3). Only 268 eyes had available postoperative automated visual fields for comparison with their preoperative study. Overall, visual fields remained stable or improved in 257 of 268 (95.9%) eyes (Table 4). Although visual acuity worsened in 32 of 568 eyes and visual fields worsened in 11 of 268 eyes, none of these were directly related to the surgery itself but attributed to progression of the underlying disorder or due to a comorbidity.

Fifteen eyes of 11 patients underwent repeat ONSD after an initially successful primary ONSD. The time from first to second ONSD ranged from 49 days to 3703 days (average, 823 days). All reoperations were performed in patients with IIH. The chief indication for repeat ONSD was progressive visual loss, as previously defined, in the setting of unresolved or recurrent papilledema. There were no intraoperative or postoperative complications associated with the second surgery. Fourteen of 15 eyes had stable or improved visual acuity. All 15 eyes experienced resolution of papilledema after the repeat ONSD. The procedure was performed with the same medial transconjunctival approach, although scar tissue was encountered in isolating the medial rectus muscle and exposing the retrobulbar optic nerve.

### Table 1. List of conditions in patients treated with optic nerve sheath decompression

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Patients</th>
<th>No. of Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIH</td>
<td>236</td>
<td>455</td>
</tr>
<tr>
<td>pNAION</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>OND</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Other*</td>
<td>40</td>
<td>63</td>
</tr>
<tr>
<td>Venous sinus thrombosis</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Diabetic papillopathy</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Meningioma</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Inflammatory ON</td>
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<td>3</td>
</tr>
<tr>
<td>Traumatic ON†</td>
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<tr>
<td>Frontal astrocytoma</td>
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<td>2</td>
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<tr>
<td>Brainstem astrocytoma</td>
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<td>2</td>
</tr>
<tr>
<td>Gun shot wound</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>AVM with SAH</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SDH from NAT</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Glioblastoma multiforme</td>
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<td>2</td>
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<tr>
<td>Polycythemia vera</td>
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<td>2</td>
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<tr>
<td>Hydrocephalus</td>
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<td>1</td>
</tr>
<tr>
<td>Close head injury</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Orbital pseudotumor</td>
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<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*All patients had optic disc swelling (acute or chronic) with progressive visual loss. These patients had presumed subdural sheath hematoma. AVM, arteriovenous malformation; IIH, idiopathic intracranial hypertension; NAT, nonaccidental trauma; ON, optic neuropathy; OND, optic nerve drusen; pNAION, progressive nonarteritic ischemic optic neuropathy; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage.

### Table 2. Complications of optic nerve sheath decompression

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esodeviation</td>
<td>14 (5*)</td>
</tr>
<tr>
<td>Exodeviation</td>
<td>6 (3*)</td>
</tr>
<tr>
<td>Corneal dellen</td>
<td>2</td>
</tr>
<tr>
<td>Conjunctival pyogenic granuloma</td>
<td>1</td>
</tr>
</tbody>
</table>

*Eight patients required strabismus surgery to treat their deviation and recovered without complication.

### Table 3. Results of visual acuity following optic nerve sheath decompression

<table>
<thead>
<tr>
<th>Visual Acuity</th>
<th>IIH (No. of Eyes)</th>
<th>pNAION</th>
<th>OND</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>75</td>
<td>23</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Stable</td>
<td>354</td>
<td>16</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>Worse</td>
<td>19</td>
<td>8</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

IIH, idiopathic intracranial hypertension; OND, optic nerve drusen; pNAION, progressive nonarteritic anterior ischemic optic neuropathy.
TABLE 4. Visual field results for the IIH, progressive NAION, OND, and other groups

<table>
<thead>
<tr>
<th>Visual Field</th>
<th>IIH (No. of Eyes)</th>
<th>pNAION</th>
<th>OND</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>142</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Stable</td>
<td>78</td>
<td>10</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Worse</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

IIH, idiopathic intracranial hypertension; OND, optic nerve drusen; pNAION, progressive nonarteritic ischemic optic neuropathy.

DISCUSSION

This retrospective series represents one of the largest cohort of patients undergoing ONSD by a single surgeon in the same institution over 2 decades. Although a similar study previously has been published reviewing ONSD for IIH alone (9), this review specifically examines the safety and efficacy of ONSD for multiple disorders. The 3 conditions accounting for 88% of patients who underwent surgical intervention for progressive visual loss were IIH, pNAION, and OND.

Idiopathic Intracranial Hypertension

Our study is consistent with previous reports of ONSD as a safe and effective intervention for progressive visual loss in the setting of IIH (5–9, 14). The goal of ONSD is to either halt the progression or improve visual function. We found a 96% rate (429 of 448 eyes) of visual acuity stabilization or improvement among the IIH cohort. We further stratified the preoperative visual acuity of IIH patients into 3 groups (20/20–20/50, 20/60–20/200, or less than 20/200) to examine any differences in visual acuity outcome based on preoperative acuity (Table 5). Visual acuity results among the IIH patients based on preoperative vision revealed stability or improvement of 96.2% for the first group, 88.4% for the second, and 100% for the third. The results suggest that the majority of IIH patients experience halting of vision loss following ONSD, regardless of initial visual acuity. It also demonstrates that approximately half of the patients with a preoperative vision of 20/60 or worse experience improvement in visual acuity after ONSD.

Visual field stabilization or improvement was seen in 97% of our patients. However, postoperative visual field data were only available for 227 of 455 eyes in IIH patients. Many of these patients only presented for their 1-week or 1-month postoperative visit without undergoing a visual field testing before returning to their own ophthalmologist for continued care.

Complications were seen in 17 of 236 IIH patients (7.2%), with 15 patients developing a postoperative ocular misalignment and 2 patients with self-limiting corneal dellen. Four patients with postoperative esotropia and 2 patients with postoperative exotropia eventually required strabismus surgery, and all patients achieved resolution of their diplopia. There were no cases of visual loss due to ONSD surgery. These results compare favorably with 2 of the largest previously published series of ONSD for IIH (8, 9).

Progressive Nonarteritic Ischemic Optic Neuropathy

Our findings for ONSD performed on patients with progressive nonarteritic ischemic optic neuropathy (pNAION) revealed visual acuity stabilization or improvement in 39 of 47 eyes (83%). There was improvement in 48.9% of eyes and worsening in 17%. The IONDTS showed visual acuity improvement of 3 or more lines in 42.7% and worsening in 12.4% of patients in their observation group at 6 months (11). It is important to note that the observation group in the IONDTS included both patients with progressive and static nonarteritic ischemic optic neuropathy (NAION). The retrospective design in our study and the absence of a controlled NAION cohort does not allow comparison with the prospectively designed IONDTS. There remains uncertainty as to the frequency of vision recovery in patients with pNAION and perhaps this warrants further study.

In our experience, patients with NAION are typically composed of static NAION, p-NAION (typically progressing over 2–4 weeks), and a smaller group of younger patients (<50 years old) with chronic progressive NAION (progressing over a month) and associated with diabetes mellitus. This last group typically is diagnosed with diabetic papillopathy. In our study, ONSD was performed on 6 patients (8 eyes) with diabetic papillopathy, with all demonstrating postoperative stability or improvement in visual acuity. Postoperative visual field results were only available for 5 of the 8 eyes, with 4 demonstrating visual field improvement or stability.

In light of the findings from our study and the high percentage of patients who spontaneously recover vision as demonstrated in the IONDTS, we no longer recommend ONSD for pNAION at our institution.

Optic Nerve Drusen

We examined the safety of ONSD for progressive visual loss due to OND. Our findings are based on 11 patients (13 eyes); however, postoperative visual acuity data were only available for 12 eyes and postoperative visual field information for 9 eyes. Preoperatively, all patients had developed progressive visual field loss and 3 patients demonstrated central visual acuity loss as an indication for surgical intervention. Eight patients (8 eyes) with OND had concomitant
disc swelling that was not due to an inflammatory, demyelinating, or compressive etiology. We believed that the patients experienced drusen-associated anterior ischemic optic neuropathy (15). Although our sample size was small, ONSD showed stabilization or improvement of visual acuity in all 12 eyes and visual field stabilization or improvement in 8 of 9 eyes. We are unsure why patients with OND and progressive visual loss seem to benefit from ONSD. Although we suggest that ONSD may be beneficial in halting progressive visual loss due to OND, the published data for this indication are scarce and warrants further study.

**Overall Safety**

Although previous authors have reported sight-threatening surgical complications, such as central retinal artery occlusion and traumatic optic neuropathy, none were encountered in our series. Our overall complication rate of 6.9% compares favorably with the 4.9% complication rate reported by Spoor and McHenry (16) in reviewing 327 ONSD procedures. Although the risk of complications is greater with repeat ONSD (8,17), no complications were encountered in the 11 patients who underwent a second ONSD.

The majority of our complications were related to postoperative ocular misalignment (20 of 331 patients). We attribute this finding to the medial transconjunctival technique that requires disinsertion and manipulation of the medial rectus muscle. All of our patients experiencing postoperative diplopia had spontaneous resolution of symptoms or were successfully managed with either prism spectacle correction or strabismus surgery.

We recognize the limitations of our study that are inherent in any retrospective case series. Our visual field results are based on less than half of the study population due to the variable follow-up intervals and inconsistent availability of postoperative visual field data. The overall favorable results of visual field stabilization or improvement following ONSD must be viewed with caution. Although our retrospective study did not determine the therapeutic efficacy of ONSD for progressive visual loss due to pNAION or OND, we believe our results suggest that further study of the role of ONSD in this condition is warranted.

The medial transconjunctival approach (5,6,8,9,13) is one of the most popular approaches for ONSD with an impressive safety profile. However, newer techniques without detaching an extraocular muscle may prove to possess even less morbidity. The superomedial lid crease approach requires no muscle disinsertion and provides exposure to the medial intraconal space for ONSD (18,19). We are currently studying a superomedial transconjunctival approach for ONSD, also without the need of disinserting the medial rectus, in hopes to reduce our incidence of postoperative diplopia. Although only described in a cadaveric study, the endoscopic medial transconjunctival approach (20) requires little to no manipulation of the muscles and may be a minimally invasive technique of the future for optic nerve sheath decompressions. Further investigation with long-term safety and efficacy data of newer techniques are needed.

**Acknowledgments**

The authors thank Michele Riggins, MD; Yoonsang Kim, PhD, MPH; Sara Fransen, MD; and Paul Tluczek, MD.

**REFERENCES**

Optic Atrophy and a Leigh-Like Syndrome Due to Mutations in the C12orf65 Gene: Report of a Novel Mutation and Review of the Literature

Gena Heidary, MD, PhD, Laurel Calderwood, MS, CGC, Gerald F. Cox, MD, PhD, Caroline D. Robson, MBChB, Lisa A. Teot, MD, Jennifer Mullon, MD, Irina Anselm, MD

Abstract: Combined oxidative phosphorylation deficiency type 7 (COXPD7) is a rare disorder of mitochondrial metabolism that results in optic atrophy and Leigh syndrome–like disease. We describe 2 siblings with compound heterozygous mutations in the recently identified C12orf65 gene who presented with optic atrophy and mild developmental delays and subsequently developed bilateral, symmetric lesions in the brainstem reminiscent of Leigh syndrome. Repeat neuroimaging demonstrated reversibility of the findings in 1 sibling and persistent metabolic stroke in the other. This article highlights the phenotypic manifestations from a novel mutation in the C12orf65 gene and reviews the clinical presentation of the 5 other individuals reported to date who carry mutations in this gene.

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Combined oxidative phosphorylation deficiency type 7 (COXPD7) was first described in 2010 as a rare disorder of mitochondrial metabolism caused by mutations in the C12orf65 gene (chromosome 12 open reading frame 65) that may manifest as optic atrophy, external ophthalmoplegia, and Leigh syndrome–like encephalopathy (1). The C12orf65 gene encodes a mitochondrial matrix protein that is critical for the release of newly synthesized proteins from mitochondrial ribosomes. Loss-of-function mutations impair the translation of mitochondrial proteins, with a resultant decrease in the protein complexes necessary for effective oxidative phosphorylation (1,2). The COXPD7 phenotype has been described in 2 distinct pedigrees by Antonicka et al (1). A third family has been reported with mutations in the C12orf65 gene with optic atrophy and spastic paraplegia (3). We further delineate the COXPD7 phenotype with the report of 2 siblings who harbor 1 previously reported mutation and 1 novel mutation in the C12orf65 gene.

CASE REPORTS

Case 1

A 7-year-old boy, the third of 9 children born to healthy Caucasian, nonconsanguineous parents, experienced developmental delay, including speech, and decreased energy compared with his siblings. His parents noted the onset of nystagmus by 9 months of age. At 2 years, visual acuity was 20/130 with each eye tested by preferential looking and on examination there was vertical nystagmus and persistent metabolic stroke in the other. This article highlights the phenotypic manifestations from a novel mutation in the C12orf65 gene and reviews the clinical presentation of the 5 other individuals reported to date who carry mutations in this gene.

Departments of Ophthalmology (GH, JM), Neurology (LC, IA), Genetics (GFC), Radiology (CDR), and Pathology (LAT), Boston Children’s Hospital and Harvard Medical School, Boston, Massachusetts; and Clinical Development Program, Genzyme (GFC), A Sanofi Company, Cambridge, Massachusetts.

The authors report no conflicts of interest.

G. Heidary and L. Calderwood contributed equally to the work.

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tegmentum and facial colliculi, terminating in the dorsal aspect of the central medulla (Fig. 1). These areas were not associated with brainstem expansion or volume loss. Diffusion-weighted imaging (DWI) demonstrated mixed diffusion characteristics with areas of low and high diffusivity. Magnetic resonance spectroscopy showed nonspecific mildly elevated choline–N-acetylaspartate ratio within the region of signal abnormality of the right midbrain. This constellation of findings was suggestive of Leigh syndrome.

Plasma and cerebrospinal fluid (CSF) lactate levels were normal, as was pyruvic acid in whole blood and plasma creatine kinase levels. Lumbar puncture revealed decreased glucose of 56 mg/dL (normal: 60–80 mg/dL) and low protein of 13.8 mg/dL (normal: 15.0–45.0 mg/dL), with normal CSF amino acids, neurotransmitters, sialic acid, and 5-methyltetrahydrofolate. Mitochondrial DNA analysis showed 2 nonpathogenic homoplasmic Leber heredity optic neuropathy secondary mutations: m.4216T>C and m.13708G>A, but was otherwise normal. Testing of a 16-gene panel for optic atrophy and progressive external ophthalmoplegia (GeneDx, Gaithersburg, MD) demonstrated 2 frameshift mutations in the C12orf65 gene that were predicted to be pathogenic: c.96_99dupATCC (p.Pro32IlefsX25) and c.210delA (p.Gly70AlafsX13), confirming the diagnosis of COXPD7. These 2 mutations are known to be on separate C12orf65 alleles (in trans) because the initial testing revealed that both were present in the same amplicon by Next Generation sequencing. No sequence or deletion/duplication mutations were identified in the AUH, C10ORF2, CISD2, NDUFSI, OPA1, OPA3, POLG1, POLG2, RRM2B, SLC25A4, SPG7, TIMM8A, TMEM126A, TMP, and WFS1 genes. The patient was prescribed multivitamins and ubiquinol.

Follow-up ophthalmic examination showed resolution of the esotropia and subsequently an intermittent left exotropia. The patient eventually regained normal ocular alignment over several months. Visual acuity remained unchanged at 20/200, right eye, and 6/200, left eye. Examination at 8 years of age demonstrated moderate improvement of facial asymmetry. Repeat brain MRI 6 months later showed a decrease in the extent of the T2 prolongation previously identified within the midline medulla, ventral pons, and periaqueductal regions, with extension into the midbrain around the red nucleus. The optic nerve sheaths remained dilated bilaterally (Fig. 2).

**Case 2**

The younger sister of Case 1, and the fifth of 9 children in the sib-ship had ophthalmic evaluation at 4 years of age and was found to have 20/200 vision in each eye and diffuse bilateral optic atrophy. She had no history of nystagmus. The birth and developmental history were similar to her affected brother with developmental and speech delay and decreased energy. Brain MRI revealed only prominent CSF spaces surrounding each optic nerve. Neurologic testing demonstrated full and symmetric facial movements and normal strength throughout.

One year later, the patient developed acute, external ophthalmoplegia characterized by bilateral sixth nerve palsy and a precipitous decline in vision of the right eye to 4/200. Neurologic examination was notable for facial asymmetry and a deviated tongue. All deep tendon reflexes were brisk, with right greater than left in the upper extremities. There was a positive Babinski sign. Romberg was positive. Tone was noted to be increased in the lower extremities. There was a decrease in energy, stamina, and appetite and a remarkable decline in the patient’s expressive language abilities.

Magnetic resonance imaging revealed symmetric paramedian T2 prolongation in both cerebral peduncles extending inferiorly into the midbrain, dorsal pons, superior and inferior colliculi, and superior aspect of the medulla.
On DWI, these areas exhibited mildly decreased diffusion. The optic nerves, chiasm, and optic tracts were mildly atrophic but without signal abnormality. Magnetic resonance spectroscopy over the midbrain revealed a small lactate peak.

Plasma lactate and pyruvate levels were normal. Creatine kinase was mildly elevated at 189 U/L (normal: 4–150 U/L). Chemistry panel and liver function tests were normal. The patient also was positive for the same mutations in the C12orf65 gene (c.96_99dupATCC and c.210delA) and she was started on the multivitamins and ubiquinol.

Although the patient’s bilateral external ophthalmoplegia remained stable, she developed cardiomyopathy with mild left ventricular hypertrophy, as well as an irregular breathing pattern. Repeat neuroimaging 4 months later showed brainstem lesions to be unchanged. The patient died from respiratory failure less than 1 year after the onset of her brainstem changes. Autopsy was declined.

Both siblings had skin biopsies with testing of cultured skin fibroblasts for electron transport chain enzyme activity. Electron microscopy demonstrated increased numbers and enlargement of mitochondria in essentially all types of cells visualized, including endothelial cells, epithelial cells of the sweat ducts, fibroblasts, myelinated and nonmyelinated nerves, and lymphocytes. The enlarged mitochondria had prominent, often densely packed cristae, including wavy or stacked forms. The mitochondrial matrix was finely granular with scattered, small, electron dense deposits (Fig. 4). Activity of complex IV (cytochrome c oxidase) was reduced to below 40% of normal controls in Case 1 and below 30% in Case 2.

Their remaining siblings, with the exception of an infant brother, underwent ophthalmic evaluations that were normal. Genetic testing of other family members has not been performed. There is no family history of metabolic or mitochondrial disorders, seizures, developmental delay, or genetic disorders.
DISCUSSION

We report the fourth pedigree of patients to harbor mutations in the C12orf65 gene and whose clinical phenotype is consistent with a diagnosis of COXPD7. In both siblings, the initial manifestation of the disease was optic atrophy. Later in the disease course, each patient developed neurologic impairment and neuroimaging findings resembling those seen in Leigh syndrome. The appearance of optic atrophy antedating neurologic decline distinguishes COXPD7 from typical Leigh syndrome and other similar pediatric neurodegenerative disorders in which optic atrophy occurs concomitantly with clinical manifestations of neurologic or systemic disease (4). In the older brother, there was clinical and radiographic improvement, but the young sibling’s clinical course was characterized by a precipitous decline from which she did not recover. Neither patient had a significant elevation of plasma or CSF lactate, indicating that normal values in these first-tier assessments do not exclude the diagnosis of COXPD7. In addition to the neurologic complications from this disease process, Case 2 developed cardiomyopathy, a feature seen in other mitochondrial diseases.

In 2010, Antonicka et al (1) described the first cases of COXPD7 in 3 individuals from 2 families. The first patient was of Turkish descent and born to consanguinous parents. She presented with developmental regression after age 1 year and external ophthalmoplegia and ptosis at 18 months. Magnetic resonance imaging at 2 years of age revealed bilateral lesions involving the thalami and brainstem, and a presumed diagnosis of Leigh syndrome was made. Optic atrophy was confirmed at 5 years of age and the patient died at 8 years of age. Genetic testing revealed a homozygous 1-base pair deletion, c.248delT, causing a frameshift. The second pedigree involved 2 brothers of nonconsanguinous Dutch origin. Both developed nystagmus within the first 2 years of life and both developed optic atrophy. Each had normal MRI of the brain, as was the case for our 2 siblings. Between 3 and 8 years of age, each of the Dutch children suffered from progressive cognitive and neurologic decline. The brothers were homozygous for a 1-base pair deletion, c.201delA, causing a frameshift.

More recently, Shimazaki et al (3) reported a consanguinous Japanese family with homozygous nonsense mutation c.C394T (p.R132X) in C12orf65 that manifested clinically as optic atrophy and spastic paraplegia. In this family, 2 affected brothers showed loss of visual acuity by 7 years of age, with the onset of peripheral neuropathy and spasticity of the lower extremities by 10 years of age, which progressed into adulthood. Final reported vision was in the range of legal blindness for each brother.

To date, all the mutations associated with the COXPD7 phenotype have been homozygous loss-of-function mutations involving either frameshifts or nonsense mutations. One of the 2 mutations identified in our cases was c.210delA, a frameshift mutation that was previously observed in the homozygous state in 2 Dutch siblings with a similar phenotype (1). It is predicted to cause a loss of normal protein function through protein truncation. The second mutation found in our siblings, c.96_99 dupATCC, is a novel one. It is predicted to cause a frameshift at codon 34, changing the proline to isoleucine and creating a premature stop codon at position 25 of the new reading frame (p.Pro34IlefsX25). It may cause a loss of normal protein function either through protein truncation or nonsense-mediated messenger RNA decay.

Electron transport chain activity in patients in these cohorts has been previously described as abnormal with severe assembly defects in complexes I, III, IV, and V (1,3). Kogure et al (2) found that knockdown of the C12orf65 protein in cell culture assays resulted in an increase in reactive oxygen species and apoptosis. Mitochondrial dysfunction was demonstrated by impaired cytochrome c oxidase activity.

To date, the ultrastructural features of mitochondria have not been reported in patients with C12orf65 mutations. In our 2 patients, electron microscopy revealed enlarged mitochondria engorged by an abnormal number of densely packed cristae. The features identified are similar to the ultrastructural findings described to be present in Leber hereditary optic neuropathy (5–7).
Our cases have characteristics similar to previously reported patients with COXPD7 deficiency but also have several unique features. All cases demonstrated optic atrophy preceding the development of other neurological symptoms. Leigh-like disease features on brain MRI previously reported in the literature are reminiscent of those seen in our patients. Reduced activity of complex IV of the electron transport chain noted in a previous report (1) was also demonstrated in our patients. We add 2 new observations. One of our 2 patients experienced significant improvement in neurological symptoms and almost complete reversal of MRI abnormalities. His sibling developed abnormal breathing and cardiomyopathy that seem related to the underlying disease.

Our report suggests that in pediatric patients with acquired optic atrophy, clinicians should probe the clinical history for other neurological symptoms and consider the need for broad genetic testing. Genotype confirmation will guide appropriate management and treatment from the limited options currently available as well as provide important information regarding the recurrence risks of optic atrophy and other medical concerns for the affected families.

REFERENCES


Infiltration of the Optic Chiasm, Nerve, and Disc by Gliomatosis Cerebri

Ilana Traynis, BS, Samuel Singer, MD, Jacqueline Winterkorn, MD, PhD, Marc Rosenblum, MD, Marc Dinkin, MD

Abstract: An 18-year-old man with gliomatosis cerebri (GC) developed tumor infiltration of the optic chiasm and right optic nerve including the optic disc. Although papilledema often is seen with GC, tumor invasion of the optic nerve head is observed.

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An 18-year-old, previously healthy, male college student presented with generalized tonic–clonic seizures and was found to have an area of abnormal T2 signal without enhancement in the right frontal lobe on magnetic resonance imaging (MRI). He was treated with anticonvulsants for 16 months until he developed severe morning headaches, blurred vision, and diplopia. Examination revealed bilateral papilledema, and the MRI demonstrated expansion of the fluid attenuated inversion recovery (FLAIR) abnormality to occupy most of the right cerebral hemisphere and a part of the left frontal lobe (Fig. 1). Magnetic resonance imaging of the anterior visual pathways was unremarkable. Brain biopsy showed World Health Organization Grade 3 astrocytoma (Fig. 2), and in conjunction with the MRI and clinical findings, gliomatosis cerebri (GC) was diagnosed. The patient underwent subtotal resection of the right frontal tumor, followed by radiotherapy and concurrent temozolomide. Papilledema resolved and the vision remained stable for approximately 20 months, when the patient complained of progressive visual decline in the right eye. Magnetic resonance imaging demonstrated enlargement, with some enhancement of the right optic nerve and chiasm, consistent with infiltration by glioma (Fig. 3).
We first evaluated the patient 12 months after onset of visual loss. Visual acuity was no light perception in the right eye and 20/60 in the left eye. Funduscopic examination of the right eye showed a large white mass within the optic disc, and the left optic disc was pale (Fig. 4). Automated perimetry in the left eye showed temporal visual field loss, and optical coherence tomography of the right optic nerve head showed loss of normal structure with cystic spaces.

Over 3 months, the patient’s neurologic condition deteriorated, despite a number of chemotherapeutic regimens. He ultimately died, and an autopsy was not obtained.

First described in 1938 by Nevin (1), the current World Health Organization’s classification of brain tumors defines GC as a diffuse, neoplastic, glial infiltration of the brain involving more than 2 cerebral lobes, with no identified tumor mass and with preservation of the architecture of the surrounding tissues (2). Most often, GC develops in men in the third and fourth decades (3).

FIG. 2. Markedly atypical astrocytes permeate the neuro-parenchyma, characteristic of a diffusely infiltrating glioma (hematoxylin and eosin, ×40).

FIG. 3. Two years after presentation, magnetic resonance imaging reveals tumor infiltration of the anterior visual pathways. A. Contrasted axial BRAVO image (inversion recovery gradient echo) demonstrates diffuse enlargement and enhancement of the right optic nerve. Contrast-enhanced T1 coronal MRI shows enlargement and mild enhancement of the canalicular right optic nerve (B, arrow) and optic chiasm (C, arrow).

FIG. 4. A. There is a massive infiltration of the right optic disc by glioma with extension into the macula. Note the fine vascularity on the surface of the tumor and surrounding subretinal fluid. B. The left optic disc is diffusely pale.
Diagnosis of GC can be challenging, as the clinical presentation is variable. Early symptoms include cognitive and personality changes and seizures, followed by signs and symptoms of increased intracranial pressure. Focal neurologic findings may develop within months, but visual field deficits are infrequent. Gliomatosis cerebri often involves the hypothalamus, basal ganglia, and corpus callosum (4).

Magnetic resonance imaging has facilitated the diagnosis of GC, but because of its multifocal nature, this neoplasm may be mistaken for other neurologic disorders, such as multiple sclerosis (5) or progressive multifocal leukoencephalopathy (3). Gliomatosis cerebri is difficult to treat because large tumor volumes increase the morbidity associated with radiation therapy. Response rates to chemotherapy are poor, and median survival has been reported at less than 3 years (6).

Invasion of the optic nerves and chiasm occurs in approximately 10% of GC cases (4). Felsberg et al (7) described the case of a young pregnant woman with GC infiltration of the optic nerves and chiasm whose signs and symptoms were initially attributed to multiple sclerosis.

In our patient, GC originated in the right frontal lobe but progressed to involve the optic chiasm and right optic nerve, including the optic disc. We are unaware of similar reports of optic disc infiltration in patients with GC, although a similar optic disc appearance has been described in a patient with optic nerve glioma (8). Early recognition of GC may allow for palliative preservation of vision with focal radiotherapy to the optic apparatus. Additionally, direct visualization of tumor on funduscoppy provides a potential opportunity to follow progression of disease or treatment response as an adjunct to neuroimaging.

REFERENCES
Neuro-Ophthalmologic Features of Chordoid Glioma

Nagham Al-Zubidi, MD, Margaret M. McGlynn, BA, Patricia Chévez-Barrios, MD, Sushma Yalamanchili, MD, Andrew G. Lee, MD

Abstract: Chordoid glioma is a rare intracranial tumor typically arising in the third ventricle, particularly along the anterior aspect of the hypothalamic wall. We describe the clinical, neuroimaging, and pathologic factors of this neoplasm in a patient presenting with a chiasmal syndrome.

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A 37-year-old man reported a 5-year history of progressive “hazy vision” in both eyes. He had no other systemic complaints and the remainder of his medical, social, family, allergy, and medication history was noncontributory. Visual acuity was 20/40 in the right eye and 20/50 in the left eye. Pupils were isocoric, and there was a right relative afferent pupillary defect. Anterior segment, intraocular pressure, and ocular motility examinations were normal, and automated visual field testing demonstrated a bitemporal hemianopia. Funduscopic examination showed mild bilateral temporal...
optic disc pallor. Optical coherence tomography showed global retinal nerve fiber layer (RNFL) thickness of 95 μm (right eye) and 93 μm (left eye) with papillomacular bundle RNFL dropout in each eye.

Magnetic resonance imaging (MRI) of the brain showed a lobulated, well-circumscribed enhancing mass 28 × 39 × 19 mm in the anterior-inferior third ventricle with displacement of neighboring structures (Fig. 1).

The patient underwent craniotomy with subtotal resection of the tumor. Histopathologic findings included cords and clusters of eosinophilic epithelioid tumor cells with bland oval nuclei within a mucinous matrix with occasional lymphocytes and plasma cells (Fig. 2A, B). Tumor cells were positive for S100 protein, pancytokeratin, and glial fibrillary acidic protein (Fig. 2C). Rare tumor cells were positive for epithelial membrane antigen. Ki-67 labeling index was 5.0%. These features were consistent with World Health Organization grade II chordoid glioma.

Six months later, visual acuity was 20/40 in the right eye and 20/60 in the left eye. Funduscoppy revealed mild, bilateral temporal optic disc pallor, and MRI showed postoperative changes but without tumor recurrence.

Chordoid gliomas are rare tumors with both glial and chordoid characteristics. First described in 1998 by Brat et al (1,2), subsequently they were classified as World Health Organization grade II in 2000 (2–6). Chordoid gliomas demonstrate features of specialized ependymal differentiation and have a predilection for the third ventricle, particularly the anterior aspect of the hypothalamic wall. The collective features point to an anatomical origin from the vicinity of the lamina terminalis (7). They are slow-growing and noninvasive neoplasms and more commonly affect women with a mean age of 46 years (2,4,6). Because chordoid gliomas typically arise from the anterior third ventricle, a majority of patients present with neuro-ophthalmic signs including loss of visual acuity, visual field defects, and papilledema (2,4–7). Patients may also present with headache, memory loss, or endocrine symptoms (2).

Chordoid gliomas have nonspecific MRI features: isointense on T1 sequences, contrast enhancing, and hyperintense on T2 images (2,4,6). These findings may cause diagnostic confusion with craniopharyngioma or pituitary adenoma. Some features that may distinguish chordoid gliomas include location in the anterior third ventricle, ovoid shape, hyperdense to gray matter on computed tomography, and uniform contrast enhancement by both intensity and density (8).

Treatment of chordoid gliomas often requires multiple modalities. Because of its proximity to the hypothalamus, aggressive surgery carries significant risk. Stereotactic radiosurgery with or without conventional radiation is believed to be superior to conventional radiation alone. Subtotal resection followed by stereotactic radiosurgery is another therapeutic option. Although chemotherapy has been used

![Histopathology of chordoid glioma. A. Within a myxoid background are clusters of epithelioid cells (hematoxylin and eosin, ×40). B. Epithelioid cells have round bland nuclei in a vacuolated basophilic stroma (hematoxylin and eosin, ×100). C. Gliarial fibrillary acidic protein (GFAP) highlights the cytoplasm of glioma cells (immunohistochemistry with 3,3′-Diaminobenzidine chromogen, GFAP antibody, ×40).](image-url)
in some cases, it remains of unproven benefit. The overall postoperative morbidity has been reported up to 60% and mortality ranges between 28% and 32% (4,9,10).

REFERENCES
Sneddon Syndrome Presenting With Unilateral Third Cranial Nerve Palsy

David Jiménez-Gallo, MD, Cristina Albarrán-Planelles, MD, Mario Linares-Barrios, PhD, MD, Julio A. González-Fernández, PhD, MD, Raúl Espinosa-Rosso, MD, José M. Báez-Perea, PhD, MD

Abstract: Sneddon syndrome is a rare systemic vasculopathy affecting the skin as livedo racemosa and the central nervous system as stroke. A 31-year-old man with a history of livedo racemosa presented with a partial left third nerve palsy. Skin biopsy showed signs of endotheliitis with obliteration of dermal blood vessels due to intimal proliferation and fibrin thrombi consistent with Sneddon syndrome. The patient was treated with platelet antiaggregant therapy with complete resolution of his third nerve palsy. Clinicians should be aware of Sneddon syndrome because prompt diagnosis and treatment may prevent potential morbidity and mortality.

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Sneddon syndrome (SS) is a rare systemic vasculopathy affecting the skin as livedo racemosa (LR) and the central nervous system as stroke. It predominantly affects young women, and neurological involvement usually appears years after the appearance of skin findings (1,2).

Definitive diagnosis requires correlation of clinical symptoms with skin histopathology. It is essential to make an early diagnosis of SS and begin anticoagulant or antiplatelet treatment promptly to reduce the morbidity and mortality of this disorder (3).

CASE REPORT

A 31-year-old man, with an unremarkable medical history, came to the emergency department with sudden onset of left eyelid ptosis and diplopia. He denied fever, headache, and eye pain but reported purple spots on the skin of his legs and trunk of 4-year duration. Skin lesions were accompanied by ulceration in distal areas of both lower limbs. There was no family history of similar skin lesions.

The patient had ptosis of the left eye and limited eye movement consistent with a third nerve palsy. Visual acuity, pupils, slit-lamp examination, and funduscopy were normal. The skin on the patient’s trunk and legs showed a reticulated pattern with irregular and open trabeculae. There were ulcerations in the distal third of both lower limbs (Fig. 1). The remainder of the physical and neurological examinations were normal.

Laboratory testing included complete blood count, serum chemistries, thyroid panel, protein immunoglobulin and complement levels, and hypercoagulability studies that were all normal. Autoimmunity studies, including antinuclear antibody, anti-neutrophil cytoplasm, cryoglobulins, anti-DNA, anti-Sm, anti-Ro, anti-La, anti-RNP, anti-citrullinated peptide, anti-mitochondrial, and anti-phospholipid antibodies, were negative. Serological analysis for hepatitis B virus, hepatitis C, human immunodeficiency virus, syphilis, and...
Borrelia was negative. Unremarkable imaging studies included chest x-ray, abdominal ultrasound, echocardiography, single photon emission computed tomography, and magnetic resonance angiography of the brain. Examination of the cerebrospinal fluid was normal. Skin biopsy was taken from the edge of one of the leg ulcers. Histopathological findings included signs of endotheliitis and obliteration of the lumen of dermal blood vessels due to intimal proliferation and fibrin thrombi, with no signs of vasculitis (Fig. 2).

Correlating the neurological symptoms (third nerve palsy), the presence of LR, the negative studies for autoimmune and infectious causes, and pathological findings on skin biopsy, we reached the diagnosis of SS. We began treatment with acetylsalicylic acid, 300 mg/day. No new neurological symptoms developed in 2 years of follow-up and the skin ulcerations resolved. The patient’s third nerve palsy completely recovered within 3 months.

**DISCUSSION**

SS is a rare systemic, progressive, noninflammatory vasculopathy, characterized by the presence of generalized LR and cerebrovascular symptoms due to involvement of small- and medium-sized skin and brain blood vessels (1,4). This association was first described in a patient by Champion and Rook (5) and, in 1965, Sneddon (6) documented these findings in 6 additional patients. The incidence is 4 cases/1,000,000/y with a mortality of approximately 9.5% (3). The disease is more common in women aged 20–40 years (2) and appears spontaneously (7). When SS appears in men, it usually occurs at a later age (7). Isolated familial cases have been reported, suggesting a genetic predisposition (6).

Neurological involvement typically appears after the onset of livedo racemosa. Findings include headache, dizziness, seizures, and progressive dementia (8). The most common neurological manifestations are transient ischemic attack and stroke usually affecting the middle cerebral artery. Reported ophthalmologic complications include central retinal artery occlusion, central retinal vein occlusion, retinal neovascularization, homonymous visual field defects, and internuclear ophthalmoplegia (9–13).

The pathogenesis of SS is not fully understood and its association with autoimmune disease, such as primary anti-phospholipid antibody syndrome, systemic lupus erythematosus, and hypercoagulable states, such as mutation in the factor V Leiden, is in dispute (1).

Skin biopsy is useful for the diagnosis, although it may require multiple biopsies to reach a diagnostic yield of 80%. The biopsy should be performed in the central area of the LR reticle. Histologic findings are endotheliitis, vascular occlusion by fibrin thrombi, and the proliferation of the intima and media without evidence of vasculitis primarily involving arteries of the reticular dermis (7,14). The differential diagnosis of SS includes anti-phospholipid antibody syndrome, multiple sclerosis, coagulopathy, and infectious conditions, such as syphilis and Lyme disease (3).

Forty to fifty percent of patients with SS have positive anti-phospholipid antibodies (15). If they are negative, platelet antiaggregant therapy is indicated, and if positive, the patient should be anticoagulated. Cardiovascular risk factors should be treated and the patient should avoid tobacco use and oral contraceptives (3). The efficacy of immunosuppressive therapy is controversial (1).

Our patient with SS developed the microvascular complication of a third nerve palsy. It is essential that SS be recognized and treated appropriately to avoid more severe vascular involvement that can be life-threatening.

**REFERENCES**

Patients With Homonymous Hemianopia Become Visually Qualified to Drive Using Novel Monocular Sector Prisms

Adam M. Moss, MD, MBA, Andrew R. Harrison, MD, Michael S. Lee, MD

Abstract: Patients with homonymous hemianopia (HH) often fail to meet visual field (VF) requirements for a driver’s license. We describe 2 patients with complete HH, who met the minimum VF requirements for driving using a novel, high-power, monocular sector prism system. Baseline VFs were assessed using automated and kinetic perimetry. Patients were fitted with glasses and press-on 57-PD peripheral monocular sector prisms placed on the lens ipsilateral to the VF defect above and below the visual axis with prisms oriented obliquely. Kinetic perimetry was reassessed both monocularly and binocularly, with and without prisms. The 2 patients had 95° and 82° angle of continuous, horizontal, binocular VF. With the use of the prism system, the binocular VF increased to 115° and 112° angles. Both patients reported improvement in quality of life and each holds a valid driver’s license and has successfully operated a motor vehicle without any restrictions or accidents. These findings suggest that the addition of oblique 57-PD prisms to the ipsilateral spectacle lens above and below the visual axis, which may help an individual become visually qualified to obtain a driver’s license.

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Homonymous hemianopia (HH) occurs after damage to the contralateral retrochiasmal visual pathways. Despite adapting to the visual field (VF) defect, patients experience compromised independence from an inability to meet driving requirements. Although the specific VF requirements to obtain a driver’s license vary by state, Minnesota requires that one should have at least 105° angle of binocular VF (1). In an attempt to expand the VF in patients with HH, a number of optical therapies have proposed a variety of mirrors, telescopes, and prisms. A novel approach utilizing monocular sector prisms limited to the peripheral field has been described by Peli (2). The prism is placed across the entire width of the lens above and below the visual axis, thus creating peripheral exotropia. Peli proposed that this would effectively expand the VF in all lateral positions of gaze while maintaining bifoveal alignment and eliminating diplopia.

Recently, Bowers et al (3) described a modified technique using obliquely oriented prisms. Two Fresnel press-on 40-PD prism segments (3M Press-On Optics) were placed, base-out, at the upper and lower part of the spectacle lens ipsilateral to the VF defect with its central edge at the level of the limbus, spanning the entire width of the lens (Fig. 1). The individual prism segments were oriented obliquely at 45° angle from the horizontal axis, 7–8 mm apart. At the conclusion of the trial period, prisms were permanently ground and fixed into the lenses (Chadwick Optical, White River Junction, VT). Patients were instructed to gaze through the central, prism-free zone of the lens, rather than looking directly through the prism. No additional formal training was administered.

In this report, we describe successful use of the prism system for the treatment of 2 patients with HH, which expanded VFs to allow each to meet minimum requirements for driver licensure in the state of Minnesota. This study was approved by the Institutional Review Board at the University of Minnesota.

CASE REPORT

Case 1
A 24-year-old man suffered a right occipital lobe stroke in April 2011. He was emmetropic with a visual acuity of...
20/20 at distance in both eyes. Visual field testing revealed a complete left HH, which remained stable for more than 9 months. The rest of his neuro-ophtalmic examination was unremarkable.

Case 2

A 31-year-old man underwent resection of a right parieto-occipital oligoastrocytoma measuring $5 \times 5 \times 6$ cm in 2006. Postoperatively, he sustained a right posterior cerebral artery stroke. Visual acuity was 20/20 in both eyes, and visual fields demonstrated a complete left HH. The rest of his neuro-ophtalmic examination showed normal results. Both patients were otherwise intact neurologically without evidence of neglect or cognitive impairment.

In both cases, VFs were assessed monocularly using Humphrey visual field 24-2 SITA Fast with a size-III stimulus. Kinetic perimetry was performed using dynamic mapping and static perimetric probing with a size-III stimulus. Visual fields were reassessed at multiple time points to confirm stability of the HH. Kinetic perimetry was assessed both monocularly and binocularly with and without the prisms. Fixation was monitored closely for any saccades into the blind hemifield.

Case 1 had a left HH with $95^\circ$ and $65^\circ$ angle of remaining horizontal VF in the right and left eyes, respectively, and

**FIG. 1.** Two 57-PD prism segments placed at the upper and lower part of the eyeglass lens ipsilateral to the visual field loss with the central edges at the level of the limbus, spanning the entire width of the lens. The individual prism segments are placed obliquely at $45^\circ$ angle to the horizontal with the upper prism oriented base out and down and the lower prism oriented base out and up.

20/20 at distance in both eyes. Visual field testing revealed a complete left HH, which remained stable for more than 9 months. The rest of his neuro-ophtalmic examination was unremarkable.

**FIG. 2.** Case 1. Top, kinetic perimetry of each eye without prisms. Bottom, binocular kinetic perimetry with prisms.
95° angle binocularly. With the use of the prism system, the binocular VF increased to 115° angle of continuous, horizontal VF (Fig. 2). Case 2 had a left HH with 79° and 40° angle of remaining VF in the right and left eyes, respectively, and 82° angle binocularly. With the use of the prism system, the binocular VF increased to 112° angle of continuous horizontal VF (Fig. 3). Both patients reported an immediate improvement in their VF and spatial awareness and rapidly adapted to the prisms over several weeks. Although no standardized questionnaire or formal assessment was conducted, both patients noted significant improvement in quality of life. They denied diplopia and visual confusion and reported satisfaction with their prism glasses. Case 1 passed an on-road driver evaluation administered by a driving rehabilitation specialist after several weeks of adapting to the prisms. Case 2 began driving after adapting to the prisms for approximately 6 months. Each holds a valid driver’s license in the state of Minnesota and has successfully operated a motor vehicle without any restrictions or accidents for 1 and 5 years, respectively.

**DISCUSSION**

Optical devices can provide field-of-view relocation or expansion. Relocation simply shifts the position of the scotoma (binocular sector prisms), whereas expansion actually allows the patient to monitor a larger amount of his environment at any given moment (monocular peripheral prisms). The peripheral placement of the prisms avoids diplopia that could occur with prisms in the visual axis. The oblique orientation of the prisms creates overlapping fields along the horizontal meridian, which may produce superior augmentation of continuous horizontal VF (Fig. 4) as required by most driver licensing agencies. These findings have led to a multicentered randomized clinical trial of these lenses in patients with HH (4).
Augmentation of VF in a patient with a HH using monocular sector prisms is not surprising, but we have shown that our patients achieved the 105° VF requirement from the Department of Motor Vehicles in Minnesota. There are conflicting data regarding quantifying the impact of VF loss on the ability to operate a motor vehicle. In patients with glaucoma, it has been documented through the use of driving simulators and real-world self-reported data that having a horizontal VF of 100° angle or less is associated with a significantly higher risk of accidents (5). In patients with HH, Bowers et al (6), using a driving simulator, showed a decreased blind-side detection of obstacles, while Niehorster et al (7) employed visual displays to demonstrate a reduction in visual motor control. However, Wood et al (8,9), using on-road driving performance, have reported that some individuals with homonymous VF defects may be safe to drive. Further study is required to better define the relationship of driving simulators to on-road performance and to determine the minimum VF required to drive safely.

The state of Minnesota requires that individuals have at least 105° angle of horizontal VF to obtain a license to operate a motor vehicle (1). Both of our patients were able to meet these requirements with the use of the prism system and subsequently have been driving accident free. To the best of our knowledge, the oblique orientation of the peripheral prism segments to meet the driver license requirements has not been reported. It should be emphasized that patients with HH may benefit from a training and adaptation period during which they learn to safely utilize their prism system before driving on the open road (10).

We acknowledge the limitations of our report. We only evaluated 2 patients with HH. Both were young without other neurological deficits. Our findings may not be generalizable to all patients with a HH, particularly older patients or those with cognitive impairment or neglect. Nevertheless, clinicians should consider using this prismatic system in patients with HH as a potential aid in obtaining a driver’s license to operate a motor vehicle.

REFERENCES
Downbeat Nystagmus Secondary to Familial Hemophagocytic Lymphohistiocytosis

Cindy X. Cai, BS, Frank S. Siringo, MD, OD, Jeffrey G. Odel, MD, Angela Lignelli-Dipple, MD, Bryan A. Lanzman, MD, Tatyana Gindin, MD, Alexandra H. Filipovich, MD

Abstract: Hemophagocytic lymphohistiocytosis is a rare autosomal recessive disorder characterized by severe inflammation induced by defective natural killer cell function, which triggers a state of highly stimulated but ineffective immune response. This disorder can affect multiple organ systems, and neurologic manifestations include irritability, seizures, impaired consciousness, meningismus, and cranial nerve palsies. We describe a unique case of hemophagocytic lymphohistiocytosis in which downbeat nystagmus developed due to cerebellar swelling with compression of the cervicomedullary junction.

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Hemophagocytic lymphohistiocytosis (HLH), which may be familial or acquired, is a severe inflammatory disorder caused by disruption of T-cell function that triggers a state of hypercytokinemia, resulting in a highly stimulated but ineffective immune response. Downbeat nystagmus (DBN) is an uncommon disorder of ocular motility that typically localizes to the posterior fossa, particularly the cervicomedullary junction. We are unaware of previous reports of DBN occurring in the setting of HLH.

CASE REPORT

A previously healthy ex-full-term 10-month-old dizygotic twin girl was brought by her parents to the emergency department for second opinion after suffering 2 months of intermittent fevers to 40.5°C, diarrhea, and progressive abdominal distension. Previously, she had been hospitalized for intensive supportive care including empiric intravenous cefazidime and gentamicin. Her course had been further complicated by hepatosplenomegaly, lymphadenopathy, and disseminated intravascular coagulation. Because of new-onset strabismus, the ophthalmology service was consulted.

On examination, the patient was hypotonic with open and flat anterior fontanelles. She could fix and follow with each eye but had a marked abduction deficit with saccadic slowing of the left eye. Pupils were equal and reactive without a relative afferent defect. The anterior and posterior segments were normal. The examination was most notable for prominent primary position downbeat nystagmus (DBN).

Laboratory testing demonstrated a white blood cell count of 5,400/cm³ (normal: 6,000–17,500/cm³), hemoglobin of 8.5 g/dL (normal: 9.5–13.5 g/dL), platelet count of 134,000/cm³ (normal: 165,000–415,000/cm³), mild hyponatremia, and normal hepatic function tests. Erythrocyte sedimentation rate was 120 mm/hr, triglycerides 1,065 mg/dL (normal: 30–200 mg/dL), and fibrinogen 151 mg/dL (normal: 99–466 mg/dL). Opening pressure on lumbar puncture was normal, and cerebrospinal fluid (CSF) analysis showed a polyclonal, predominantly T-cell population highlighted with CD45 gating. Cultures for bacteria and fungus and parasitology studies were negative; polymerase chain reaction for cytomegalovirus, Epstein–Barr virus and Parvovirus B19 was negative. Further testing revealed increased ferritin of 2,284 ng/mL (normal: 10–150 ng/mL), increased mean channel fluorescence of perforin in natural killer (NK) cells, absent NK cell function, cell function, decreased NKT cells, increased CD8 T lymphocytes (26%; normal: 0%–4%), and increased sIL-2 receptor (CD25) (>3000; normal: 0–1033).

Magnetic resonance imaging (MRI) of the brain showed diffuse cerebral atrophy with mild increase in cerebellar volume (Fig. 1A) and leptomeningeal enhancement of the cerebellum (Fig. 1B). The cerebellar tonsils were low-
lying and crowded with decreased CSF space at the cervi-
comedullary junction, but no Arnold-Chiari malformation
was noted.

Bone marrow aspirate demonstrated hemophagocytosis
(Fig. 2A) with increased bone marrow macrophages (Fig.
2B). Results of flow cytometry from the bone marrow were
similar to those obtained from the CSF.

Genetic testing revealed a mutation in the STXBP2
gene with normal UNCl3D. There was no known history of
consanguinity in the parents.

The patient was treated with etoposide and dexameth-
asone, and, after 48 hours, there was improvement in
mental status with resolution of DBN and the left sixth
nerve palsy. Follow-up MRI revealed decreased cerebellar
swelling (Fig. 3). The patient received an allogenic hemato-
opietic stem cell transplant (HSCT) 6 months after the
initial presentation and had 90% engraftment with normal
antibody titers 18 months later.

DISCUSSION

Hemophagocytic lymphohistiocytosis (HLH) is part of
a heterogeneous group of disorders initially described in
1952 by Farquhar and Claireaux (1). The frequency of this
disorder is difficult to assess but estimated as 1 in 50,000–
100,000 live births (2,3). On the molecular level, familial
forms of the disorder often are caused by defects in perforin
or other proteins involved in granule-dependent cytotoxicity
(4–7). NK and cytotoxic T lymphocytes normally store per-
forin and granzyme proteins in specialized secretory lysosomes
that are released upon encountering a target cell, leading to
target cell apoptosis (8). When this mechanism is dysfunc-
tional, there is an abnormal and excessive production of
T-cell–derived cytokines (“cytokine storm”) leading to uncon-
trolled accumulation of activated T lymphocytes and activated
histiocytes (macrophages) in various tissues, resulting in
hemophagocytosis and organ damage (8–10).

Genetic defects in familial hemophagocytic lymphohis-
tiocioties (fHLH) are autosomal recessive and continue to
expand. Currently, 5 genetic loci (FHL 1–5) have been
identified (9). FHL1 encodes an as-yet unidentified protein.
FHL2 accounts for up to one-third of fHLH cases because
of defects in PRF1 (perforin), a cytolytic protein used by
NK and cytotoxic T lymphocytes. Perforin polarizes to
the plasma membrane of target cells, delivering cytotoxic
enzymes (granzymes) to the target cell, inducing apoptosis.

FIG. 1. A. Precontrast T1 sagittal magnetic resonance imaging shows diffuse cortical atrophy, cerebellar swelling with low-
lying tonsils. B. Postcontrast T1 axial magnetic resonance imaging reveals cerebellar leptomeningeal enhancement.

FIG. 2. Bone marrow aspirate. A. There are abundant macrophages with soft granular cytoplasm and evidence of eryth-
rocytes undergoing phagocytosis (arrows) (hematoxylin and eosin, x400). B. CD68 immunostaining demonstrates numerous
macrophages (x400).
Other genetic loci in fHLH encode proteins facilitating delivery of perforin to target cells, including a priming factor munc13-4 (UNC13D), and membrane fusion proteins syntaxin 11 (STX11) and munc18-2 (STXB2).

The clinical syndrome of HLH also can be trigged by infection, autoimmune disease, and malignancy, and are designated acquired HLH (7,11). Macrophage activation syndrome typically is used to designate HLH due to autoimmune diseases, particularly juvenile arthritis and systemic lupus erythematosus (11,12). The pathophysiologic mechanism of acquired HLH is not well understood; as genetic testing has improved, it has become evident that some cases may in fact represent fHLH (13). Interestingly, the same conditions associated with acquired HLH can trigger it in familial forms. Given the increasingly blurred distinction between familial and acquired forms of HLH, some believe that the syndrome should not be classified into distinct subtypes. Rather, there may be a continuum of risk to developing HLH, including both genetic and environmental factors (14).

Regardless of etiology, HLH remains a syndrome diagnosed by a unique pattern of clinical findings. HLH diagnostic guidelines have been published (15) (Table 1) and our patient exhibited 7 of the 8 diagnostic criteria: fever, splenomegaly, hypertriglyceridemia, hemophagocytosis, absent NK cell activity, elevated ferritin, and elevated soluble interleukin-2 receptor.

Although not listed as part of the diagnostic criteria, neurological symptoms can predominate the initial clinical presentation of HLH. Deiva et al (16) reported that approximately 63% of children have neurologic symptoms at the onset of fHLH, including irritability, seizures, impaired consciousness, meningismus, and cranial nerve palsies. Parenchymal edema of the brain, which may occur in HLH, can affect the cerebellum (17,18). In the most extreme cases, this can lead to fatal tonsillar herniation.

Neuropathologic staging of HLH has been established and correlated with clinical manifestations: Stage 1—leptomeningeal infiltrates of lymphocytes and histiocytes; Stage 2—adjacent parenchymal involvement with perivascular infiltration; Stage 3—massive parenchymal infiltration via lymphocytes and histiocytes, with tissue necrosis (19). These cellular changes lead to neuroimaging findings, including edema, focal areas of necrosis with parenchymal volume loss, diffuse white matter abnormalities, and leptomeningeal or perivascular enhancement (20).

There is a single report of vertical nystagmus in a patient with HLH (21). This occurred in a 13-month-old boy accompanied by a bulging fontanelle, papilledema, and CSF pleocytosis. Computed tomography of the brain showed “no specific abnormality,” and the patient’s condition improved with steroid therapy.

Treatment of HLH to stabilize signs and symptoms involves the use of immunosuppressive agents, including dexamethasone, etoposide, cyclosporine A, and intrathecal methotrexate (15). Curative therapy is HSCT (22). Even

**TABLE 1. 2004 Diagnostic guidelines for HLH**

<table>
<thead>
<tr>
<th>The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled</th>
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</thead>
<tbody>
<tr>
<td>1. A molecular diagnosis consistent with HLH</td>
</tr>
<tr>
<td>2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Splenomegaly</td>
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<tr>
<td>Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood):</td>
</tr>
<tr>
<td>Hemoglobin &lt;90 g/L (in infants &lt; 4 wk: hemoglobin &lt;100 g/L)</td>
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<tr>
<td>Platelets &lt;100 × 10^9/L</td>
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<tr>
<td>Neutrophils &lt;1.0 × 10^9/L</td>
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<tr>
<td>Hypertriglyceridemia and/or hypofibrinogenemia:</td>
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<tr>
<td>Fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥ 265 mg/dL)</td>
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<tr>
<td>Fibrinogen ≤ 1.5 g/L</td>
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<tr>
<td>Hemophagocytosis in bone marrow or spleen or lymph nodes</td>
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<tr>
<td>Low or absent NK cell activity</td>
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<tr>
<td>Ferritin ≥ 500 μg/L</td>
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<tr>
<td>Soluble CD25 (i.e., soluble IL-2 receptor) ≥ 2400 U/mL</td>
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Adapted from Henter et al (15).

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HLH, hemophagocytic lymphohistiocytosis; IL, interleukin; NK cell, natural killer cell.
with HSCT, the estimated overall 3-year probability of survival has been reported at approximately 64% (15). Reduced-intensity conditioning HSCT has significantly improved survival, with the current reports of approximately 92% survival at 3 years (23). Despite these recent advances, untreated HLH is still a rapidly fatal disease that warrants urgent diagnosis and intervention.

Our case is unique in both documenting the occurrence of DBN in HLH and the resolution of DBN with treatment of cerebellar edema.

REFERENCES

Isolated Rotational Vertigo Due to Internal Capsular Infarction

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Abstract: Isolated rotational vertigo is most often associated with disorders of the semicircular canals, vestibular nerve, brainstem, or cerebellum but rarely observed following a supratentorial stroke. A 64-year-old man developed sudden onset of vertigo and horizontal right-beating nystagmus with a torsional component in primary and eccentric gazes, unsteady gait, and axial lateropulsion to the right side. Magnetic resonance imaging demonstrated an infarction in the posterior limb of left internal capsule, an unusual cause of the patient’s signs and symptoms.

CASE REPORT

A right-handed 64-year-old man reported acute onset rotational vertigo with unsteady gait. The vertigo was continuous and not affected by changes in position. He complained of nausea and vomiting but denied tinnitus, hearing loss, altered speech, sensory disturbance, or muscle weakness. His medical history was only significant for hypertension requiring medication.

Examination revealed spontaneous horizontal right-beating horizontal nystagmus with a torsional component in primary and eccentric positions of gaze, even during visual fixation (See Supplemental Digital Content, Video, http://links.lww.com/WNO/A91). The nystagmus increased in amplitude with right gaze and decreased with left gaze, without a periodic alternating component. It was not modified by vibratory stimulation, hyperventilation, or varying head position. The head impulse test was normal. The range of eye movement was full. The patient could stand unassisted but was unable to stand with the feet together (Rhomberg sign). He also fell to the right when ambulating. He did not demonstrate problems of appendicular coordination, such as dysmetria and dysdiadochokinesia. Motor and sensory examinations were unremarkable and deep tendon reflexes were normal, as was the remainder of the neurological examination.

Laboratory studies included complete blood count, electrolyte profile, glucose level, urinalysis, renal, liver, and thyroid function tests; all were within normal limits. Magnetic resonance imaging (MRI) performed 2 days after onset of symptoms revealed infarction in the posterior limb of the left internal capsule (Fig. 1). MRA of the intracranial vasculature and major vessels of the neck was unremarkable. Diffusion tensor imaging–fiber tractography showed that the left corticospinal tract was not disrupted by the internal capsular stroke.
(Fig. 2). Video-oculography (VOR) performed 8 days after onset of symptoms documented resolution of spontaneous nystagmus, with only left beating nystagmus observed following head shaking. Repeat MRI of the brain confirmed a cerebral infarction restricted to the left internal capsule. The patient was prescribed clopidogrel (75 mg daily) and his vertigo and gait gradually improved. He was discharged from the hospital 10 days later without any neurological deficits.

**FIG. 1.** Diffusion-weighted imaging reveals an acute infarction in the posterior limb of the left internal capsule.

**FIG. 2.** Diffusion tensor imaging–fiber tractography. A. Coronal view shows that the left corticospinal tract is similar to the one on the right. B. Axial image demonstrates that the left corticospinal tract is not disrupted by the internal capsular infarction (arrow).
DISCUSSION

Rotational vertigo is defined as the perception of spinning or movement of the person or the surrounding environment. It is usually due to an infratentorial abnormality, often involving the vestibular system (2,4) or a disturbance of the posterior cerebral circulation (5,6).

Our patient had rotational vertigo and imbalance without hemiparesis. With both clinical testing and neuroimaging studies, we carefully searched for a brainstem or infratentorial lesion, but found none. The normal head impulse test and head-shaking nystagmus in the opposite direction of spontaneous nystagmus also suggested a central cause (7). Seizure was an unlikely explanation because the patient’s symptoms were persistent and not episodic. In a study of 112 patients, Anagnostou et al. (2) reported that leukoaraiosis was associated with dizziness. Although our patient had leukoaraiosis on brain MRI, he did not complain of dizziness but rather rotational vertigo and had spontaneous nystagmus. Thus, leukoaraiosis also was an unlikely cause of his symptoms.

Only few cases of isolated rotational vertigo have been described to be caused by a supratentorial cerebral infarct. Most of these cases were caused by lesions in the parieto-insular vestibular cortex (1,8–11), which receives vestibular afferents through thalamic projections and descend to the vestibular nuclei. Any disruption along these pathways can produce vestibular dysfunction (12). Nakajima et al. (13) reported a case of rotational vertigo associated with putaminal infarction similar to the lesion in our case, but the patient also exhibited hemiparesis as a predominant symptom. We are unaware of any reports of infarction of the posterior limb of internal capsular causing isolated rotational vertigo and imbalance without hemiparesis. One possible explanation of the findings in our patient is that internal capsular infarction impaired the pathway between the thalamus and vestibular cortices. Edema from internal capsular infarction may have compressed the thalamus transiently, leading to vestibular dysfunction.

Our patient exhibited axial lateropulsion to the right side, most likely due to a disturbance of the spinocerebellar pathway. The spinocerebellar pathway originating from right cerebellum projects through the thalamus to terminate in the left cerebral cortex (14). A left supratentorial lesion, as was the case in our patient, could disturb this pathway and cause truncal ataxia. An alternate explanation for falling to the right may be transient excitation of left vestibulospinal pathway by left internal capsular infarction. Acute stroke may cause transient neuronal excitation by enhanced release of glutamate, reduced GABAergic function, mitrochondrial or receptor changes (15).

REFERENCES
Congenital Trochlear–Oculomotor Synkinesis

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Abstract: Synkinesis of the extraocular muscles forms a subset of congenital ocular motility abnormalities termed congenital cranial dysinnervation disorders. Synkinesis most frequently involves the abducens or oculomotor nerves and rarely the trochlear nerve. Only 3 such patients have been described in the literature. We report an isolated case of trochlear–oculomotor synkinesis in a healthy 6-year-old boy and discuss the proposed pathophysiology of this disorder.

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The congenital cranial dysinnervation disorders encompass a wide range of congenital ocular motility abnormalities with a presumed neurogenic etiology. This continually expanding group includes congenital fibrosis of the extraocular muscles and various synkinetic disorders of extraocular muscles. The common theme of these disorders is a congenital abnormality of ocular and/or facial muscle innervation, several of which now have an identified genetic basis (1). Many are uncommon, making their phenotypic and genotypic characterization challenging. Although aberrant innervation of the extraocular muscles occurs in Duane retraction syndrome and Marcus–Gunn jaw-winking ptosis (trigemino–oculomotor synkinesis), synkinetic lid retraction due to aberrant innervation of the levator palpebrae by a variety of cranial nerves has been reported, including inverse Duane syndrome with adduction and pseudo-Graefe with depression (oculomotor–oculomotor synkinesis) (3), with abduction (abducens–oculomotor synkinesis) (4), and with head tilt (vestibulo–oculomotor synkinesis) (5).

CASE REPORT

A 6-year-old boy was evaluated by the pediatric ophthalmology service due to parental concern that the child’s right eye did not fully depress. The boy was the product of a full-term pregnancy and unremarkable delivery and was otherwise healthy and neurologically normal. There was no family history of strabismus or ptosis.

Visual acuity was 20/20 in each eye, and stereopsis measured 40 arcseconds. Pupillary reactions and extraocular movements were normal. There was no pupil constriction associated with horizontal or vertical gaze, and no ptosis. Ocular alignment was orthophoric in all fields of gaze and on head tilt to either side. Retraction of the right upper eyelid occurred with depression of the right eye in adduction (Fig. 1). Lid retraction did not occur with chewing or other jaw movement, and the remainder of the ocular and cranial nerve examination was normal. Magnetic resonance imaging of the brain revealed a moderately sized right posterior communicating artery in contact with the right oculomotor nerve (Fig. 2). The resolution of the scan did not allow visualization of the trochlear nerves.

DISCUSSION

Synkinesis is an aberrant innervation, causing involuntary stimulation of a muscle or structure not normally supplied by that nerve. Dysinnervation of the extraocular muscles manifests most frequently as Duane retraction syndrome (oculomotor–abducens synkinesis), occurring in 1%–4% of strabismus patients (2). In addition to Marcus–Gunn jaw-winking ptosis (trigemino–oculomotor synkinesis), synkinetic lid retraction due to aberrant innervation of the levator palpebrae by a variety of cranial nerves has been reported, including inverse Duane syndrome with adduction and pseudo-Graefe with depression (oculomotor–oculomotor synkinesis) (3), with abduction (abducens–oculomotor synkinesis) (4), and with head tilt (vestibulo–oculomotor synkinesis) (5).

Trochlear–oculomotor synkinesis has been reported previously. Martorina and Porte (6) described a 4-year-old girl with a history of forceps delivery and congenital left ptosis and exophoria. Extraocular movements were full, and left eyelid retraction was noted on right downgaze. Due to forceps delivery, she was presumed to have traumatic oculomotor and trochlear nerve palsies with aberrant regeneration. Lim et al (7) reported the case of a 4-year-old girl, born prematurely with tetralogy of Fallot. She had no ptosis and was orthophoric in all gaze directions, but demonstrated left lid retraction on downgaze, more pronounced
on right downgaze. The third case reported by Kothari et al (8) was of a 7-year-old healthy boy with esophoria, left ptosis, excyclotorsion, and limitation of elevation of the left eye. He was also found to have left lid retraction when looking down and right. The authors suggested that congenital paresis of the superior division of the left oculomotor nerve resulted in aberrant innervation of the levator muscle by the trochlear nerve, either by misdirection of regenerating axons or by ephaptic transmission.

To date, all cases of presumed trochlear–oculomotor synkinesis demonstrate ipsilateral upper eyelid retraction associated with depression of the eye in adduction. As depression of the eye in adduction is mainly accomplished by the superior oblique muscle, it would seem that the most likely abnormality involves aberrant innervation of the levator palpebrae muscle by a segment of the ipsilateral trochlear nerve. However, no reported case, including the present one, has demonstrated direct anatomical or electrophysiological evidence of a connection between these nerves. In addition, a single case of deglutition–trochlear synkinesis has been reported (9). The trochlear nerve is unique, in that it is the only cranial nerve to decussate within the brainstem and the only cranial nerve to exit the brainstem dorsally. These anatomical factors may limit dysinnervation due to lack of proximity of the trochlear nerve to other cranial nerve roots.

Mechanisms of aberrant innervation that have been proposed include ephaptic transmission between nearby nerves or misdirected regeneration of axonal sprouts (2,8). Ephaptic transmission occurs when depolarization of a neuron or group of neurons induces an action potential in a nearby nerve, despite the lack of a synaptic connection. Asymmetry of the magnitude or duration of an action potential or variable defects in myelination can cause unidirectional ephaptic transmission between 2 adjacent nerves (10).

Embryonic cranial nerve axon growth is, at least, partly directed by expression of transcription factors within the nerve and release of certain growth factors, which attract the nerve to the appropriate muscle(s). In utero injury to the oculomotor nerve may lead to aberrant regeneration. In our patient, this may have been due to compression by the posterior communicating artery. Unlike the abducens nerve,
the trochlear and oculomotor nerves respond to the same growth factors (e.g., fibroblast growth factor, hepatocyte growth factor, and semaphorin-3F) (11). The trochlear nerve could potentially respond inappropriately to these signals and supply innervation to the levator muscle.

Axonal misdirection may occur during neuronal development at the level of the nucleus, brainstem, or peripheral nerve (1). We propose that trochlear–oculomotor synkinesis is unlikely to be central in origin. Although these cranial nerve nuclei lie in close proximity, the levator nucleus supplies innervation to both eyelids, and cases of aberrant regeneration have unilateral lid retraction. The oculomotor and trochlear nerve fascicles extend in opposite directions through the brainstem, with the oculomotor nerve exiting on the ventral surface and the trochlear nerve exiting dorsally. As they course anteriorly toward the superior orbital fissure, the trochlear nerve crosses over the superior division of the oculomotor nerve to enter the orbital apex outside the annulus of Zinn. This crossing is the location of closest proximity for the 2 nerves, suggesting that this may be another potential location for coinnervation.

REFERENCES
Optic Nerve Sheath Fenestration for the Treatment of Papilledema Secondary to Cerebral Venous Thrombosis

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Abstract: A 16-year-old adolescent girl with multiple risk factors for thrombosis presented with acute onset of headache, decreased vision, and papilledema. Evaluation demonstrated cerebral venous thrombosis (CVT) involving the left transverse and sigmoid sinuses and left internal jugular vein. Following bilateral optic nerve sheath fenestration (ONSF), she experienced improvement in vision and resolution of papilledema. In selected cases, ONSF is an effective surgical option for the treatment of papilledema due to CVT after medical treatment has failed.

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Cerebral venous thrombosis (CVT) may be precipitated by multiple risk factors and present clinically in a highly variable manner. The sequelae of CVT are usually due to effects of increased intracranial pressure (ICP) and cerebral infarction. The most common clinical findings are the presence of focal neurologic signs or partial seizures (1). Papilledema secondary to increased ICP is another manifestation, reported in 50% of patients (1,2). Early detection and treatment of papilledema is important to prevent progressive loss of vision (3). Although medical management with carbonic anhydrase inhibitors, corticosteroids, and lumbar drainage is the initial treatment for increased ICP, surgery, including optic nerve sheath fenestration (ONSF) and ventriculoperitoneal shunting, may be required (2,4).

CVT is rare in the adult population with reported prevalence of 1.32 cases per 100,000. It is even more uncommon in children occurring in 0.67 cases per 100,000 non-neonates (5,6). We describe a pediatric patient with multiple risk factors for thrombosis who developed papilledema and vision loss secondary to CVT. She was treated successfully with anticoagulation and ONSFs.

CASE REPORT

A 16-year-old adolescent girl complained of throbbing frontal headaches with associated nausea and vomiting for 1 week. Her only medication was oral contraceptive pills, which she began taking 2 weeks previously. Magnetic resonance venography (MRV) revealed thrombosis of the left transverse and sigmoid sinuses and the left internal jugular vein. The patient was immediately started on subcutaneous enoxaparin sodium, and acetazolamide was added 12 days later, with the dose gradually increased to 1000 mg/d. Hematological studies demonstrated positive Factor V Leiden and prothrombin G20210A mutations, elevated Factor XII, and mildly lowered antithrombin III and protein S levels.

Three weeks later, she developed horizontal diplopia and decreased vision. Opening pressure on lumbar puncture (LP) was 50 cm H₂O and cerebrospinal fluid (CSF) analysis was normal.

One month after the initial presentation, neuroophthalmologic evaluation revealed visual acuity of 20/80, right eye, and 20/200, left eye. Automated visual field (Humphrey Visual Analyzer; Carl Zeiss Meditec, Dublin, CA; central 30-2 Swedish interactive threshold algorithm) showed enlarged blind spots and paracentral scotomas bilaterally (Fig. 1A). There was marked papilledema in each eye. The patient was referred to our institution for ONSF.

At the time of our evaluation, visual acuity was 20/100, right eye, and 20/200, left eye. Pupillary reactions were normal, ocular motility revealed an abduction defect of the left eye, and high-grade bilateral papilledema was present (Fig. 1A). Medications consisted 48 mg of subcutaneous enoxaparin and 500 mg of acetazolamide, both taken twice daily.
An ONSF of the left eye was performed the following day. After disinsertion of the medical rectus muscle, careful retraction of the orbital soft tissues was performed. A rectangular window was made in the optic nerve sheath, with a large gush of CSF exiting the fenestration. Because our patient was anticoagulated, extra care was taken during the procedure to maintain hemostasis and she was hospitalized overnight for observation.

One week later, the patient reported resolution of diplopia and visual acuity was 20/100, right eye, and 20/70, left eye. Extraocular movements were full bilaterally. On funduscopy, there was still significant edema of the right optic disc but left optic disc edema was much improved. Automated visual fields showed minimal improvement.

A right ONSF with the same surgical technique and precautions was performed the following day. One week later, visual acuity was 20/200, right eye, and 20/70, left eye. Extraocular movements were full bilaterally. On funduscopy, there was still significant edema of the right optic disc but left optic disc edema was much improved. Automated visual fields showed minimal improvement.

Two months later, visual acuity was 20/40 in each eye with continued resolution of papilledema and visual field defects. At 4 months, acuity was 20/40 bilaterally and visual fields were stable, with complete resolution of papilledema.

**DISCUSSION**

Although there is general consensus that the initial treatment for CVT is anticoagulation, controversy exists regarding the management of the secondary sequelae, including elevated ICP (1). Carbonic anhydrase inhibitors and diuretics are considered first-line treatment (2,4). If the patient is anticoagulated, then serial LPs are contraindicated. In our patient, raised ICP led to papilledema and progressive visual loss despite medical therapy. Our report demonstrates that ONSF is a potential treatment for visual loss secondary to CVT. In addition, our patient illustrates how CVT can have multiple causative factors. She had an unusual combination of predisposing conditions, including Factor V Leiden mutation, G20210A mutation, Factor XII deficiency, decreased antithrombin III and protein S levels, and use of oral contraceptive pills (7–9).

Alsuhaibani et al. (10) reported significant improvement in papilledema and stability of the visual field in the fellow eye after unilateral ONSF in patients with idiopathic intracranial hypertension. Although we agree with the approach of operating on the eye with the more severe papilledema and visual field loss in attempting to avoid bilateral surgery, this was not the case in our patient. Rather, bilateral ONSFs were required.

The surgical treatment of papilledema in the setting of CVT has its own unique challenges. The use of anticoagulation complicates performing ONSF due to the increased risk of bleeding during the surgical procedure. Careful dissection during the procedure is essential to maintain hemostasis within the orbit. We recommend overnight observation following surgery to monitor for complications of bleeding. Measures can be taken to decrease the risk of hemorrhage by working with a hematologist or perhaps switching the patient to enoxaparin sodium, which has a shorter half-life than heparin.

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Neuromyelitis optica (NMO) is an autoimmune disorder of the central nervous system directed against astrocytes. Initially diagnosed in individuals with monophasic or relapsing optic neuritis and transverse myelitis, NMO is now recognized as a demyelinating disorder with pleiotropic presentations due to the identification of a specific autoantibody response against the astrocyte water channel aquaporin-4 in the majority of individuals. As visual impairment and neurologic dysfunction in NMO are commonly severe, aggressive treatment of relapses and prophylactic immunomodulatory therapy are the focus of treatment. Although there are no approved treatments for NMO, medications and therapeutic interventions for acute and chronic treatment have been the subject of retrospective study and case reports. The goal of this review is to familiarize the reader with biologic and clinical data supporting current treatments in NMO and highlight future strategies based on advancements in our understanding of NMO pathogenesis.

NEUROMYELITIS OPTICA DIAGNOSIS

Neuromyelitis optica (NMO) is a rare inflammatory disorder of the central nervous system (CNS) that commonly presents with optic neuritis (ON) or transverse myelitis (TM) (1,2). The prevalence of NMO varies considerably across studies (3–57 per million population) (3). In North America, Australia, and Europe, NMO patients represent a small fraction (1%–2%) of Caucasians with inflammatory white matter disease; however, in Asia and the West Indies, the percentage rises to almost 50% of demyelinating disorders (1,4). Initially considered a variant of multiple sclerosis (MS), NMO is now clearly recognized to be a separate disorder with distinct clinical, radiographic, pathologic, and serologic features. Within 5 years of diagnosis, more than 50% of NMO patients develop severe visual impairment (5–7); therefore, for the neuro-ophthalmologist, early diagnosis and aggressive treatment of NMO is critical for the preservation of visual and neurologic function.

The current criteria for the diagnosis of NMO require a clinical history of ON and TM accompanied by at least 2 of 3 supportive criteria: 1) brain magnetic resonance imaging (MRI) not diagnostic of MS at disease onset, 2) spinal MRI with a contiguous lesion ≥3 segments, and 3) aquaporin-4 immunoglobulin G (AQP4-IgG) seropositivity (8). In NMO, the clinical presentations of ON and TM may be simultaneous or sequential, although the frequency of AQP4-IgG seropositivity is significantly lower in individuals with simultaneous ON and TM (9). The high specificity of AQP4-IgG for NMO has permitted the identification of seropositive patients with spatially limited or atypical presentations. Termed “NMO spectrum disease,” AQP4-IgG seropositive individuals with isolated ON, longitudinally extensive TM, recurrent ON or TM, protracted nausea and vomiting, narcolepsy, and encephalopathy are considered to have forms frustes of disease (1,10).

Certain clinical, laboratory, and MRI findings may also raise clinical suspicion for NMO. For ON, these include patients with severe vision loss (<20/200) or visual field depression, poor visual recovery, severe and diffuse peripapillary retinal nerve fiber layer loss, and MRI findings of posterior optic nerve or chiasm involvement of extensive visual pathway lesions (11–17). For TM, the presence of a longitudinally extensive spinal cord lesion or central cord involvement should raise suspicion for NMO. Cerebrospinal fluid (CSF) findings suggestive of NMO include a pleocytosis greater than 50 cells per microliter, a high percentage of polymorphonuclear cells, or the presence of eosinophils (18). In rare instances, AQP4-IgG has been reported to be restricted to the CSF (19). MRI features of brain lesions...
characteristic of NMO mirror the periventricular and hypothalamic localization of AQP4 and are more commonly found around the third and fourth ventricle and the aqueduct of Sylvius than the lateral ventricles and corpus callosum as in MS (20).

**NEUROMYELITIS OPTICA PATHOPHYSIOLOGY**

Understanding the pathophysiology of NMO is fundamental in providing a framework for the treatment and the design of new therapies. Active NMO lesions demonstrate perivascular IgG, IgM, and C9neo deposition in a “rim” or “rosette-mesh” pattern, thickened and hyalinized vessels, and heavy immune cell infiltrate, composed primarily of neutrophils, eosinophils, and macrophages (21). CD3+ and CD8+ T-cell infiltration is rare, and natural killer cells are sparse in lesions (22). Possible features of glutamate excitotoxicity and disturbed water homeostasis are also observed (23,24). All NMO lesions show a widespread and early loss of AQP4 immunoreactivity, in contrast to MS lesions where AQP4 immunoreactivity is often increased (25–27).

Early NMO lesions reveal preserved myelin despite a prominent loss of the astrocytes (28). In lesioned areas devoid of astrocytes, oligodendrocytes displayed nuclear chromatin condensation indicative of apoptosis. Additional regions of reparative gliosis are highlighted by the presence of unipolar and bipolar glial fibrillary acidic protein-positive, AQP4-negative astrocyte progenitors, indicating that demyelination in NMO is secondary to the acute destruction of perivascular astrocytes. Despite the strong evidence connecting demyelination to astrocyte loss, the link between neuronal dysfunction and astrocyte, oligodendrocyte or inflammatory pathology remains unclear. The recent identification of multiple regions of distinct histopathology within NMO lesions suggests that the disruption of glial–neuronal interactions may play an important role in NMO lesion evolution (29).

**Neuromyelitis Optica Experimental Models**

This identification of AQP4 as the antigenic target in the majority of NMO cases has facilitated the development of experimental laboratory models for the investigation of lesion pathogenesis and the development of highly effective, targeted therapies. In support of these models, multiple lines of evidence now support AQP4-IgG binding as an initiating pathogenic event in NMO. First, AQP4-IgG is highly specific (97%–100%) for NMO (30), and serum and CSF AQP4-IgG titers correlate with spinal cord lesion size (31). Second, current therapies designed to reduce humoral immune activity, such as plasma exchange and B-cell depletion, ameliorate both acute and chronic disease activity (32,33). And third, NMO serum and recombinant AQP4 antibodies derived from clonally expanded NMO CSF plasmablasts can reproduce NMO-specific pathology in ex vivo and in vivo NMO models of disease (34–37).

To date, an ideal animal model of NMO with spontaneous AQP4-targeted ON and TM has yet to be created. Short of this goal, a variety of in vivo, ex vivo, and in vitro experimental systems have been used. In vivo, AQP4-IgG is co-injected into murine brain with immune cells and/or human complement proteins (36,38) or transfused following the induction of experimental autoimmune encephalomyelitis (34,35). These models recapitulate major features of human lesions, including the temporal progression from astrocyte loss to demyelination with complement deposition, immune cell infiltration, and axonal injury. An ex vivo spinal cord explant model has been used to complement the in vivo injection model and characterize mechanisms and immune cell populations mediating astrocyte damage and demyelination (37). In vitro, AQP4-IgG-mediated physiologic changes, such as glutamate excitotoxicity and water transport, are studied on primary astrocyte cell lines (39,40), cell lines transfected with AQP4 (23,40), or purified reconstituted vesicles (41). Although each model has intrinsic limitations, they have proven to be extremely valuable in expanding our knowledge of the mechanisms and progression governing NMO pathogenesis.

**Neuromyelitis Optica Lesion Formation and Repair**

Multiple lines of evidence support a primary role for antibody effector function in inducing astrocyte damage in NMO. In vitro, ex vivo, and in vivo NMO models have independently demonstrated that AQP4-IgG can induce complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC) in the presence of complement proteins or immune cells (Fig. 1) (34,37,38,42,43). This is not unexpected, as AQP4-IgG is predominantly IgG1 (42,44) and strongly activates the classical complement cascade through binding the complement protein C1q (45,46). C1q activation produces a proteolytic cascade that ultimately results in the formation of the membrane attack complex (MAC) and cell lysis. IgG1 also binds Fc receptors (FcRs) that activate ADCC. FcRs are present on a variety of immune cells, and when co-stimulated result in the release of cytotoxic granules and enzymes that cause lysis of target cells. Both CDC and ADCC are critical for mediating the widespread astrocyte loss seen in human NMO lesions (43). At the molecular level, the structural organization of AQP4 into orthogonal array of particles (OAPs) is likely to have a profound influence in antigenicity and function of AQP4 (47,48). Significant CDC activation is only observed on AQP4 isoforms assembled into OAPs, suggesting that OAP formation also enhances the ability for autoantibodies to bind C1q (46). The influence of OAP formation in directing ADCC remains unexplored.

Astrocyte loss is an early feature in the evolution of NMO lesions. In agreement with human lesions, experimental...
Neuromyelitis optica (NMO) pathogenesis. Tissue or bone marrow resident plasma cells produce aquaporin-4 (AQP4) autoantibodies that bind to AQP4 orthogonal array of particles (OAPs) on the astrocyte foot processes. AQP4-IgG binding recruits complement C1q, which initiates the classical complement cascade and produces the anaphylatoxins C3a and C5a. Complement activation leads to membrane attack complex (MAC) deposition and astrocyte destruction, promotes the recruitment of immune cells into the central nervous system, and locally stimulates immune cells in the lesion to enhance immune cell effector activity. Astrocyte damage occurs from the combined effects of MAC deposition and AQP4-IgG-mediated antibody-dependent cell-mediated cytotoxicity, and polymorphonuclear degranulation and phagocytosis. Secondary demyelination may occur due to the withdrawal of astrocyte-mediated homeostatic functions, complement activation, or immune cell degranulation. EAAT, excitatory amino-acid transfer.

FIG. 1. Mechanisms of neuromyelitis optica (NMO) pathogenesis. Tissue or bone marrow resident plasma cells produce aquaporin-4 (AQP4) autoantibodies that bind to AQP4 orthogonal array of particles (OAPs) on the astrocyte foot processes. AQP4-IgG binding recruits complement C1q, which initiates the classical complement cascade and produces the anaphylatoxins C3a and C5a. Complement activation leads to membrane attack complex (MAC) deposition and astrocyte destruction, promotes the recruitment of immune cells into the central nervous system, and locally stimulates immune cells in the lesion to enhance immune cell effector activity. Astrocyte damage occurs from the combined effects of MAC deposition and AQP4-IgG-mediated antibody-dependent cell-mediated cytotoxicity, and polymorphonuclear degranulation and phagocytosis. Secondary demyelination may occur due to the withdrawal of astrocyte-mediated homeostatic functions, complement activation, or immune cell degranulation. EAAT, excitatory amino-acid transfer.

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<table>
<thead>
<tr>
<th>TABLE 1. Current therapies for neuromyelitis optica</th>
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</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Dosage for acute attack: methylprednisolone 1,000 mg, 3–5 days</td>
</tr>
<tr>
<td>For prophylaxis: prednisone 2.5–20 mg/d</td>
</tr>
<tr>
<td>Plasma exchange</td>
</tr>
<tr>
<td>Acute attack: 1–1.5 plasma volumes per exchange, 5x</td>
</tr>
<tr>
<td>Azathioprine</td>
</tr>
<tr>
<td>Usual maintenance dosage: 2 mg·kg$^{-1}$·d$^{-1}$</td>
</tr>
<tr>
<td>Mycophenolate</td>
</tr>
<tr>
<td>Median maintenance dosage: 2,000 mg/d, range 750–3,000 mg</td>
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adopted from the treatment of MS and idiopathic ON; there has been no therapeutic trial for the acute treatment of NMO. If there is no significant clinical improvement on steroids, plasma exchange (PLEX) has been shown to be effective for both ON and TM associated with NMO. Typically, 5 cycles are administered daily or every other day. An early, randomized controlled trial of plasma exchange in steroid refractory CNS demyelinating diseases included 2 patients with NMO, of which 1 patient responded to PLEX (62). Subsequent studies and case series reported significant improvement in around 44%–75% of the NMO patients treated with PLEX (33,63–65). Male gender, preserved reflexes and early initiation of treatment were associated with moderate or marked improvement. Patients who were treated successfully improved rapidly following PLEX and improvement was sustained (65).

The efficiency of plasma exchange was independent of NMO-IgG seropositivity (64). Since published series have failed to define clinical or temporal criteria for response to IVMP, the institution of PLEX is left to the clinician’s judgment and experience.

A recent study comparing IVMP monotherapy with IVMP in combination with PLEX treatment for cases of ON associated with NMO demonstrated IVMP and PLEX in combination being more efficient than IVMP alone. High-contrast visual acuity, visual fields, and temporal retinal nerve fiber layer thickness improved significantly with PLEX treatment (66). Interestingly, low-contrast letter scores (Sloan 0.25%) and color vision (Farnsworth-Munsell 100 Hue) did not improve. These results suggest that the lack of rapid visual improvement following IVMP therapy for NMO acute ON should prompt consideration for the rapid initiation of PLEX.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Side Effects</th>
<th>Efficacy</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Inhibitor of dihydrofolate reductase and purine and thymidine synthesis</td>
<td>Leukopenia, pancytopenia, infections, hepatotoxicity, joint pain, stomatitis, nausea, diarrhea</td>
<td>Reduced ARR from 1.39 to 0.18</td>
<td>82,83</td>
</tr>
<tr>
<td>Methotrexate dosage: 17.5–50 mg/wk</td>
<td>Inhibits proliferation of T and B lymphocytes</td>
<td>Cardiotoxicity, leukemia, hepatotoxicity, leukopenia, nausea, stomatitis, diarrhea</td>
<td>EDSS was stable</td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Intercalates with DNA and inhibits topoisomerase II</td>
<td></td>
<td>Reduced ARR from 2.8 to 0.7</td>
<td>84,85</td>
</tr>
<tr>
<td>Mitoxantrone Dosage: max. cumulative doses 120 mg/m², 3–6 monthly cycles of 12 mg/m² followed by 6–12 maintenance doses</td>
<td>Suppresses development of T and B lymphocytes and macrophages</td>
<td></td>
<td>Reduced EDSS from 5.6 to 4.4</td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>Chimeric anti-CD20 monoclonal antibody</td>
<td>Infusion reactions, infections, (e.g. recurrent herpes zoster, respiratory infections, urinary tract infects), fatigue, transient leukopenia and transaminase elevation, PML</td>
<td>Reduced ARR from 1.7–2.6 to 0.0–0.93</td>
<td>23,86–91</td>
</tr>
<tr>
<td>Rituximab Usual dosage: initiation with 375 mg/m² weekly for 4 wk, 1,000 mg twice biweekly, maintenance (1,000 mg) either fixed or upon recurrence of B cells</td>
<td>Depletes B cells from pre-B cells through memory lineages</td>
<td></td>
<td>EDSS stabilized or improved</td>
<td></td>
</tr>
</tbody>
</table>

ARR, annualized relapse rate; EDSS, expanded disability scale score; PLEX, plasma exchange; PML, progressive multifocal leukoencephalopathy; TPMT, thiopurine methyltransferase.
Intravenous immunoglobulin (IVIg) and cyclophosphamide have also been used to treat acute NMO exacerbations and prevent relapses. IVIg frequently is substituted for PLEX in other neurologic disorders, including myasthenia gravis and Guillain–Barré syndrome. In idiopathic ON, however, IVIg has failed to improve the outcome of steroid resistant cases (67,68), suggesting that caution should be exercised before automatically substituting IVIg for PLEX in NMO. Recently, 2 small case series have reported benefit in NMO patients receiving either acute or short-term prophylactic IVIg therapy (69,70), indicating that IVIg therapy may warrant further investigation in NMO (71). For acute exacerbations resistant to IVMP and PLEX, some patients with acute TM have benefited from cyclophosphamide infusion (72). Interestingly, a recent case series has reported lack of efficacy for the use of cyclophosphamide in NMO relapse prevention (73), indicating that distinct immunologic mediators may drive NMO lesion onset and propagation.

**Prevention of Attacks**

Immunosuppressive therapy typically is instituted after the initial attack given the risk of severe disability associated with a single exacerbation. The decision for preventive treatment strategies is often challenging given the absence of prospective clinical trials and the risk of serious side effects. Due to the low incidence and prevalence of NMO, interventional studies with level I or II evidence are not currently available; therefore, treatment strategies are mostly based on small case series and case reports (74). Besides balancing the best available data on clinical efficacy with established short- and long-term side effects, risk factors such as age, gender, comorbid conditions, functional status, and response to previous therapies have to be taken into consideration. Predictors of high risk of disability in NMO patients include male gender, Afro-Caribbean and Asian ethnicity, and young age at onset (75).

**Corticosteroids and Plasma Exchange**

Watanabe et al (76) performed a retrospective study of 25 Japanese NMO patients treated with low-dose prednisone monotherapy (doses ranged from 2.5 to 20 mg/d) over a median observation period of 19.3 months. The median annual relapse rate (ARR) decreased from 1.48 pretreatment to 0.49 during treatment. Treatment with more than 10 mg/d of prednisone was significantly more effective than therapy with 10 mg/d or less. Another case series analyzed the efficacy of concurrent PLEX treatment in NMO relapse prevention (77). Four patients treated with oral prednisolone in combination with azathioprine or cyclophosphamide received regular PLEX for residual disease activity. Two of 4 patients stabilized with the additional therapy.

**Azathioprine**

The pro-drug azathioprine is converted to nucleotide anti-metabolites that inhibit the purine synthesis and interfere with the proliferation of cells, especially B and T lymphocytes. Costanzi et al (78) reported the largest experience of azathioprine in NMO/NMO spectrum diseases. In their retrospective study of 99 patients, 86 patients fulfilled the 2006 Wingerchuk criteria (8) while the remaining 13 patients were diagnosed with AQP4 seropositive NMO spectrum disorders. In 70 patients who had been followed up for at least 1 year, the ARR decreased from 2.20 to 0.52 relapse per year over a median treatment interval of 22 months. The improvement was not as robust in patients taking less than 2 mg/kg/day but seemed to improve with an increase in the mean corpuscular volume. Azathioprine was discontinued in 38 patients because of apparent lack of efficacy (13 patients), severe side effects (22), and lymphoma (3). A reduced level of thiopurine methyltransferase (TPMT) leads to azathioprine toxicity, so TPMT activity should be tested before administration. Additional studies of azathioprine have reported similar results. Bucchetti et al (79) noted a decrease in the ARR from 2.1 to 0.6 during therapy (2 mg/kg/day with or without steroids) in their retrospective analysis, and Sahraian et al (80) reported a reduction in the ARR from 1.13 to 0.4 (3 mg/kg/day) in their small prospective cohort.

**Methotrexate**

Methotrexate is an inhibitor of the dihydrofolate reductase and other folate-dependent enzymes necessary for purine and thymidylate synthesis. Recently, Kitley et al (82) reported a retrospective observational case series of 14 AQP4 positive NMO and NMO spectrum disorder patients treated with methotrexate (median maintenance dose 17.5 mg/wk). The median duration of treatment was 21.5 months and the median ARR decreased significantly following therapy (0.18 during treatment vs 1.39 pretreatment). Forty-three percent of the patients were relapse free, and none of the patients discontinued due to adverse effects. In an earlier case series, Minagar (83) treated 7 NMO patients with methotrexate (50 mg) weekly and oral prednisolone (1 mg/kg daily) and observed stabilization in disease activity as evidenced by unchanged or reduced EDSS.

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Mitoxantrone
Mitoxantrone, an anthracyclene antineoplastic drug, inhibits topoisomerase II and suppresses development of both lymphocytes and macrophages. The drug also induces differential inhibitory effects on subgroups of leukocytes, preferentially targeting CD19+ B cells. Kim et al (84) reported on the use of mitoxantrone in 20 NMO and NMO spectrum disorder patients (maximum cumulative doses of 120 mg/m², 3–6 monthly cycles of 12 mg/m² followed by 6–12 mg/m² maintenance doses). During the average treatment duration of 17 months, the ARR declined from 2.8 pretreatment to 0.7 posttreatment, and the mean EDSS decreased from 5.6 to 4.4. In another case series of 5 NMO patients, improvement was noted in 4 individuals, although 2 patients still had relapses during treatment (85). Serious adverse events included decline of left ventricular ejection fraction in one patient that caused discontinuation after a cumulative dose of 72 mg/m². Therapy-related leukemia, a consequence of mitoxantrone treatment in other disorders, was not observed in either study.

Rituximab
Rituximab is a chimeric mouse/human anti-CD20 monoclonal antibody that depletes naive and memory B cells. Different dosing regimens have been reported for the treatment of NMO, especially in the maintenance stage. In most studies, 375 mg/m² was administered weekly for 4 weeks followed by 1,000 mg infused twice within 2 weeks every 6 months (32,86–89); however, some patients received infusions (usually 1,000 mg) every 2–12 months (88) or depending on circulating B cell numbers (32,86,87). Recently, Greenberg et al (90) suggested a monthly monitoring of CD19 B-cell counts in the blood and the rapid readjusting of doses when B cells rise above 2%. In 2 retrospective studies, NMO patients treated with rituximab over a median interval of 19–32.5 months demonstrated a significant reduction in ARR and stabilization of EDSS. Bedi et al (88) reported decreases in the ARR from 1.87 to 0.0 relapse/patient per year, and Jacob et al (86) recorded a decline in ARR from 1.7 to 0.0. EDSS scores stabilized or improved in most patients in both studies. Two patients died during the follow-up, one due to severe brainstem relapse and the other due to septicemia (86). Kim et al (89) reported the results of a 5-year study of 30 NMO patients treated with rituximab. The ARR lowered in 26 of 30 patients (2.4 pretreatment vs 0.3 posttreatment), 18 patients became relapse free, and in 28 patients, the disability was either improved or stabilized. Pellkofer et al (91) recorded a reduction in ARR from 2.35 to 0.93 (decline in 80% of the patients) and stabilization of EDSS scores in a cohort of 10 NMO patients. In their study, NMO disease activity correlated with B-cell depletion but not with AQP4-IgG titer or B-cell cytokine levels. One patient died because of cardiovascular failure, but no significant infections were reported.

Eculizumab
Eculizumab is a humanized monoclonal antibody against complement C5 that inhibits its cleavage by C5 convertase. In NMO, eculizumab blocks AQP4-IgG–mediated CDCC. In an open-label phase II study of 14 NMO patients with refractory disease, eculizumab therapy significantly reduced attack frequency and stabilized or improved neurological disability (92). After 12 months of treatment, 12 of 14 patients were relapse free; however, 1 patient developed meningococcal sepsis and sterile meningitis but fully recovered after treatment.

Questionable Therapies
Although effective in MS, INF-β, natalizumab, and fingolimod have been reported to be inefficacious or even harmful when used for the treatment of NMO. Kim et al (93) reported a study on 40 patients with NMO spectrum disorders who had been treated with INF-β for more than 5 months. In 95% of the patients, the treatment was not effective and even worsened the disease course. The mean ARR increased from 1.49 to 2.38 and the mean EDSS scores increased from 2.72 to 4.78 points during therapy. Additional case reports have highlighted severe exacerbations following the initiation of INF-β-1b therapy in NMO patients (94–96). The biologic mechanisms by which INF-beta exerts its effects in NMO spectrum disorders are unclear but may involve the upregulation of B-cell activating factor or IL-17 levels with INF-beta therapy (97).

In a case series of 5 NMO patients who tested positive for AQP4 autoantibodies, natalizumab treatment (median duration of 8 infusions, range, 2–11 infusions) failed to control disease or worsened disease activity (98). In all patients, a total of 9 relapses occurred (median duration to relapses 120 days) and the mean EDSS increased from 4.0 to 7.0 after natalizumab therapy. In addition, a severe NMO attack in a natalizumab treated patient was described with florid active demyelination, the presence of neutrophils and eosinophils, and the massive fragmentation of glial fibrillary acidic protein-positive astrocytes (99). It has been hypothesized that the peripheral sequestration of proinflammatory T cells during natalizumab treatment may stimulate pro-inflammatory B cell populations critical to NMO disease activity. Alternatively, the increased number of peripheral eosinophils associated with natalizumab treatment (100) may exacerbate lesion formation (21,53) and facilitate the generation of new peripheral plasma cell niches (101).

Two cases of NMO exacerbations associated with oral fingolimod have recently been reported. Min et al (102) described a patient with NMO spectrum disorder who developed extensive brain lesions 2 weeks after initiation of fingolimod treatment. The patient suffered residual encephalomalacia but had no further exacerbations with steroid treatment over 3 years following the withdrawal of fingolimod. In another case, a patient with NMO spectrum disorder developed a fulminant course with multiple white matter lesions ten days after
initiation of fingolimod therapy (103). The mechanisms by which fingolimod might cause these severe exacerbations remain speculative. Similar to natalizumab, fingolimod may exacerbate NMO lesion formation by promoting bone marrow egress of eosinophils (104). Alternatively, fingolimod may alter CNS B cell trafficking and enhance the production of intrathecal autoantibodies (105).

**Therapeutic Recommendations**

Although no therapy has been evaluated in a prospective clinical trial, the previously noted retrospective and prospective case series provide a framework for guiding treatment decisions for NMO patients. For NMO patients with acute ON, TM, or CNS syndrome, IVMP should be administered rapidly and continued for 3–5 days. If clinical improvement is not noted in this time period, then plasma exchange should be initiated and repeated for a total of 5 cycles. For patients with idiopathic ON or TM and a high suspicion of NMO, an identical treatment program should be strongly considered. Currently there is no evidence to support the immediate and simultaneous administration of IVMP and PLEX for NMO or other acute demyelinating relapses. For refractory demyelinating events that are not responsive to IVMP and PLEX, treatment with cyclophosphamide or IVIg may be considered. Following relapse, a prolonged taper of prednisone (from 60 to 100 mg/d to off over 4–8 weeks) is generally advised.

Azathioprine, mycophenolate mofetil, and rituximab are the most extensively studied preventative treatments and are generally considered the first-line therapies for NMO prophylaxis. While prednisone and mitoxantrone remain alternatives for monotherapy, the lower efficacy of prednisone and the potential toxicity of mitoxantrone should limit them to add-on use for refractory cases. We recommend starting NMO patients on azathioprine, mycophenolate, or rituximab using the doses and schedules noted in Table 1. The ultimate choice of therapy will be dependent on drug availability, patient preference, mode of administration, cost, and potential side effects. Disease relapse on therapy should prompt a re-evaluation of the treatment regimen. Before considering a change in therapeutics, careful consideration should be given to critical factors that may influence therapeutic response: drug dosage, treatment duration, adherence, and treatment resistance (anti-chimeric antibodies or B cell repletion with rituximab). For patients failing azathioprine or mycophenolate, a switch to rituximab is advised. If rituximab is not available, the addition of oral prednisone remains an alternative. For NMO patients failing rituximab therapy, combination therapy with azathioprine or mycophenolate or the off-label use of tocilizumab, are two potential approaches.

**Emerging Neuromyelitis Optica Therapeutics**

Improved understanding of NMO pathophysiology has facilitated the development of novel approaches to the treatment of disease (Fig. 2). Although many strategies remain focused on immunosuppression and immunomodulation, some potential therapies are engineered to interfere with the targeted immune response against AQP4.

**B Cell and Plasma Cell Targeted Therapies: Anti-CD20 and Anti-CD19**

As noted previously, multiple clinical studies have shown that depletion of CD20+ naive and memory B cells reduces relapse frequency in NMO patients. CD20, however, is not expressed on plasmablasts and plasma cells; B cell populations considered to be critical for the production of AQP4-IgG. CD19 is a B cell marker that is, expressed later in the B cell lineage and is retained on the surface of plasmablasts and some plasma cells (106). A CD19-depleting antibody may offer a promising avenue to directly deplete AQP4-IgG-producing B cells and reduce pro-inflammatory lymphocyte populations in NMO. Although there are no clinical trials initiated to date, CD19 depleting therapies are currently under active investigation (107).

**Cytokine Modulation: Interleukin-6 and Interleukin-17**

The cytokines IL-6 and IL-17 have both been implicated in NMO pathology. IL-6 signaling prolongs long-term plasma cell survival in vitro (108) and promotes anti-AQP4 antibody production by circulating plasmablasts (109). Since IL-6 is elevated in the CSF of NMO patients (110), IL-6 signaling may enhance the survival of CNS B cells and increase intrathecal autoantibody production. In addition, IL-6 may polarize T cells toward a pro-inflammatory TH17 phenotype (111). Tocilizumab is a monoclonal antibody that binds to the IL-6 receptor and blocks binding of IL-6 signaling. Two case reports have suggested that tocilizumab may be beneficial for the treatment of NMO. Araki et al (112) and Kieseier et al (113) reported on clinical and radiographic improvement in treatment-resistant NMO patients following IL-6 receptor blockade.

Based on the histopathology and cytokine signature of NMO, several groups have posited a central role for the TH17 pathway in NMO pathogenesis (114,115). Acute NMO lesions demonstrate prominent granulocytic infiltration (21), IL-17 levels are elevated in the serum of NMO patients (115), and AQP-4-specific T cells recovered from the peripheral blood of NMO patients demonstrate a TH17 bias (111). Blockade of IL-17 signaling offers a novel approach to NMO therapy by hindering the development of TH17 T cells and reducing the infiltration of polymorphonuclear cells into active lesions.

**Neutrophil and Eosinophil Inhibitors**

Neutrophils and eosinophils are a significant component of the inflammatory infiltrate in NMO lesions and contribute to local CNS injury through ADCC and phagocytosis. Sivelestat, a potent neutrophil elastase inhibitor, reduces lesion formation in both animal and ex vivo slice models of NMO (54). Currently, sivelestat is only approved in Japan for the treatment acute respiratory distress syndrome. It may be
Useful as a corticosteroid-sparing agent in the treatment of acute NMO exacerbations by inhibiting both CNS neutrophil migration and tissue damage. Recently, the eosinophil stabilizers cetirizine and ketotifen were shown to reduce NMO lesion formation in the intracerebral injection model (53). Improved understanding of the therapeutic window for delivery for these drugs would aid in determining how these agents may be used individually or in combination to treat acute NMO exacerbations or lessen the severity of future attacks.

**Competitive Inhibitors of NMO IgG: Aquaporumab and Small Molecules**

Disrupting the binding of pathogenic AQP4 autoantibodies to target astrocytes is an attractive nonimmunosuppressive therapeutic strategy for AQP4-IgG seropositive NMO patients. To date, both blocking antibodies and small molecule inhibitors have been investigated in in vitro, ex vivo, and in vivo assays. An engineered, monoclonal AQP4 antibody that exhibits tight AQP4 binding and slow dissociation kinetics was mutated to make the Fc domains nonpathogenic by eliminating both CDC and ADCC effector activity (116). This mutated competitive blocking antibody, termed “aquaporumab,” was observed to outcompete pathogenic AQP4 serum autoantibodies and inhibit NMO lesion formation in vivo and ex vivo. High-throughput screening has been used to identify small molecule blockers that prevent NMO IgG binding to the extracellular surface of AQP4 (117,118). Both small molecule and antibody blocking therapies may be used for disease prevention or during disease exacerbations. To date, no blocking therapy or engineered AQP4 antibody has been shown to disrupt AQP4 water channel function (41,119). Therefore, it is less likely that blocking therapies will disrupt the normal function of AQP4 and produce undesirable toxicity.

**Antibody Modulation: Deglycosylation of NMO IgG and Fc Cleavage**

IgG effector functions are dependent on the presence of an intact and glycosylated Fc region. Endoglycosidase S (EndoS) and IgG-degrading enzyme (IdeS) from *Streptococcus pyogenes* are 2 distinct enzymes that may be used to modify endogenous AQP4 autoantibody pathogenicity. EndoS is an enzyme that selectively cleaves asparagine-linked glycans (120). Tradrantip et al (121) showed that treatment of patient sera with EndoS neutralizes NMO sera pathogenicity and prevents lesion formation in ex vivo and in vivo NMO models. IdeS is an enzyme that cleaves the Fc domain of immunoglobulin to produce a nonpathogenic Fab (122,123). IdeS co-injection with human complement into a murine brain 15 minutes after AQP4 autoantibody injection interrupts the lesion development (121). During acute relapses, antibody modulatory therapies may enhance the efficacy of apheresis to combat the pathogenicity of AQP4-IgG. The potential immunogenicity of these enzymes, however, may limit their chronic applications in humans.

**FIG. 2.** Current and emerging therapeutic strategies for NMO. Therapeutics (red) that are current (bold) and novel are listed individually next to the process that they inhibit. Immunosuppressant medications are designed to decrease the activity of antibody-producing B cells and pro-inflammatory T cells. Aquaporin-4 immunoglobulin G (AQP4-IgG) modulation may block the pathogenic action of autoantibodies. Blocking therapies are designed to prevent the binding of pathogenic autoantibodies to their astrocytic target. Reducing orthogonal array of particle (OAP) formation is intended to modify the assembly of AQP4 target to decrease antibody binding. Neutrophil and eosinophil inhibitors are intended to limit Fc receptor–mediated destructive mechanisms. Complement inhibition is designed to limit complement-dependent cytotoxicity (CDC) and membrane attack complex formation. Definitive therapies to promote remyelination in lesioned tissue remain to be developed. ADCC, antibody-dependent cell-mediated toxicity; APP, amyloid precursor protein; LFB, luxol fast blue.
Modulation of AQP4 OAP Formation

CDC activation is critical for the development of lesions in NMO animal models (43,49). As CDC activation is dependent on OAP formation (46), disrupting OAP formation may limit CDC activation and represents a novel approach to decrease further immune activation in the presence of NMO IgG. The utility of this approach remains uncertain, as the endogenous roles of OAP formation in the CNS remain unclear. Likewise, disrupting OAP formation in other areas where AQP4 is highly expressed may produce undesirable toxicity. The utility of such agents for both acute and chronic therapy will require careful investigation.

CONCLUSIONS

Current NMO therapeutics are centered on immunosuppression. Improved understanding of NMO pathogenesis has led to the development of novel therapeutic strategies designed to limit AQP4-IgG-mediated inflammatory injury, pro-inflammatory B-cell development, and cell-mediated injury. A variety of novel approaches are either in development, beginning early phase clinical testing, or beginning drug registration trials. They include targeted immunosuppressive AQP4-IgG blocking therapies, complement inhibitors, cytokine modulators, and agents that minimize granulocyte or eosinophil toxicity. The expanding armamentarium of potential NMO therapeutics provides a promising environment for the initiation of formal treatment trials and the development of evidence-based approaches that minimize visual and neurologic morbidity in disease.

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An Orbital Mass in a 5-Year-Old Girl

Mark R. Melson, MD, Daniel Brat, MD, PhD, Patricia J. Hudgins, MD

Dr. Melson:

A 5-year-old girl presented for evaluation of a right orbital mass displacing the globe superiorly. She had a 5-week history of swelling around her right eye. Her medical history and ocular history were unremarkable. She was adopted at the age of 7 months, and there was no known history of prenatal or perinatal problems. She was home-schooled and enjoyed playing outdoors. She had no preceding illness or trauma and no known contact with anyone ill. Her pediatrician diagnosed a blocked tear duct and referred her to an ophthalmologist. She failed empiric treatment for orbital cellulitis and was subsequently referred to an orbital surgeon. Computed tomography (CT) of the orbits was performed.

Dr. Hudgins:

Noncontrast axial and coronal CT images of the orbits show a poorly defined mass, that is both intraconal and extraconal in the lateral and inferior quadrants of the right orbit (Fig. 1). There is soft tissue present on superior and medial maxillary sinus walls.

Dr. Melson:

The family was told that the child probably had cancer and needed urgent treatment and was referred to our service. In the week before seeing us, her family began giving the patient commercially marketed supplements for cancer treatment. In the meantime, she complained of swelling around the right eye, mild discomfort along the right inferior orbital rim, and intermittent, binocular horizontal diplopia.

On examination at our institution, the patient’s visual acuity was 20/40, right eye, and 20/20, left eye. There was limitation of induction and abuction of the right eye and 3 mm of relative right proptosis with superior displacement of the globe (Fig. 2). There was no relative afferent pupillary defect. The anterior segment and funduscopic examinations were unremarkable. Magnetic resonance imaging (MRI) of the orbits was obtained (Fig. 3).

Dr. Melson:

The MRI report described a “large, enhancing, ill-defined mass arising from the inferior rectus muscle … invades right maxillary and right ethmoid sinuses … abuts posterior wall of the globe and inferior orbital nerve sheath … most likely represents rhabdomyosarcoma.” Because of concern for a malignancy, we performed a right anterior orbitotomy at which time we identified a firm, white orbital mass that appeared to extend through the orbital floor. A biopsy of the lesion was performed, with frozen sections interpreted as a “moderately cellular spindle cell lesion with mixed inflammatory infiltrate.”

Dr. Hudgins:

The images do not show a discrete mass but rather a process, that is diffuse, both intraconal and extraconal, and now in the extra-orbital pterygomaxillary fissure. The maxillary sinus disease is likely related, but because it does not enhance, it probably is fluid and not part of the mass.

Section Editors: Neil R. Miller, MD
Janet Rucker, MD

Clinical-Pathological Case Study

**Dr. Melson:**

The patient recovered uneventfully and was discharged home. The pediatric oncology service was contacted about meeting the patient once final pathology was known.

On postoperative day 3, the patient’s parents reported increased swelling and chemosis around the child’s right eye. On the same day, we received the pathology report from the initial biopsy.

**Dr. Melson:**

Permanent sections were read as showing a fungal process. Accordingly, we contacted the family and had them bring the patient back to the hospital immediately so that she could be admitted for surgical debulking. At the time of surgery, the bulk of the mass was removed. The floor of the maxillary sinus was intact except for a focal area of dehiscence.

**Dr. Brat:**

Histologic sections and special stains obtained on the specimen from the debulking procedure showed findings identical with those from the first specimen and were consistent with an active, necrobiotic fungal infectious disease.

**Dr. Melson:**

At surgery, a catheter was placed in the orbit for direct orbital and sinus irrigation with antifungal medication. Amphotericin B was given intravenously and intraorbitally until catheter was dislodged on postoperative day 2. Immunologic evaluation was performed that revealed no evidence of systemic immune compromise. Posaconazole was added, and the patient was discharged home 10 days after the surgery, once it was clear that her disease was not clinically progressing. She subsequently received intravenous amphotericin B as an outpatient for 3 months and oral posaconazole for 15 months, during which time her examination normalized and imaging evidence of disease resolved (Fig. 5). Cultures from the surgical specimens never grew any organism. The patient’s examination normalized and follow-up MRI showed gradual resolution of her orbital infection.

**Dr. Hudgins:**

Contrast-enhanced T1 coronal MRI shows that the infectious process has decreased in extent but is still present (Fig. 5). Imaging findings, especially in the setting of infection, often lag behind the clinical examination. In light of the...
improvement in the patient’s physical examination, persistent disease should not be interpreted as treatment failure.

**Final Pathologic Diagnosis:**
Invasive fungal orbital cellulitis in an immunocompetent child.

**Dr. Melson:**
Orbital zygomycosis in immunocompetent patients, especially children, is a rare cause of an orbital mass mimicking cellulitis (1,2). Management usually includes surgical debulking, long-term antifungal medication, and evaluation for immune suppression dysfunction (1,3). Emerging organisms, such as *Apophysomyces elegans*, may make these presentations more common in the future. These cases typically are associated with some form of traumatic inoculation. In others, the mechanism of disease may not be evident, as in our case (4,5). Although our patient’s family noted that she enjoyed playing outside and particularly in the dirt, they could not recall an episode where she had any sort of injury that could have caused her infection.

Invasive fungal disease was one of our diagnostic considerations but so were other orbital inflammatory disorders, including Langerhans cell histiocytosis and idiopathic orbital inflammatory disease (orbital pseudotumor). Our patient’s family had been told that she had an orbital malignancy by the first orbital surgeon; the first MRI report stated that she likely had rhabdomyosarcoma, and the intraoperative frozen section pathology was inconclusive. The child had no signs or symptoms of systemic infection and the orbital mass appeared solid with no evidence of purulence or tissue necrosis. Therefore, treatment for fungal disease was not initiated after the first surgery and cultures were not obtained. Once the final pathologic diagnosis was known, we chose to debulk the lesion and institute intraorbital irrigation and systemic treatment with antifungal medication. Duration of treatment was determined in consultation with the infectious disease specialists whose recommendations were guided by clinical and imaging findings in her orbit. Once she showed no evidence of residual

**FIG. 3.** Magnetic resonance imaging, coronal sections, performed 5 weeks after the onset of symptoms. **A.** Noncontrast T1 image shows a poorly defined, diffuse orbital mass and worsening of the maxillary sinus opacification since the previous computed tomographic scan. **B.** Postcontrast T1 image with fat saturation shows enhancement in the mass. Note that the neighboring rectus muscles cannot be differentiated from the lesion. **C.** Image slightly posterior to (B) shows enhancement in the pterygomaxillary fissure (arrows).

**FIG. 4.** Histopathology of orbital mass. **A.** Low-magnification section shows an active inflammatory process, with regions of reactive stroma and granulation tissue, chronic inflammation, and necrosis (hematoxylin and eosin, ×40). **B.** Higher magnification shows necrobiotic material, dense spindle cell proliferation, and chronic inflammation composed mostly of lymphocytes and plasma cells (hematoxylin and eosin, ×200). **C.** Numerous fungal hyphal elements are present (Gomori methenamine silver, ×40). Inset: Fungal morphology from area indicated by arrow is consistent with *Aspergillus* sp. or zygomycosis (Gomori methenamine silver, ×400).
Institute of Allergy and Infectious Disease, and a clinical trial (NCT01386437) currently is under way to identify genetic factors that may predispose patients to these types of infections even when no primary immune deficiency has been identified with conventional testing (6). The study proposes to use information gathered from patients to help gain new insights into the pathogenesis of these infections in immunocompetent hosts and to identify potential targets for novel therapies. It is critical that the clinician consider the possibility of fungal disease in any patient who develops an orbital process, regardless of their immune status.

REFERENCES


FIG. 5. Three months after treatment with antifungal agents, postcontrast T1 coronal magnetic resonance imaging with fat suppression shows almost complete resolution of the right orbital process.
Literature Commentary


Purpose: To estimate the proportion of patients presenting with isolated third, fourth, or sixth cranial nerve palsy of presumed microvascular origin vs other causes.

Design: Prospective, multicenter, observational case series. Participants: A total of 109 patients aged 50 years or older with acute isolated ocular motor nerve palsy.

Testing: Magnetic resonance imaging (MRI) of the brain.

Main Outcome Measures: Causes of acute isolated ocular motor nerve palsy (presumed microvascular or other) as determined with early MRI and clinical assessment.

Results: Among 109 patients enrolled in the study, 22 had cranial nerve III palsy, 25 had cranial nerve IV palsy, and 62 had cranial nerve VI palsy. A cause other than presumed microvascular ischemia was identified in 18 patients (16.5%; 95% confidence interval, 10.7–24.6). The presence of 1 or more vasculopathic risk factors (diabetes, hypertension, hypercholesterolemia, coronary artery disease, myocardial infarction, stroke, and smoking) was significantly associated with a presumed microvascular cause (P = .003, Fisher exact test). Vasculopathic risk factors were also present in 61% of patients (11/18) with other causes. In the group of patients who had vasculopathic risk factors only, with no other significant medical condition, 10% of patients (8/80) were found to have other causes, including midbrain infarction, neoplasms, inflammation, pituitary apoplexy, and giant cell arteritis (GCA). By excluding patients with third cranial nerve palsies and those with GCA, the incidence of other causes for isolated fourth and sixth cranial nerve palsies was 4.7% (3/64).

Conclusions: In our series of patients with acute isolated ocular motor nerve palsies, a substantial proportion of patients had other causes, including neoplasm, GCA, and brainstem infarction. Brain MRI and laboratory workup have a role in the initial evaluation of older patients with isolated acute ocular motor nerve palsies regardless of whether vascular risk factors are present.

This is a thought-provoking article, which calls into question the common practice of following elderly patients with presumed vasculopathic ocular motor cranial nerve palsies without neuroimaging. Although on initial calculation, 16.5% had a non-microvascular cause, the authors claim that for those with third nerve palsy, there is little controversy and most neuro-ophthalmologists will agree on imaging. In analyzing the message of this article, we should concentrate on where there is controversy (fourth and sixth nerve palsy), that 3/64 patients were found to have structural lesions. Let us see what difference it would have made had they not been immediately imaged. The first was a patient with vasculopathic risk factors and a midbrain infarct in whom the treatment of risk factors is identical with or without a small, likely lacunar, infarct. The second was a woman with petroclival meningioma subsequently treated with surgery. In her case, when the diplopia did not resolve in a few months, she could have been imaged and subsequently treated with surgery. The third case was a man with lymphoma. He too could have been diagnosed when he worsened or did not recover within the following few months. One could make the case that in this patient population, the authors point out the importance of MRI in reassuring those who want to know there is no lesion. Although this is true, there is an approach to patients who want reassurance that they do not need an MRI. Explaining to them that there is a small risk of a lesion and that I am willing to follow them and not obtain an MRI also reassures patients who are below 60 years old.

The authors point out the importance of MRI in reassuring those who want to know there is no lesion. Although this is true, there is an approach to patients who want reassurance that they do not need an MRI. Explaining to them that there is a small risk of a lesion and that I am willing to follow them and not obtain an MRI also reassures this patient population.

In my 30 years in the neuro-ophthalmology world, I cannot recall a patient with a fourth or sixth palsy where the delay in imaging made a difference in outcome. So for me, I will likely scan a few more patients and perhaps follow only those a little older, but not yet ready to get MRI on all patients.

—Mark L. Moster, MD

Like you, Mark, I was trained to follow patients with vascular risk factors who have complete third nerve palsies.
with pupil sparing and fourth and sixth nerve palsies. If the patient did not show improvement in 6 weeks, I would scan them. I have not run into trouble with this practice, but I have not been practicing for 30 years!

More and more, I am moving toward ordering neuroimaging for the patient with complete third nerve palsy and pupil sparing. Interestingly, in this article, a patient such as this had pituitary apoplexy. I also have a lower threshold for imaging the patient with an isolated fourth or sixth because of the easy availability of neuroimaging and the patient-centered environment in which we exist. I think about other cranial nerve issues that we encounter such as trigeminal neuralgia (10% have compressive lesions) and hemifacial spasm (1% have a neoplastic cause). My practice has been to image these patients, and I believe that most literature supports that recommendation. The question is “What is our threshold for fourth and sixth nerve palsies?” I think it is both reasonable to image and also reasonable to hold off initial imaging for the patient with an isolated fourth or sixth nerve palsy. I agree with you that much of it depends on the face-to-face interaction in obtaining a detailed history and performing a careful neuro-ophthalmic examination.

—Michael S. Lee, MD


The pseudotumor cerebri syndrome (PTCS) may be primary (idiopathic intracranial hypertension) or arise from an identifiable secondary cause. Characterization of typical neuroimaging abnormalities, clarification of normal opening pressure in children, and features distinguishing the syndrome of intracranial hypertension without papilledema from intracranial hypertension with papilledema have furthered our understanding of this disorder. We propose updated diagnostic criteria for PTCS to incorporate advances and insights into the disorder realized over the past 10 years.

The authors propose updated criteria for the probable and definite diagnosis of PTCS. I think the most striking findings from this article include the following:

1. PTCS without papilledema is a definite diagnosis only if the patient has a sixth nerve palsy (and meets the rest of the Dandy criteria).
2. If the patient does not have a sixth nerve palsy, PTCS without papilledema is probable if the patient has at least 3 neuroimaging findings such as flattened globes, partially empty sella, narrowed transverse sinuses, and widened perioptic subarachnoid space (and meets the rest of the Dandy criteria).
3. The threshold for opening pressure in sedated or obese children (280 mm H2O) may be higher than adults (250 mm H2O).

Interestingly, the authors suggest that a gadolinium-enhanced brain MRI alone is adequate in typical (female and obese) patients to rule out intracranial causes. They note that a brain MRV is only required for atypical patients to rule out cerebral venous sinus thrombosis (CSVT). I tend to order both brain MRI and MRV for all patients including the obese woman because they can also have CSVT. In one study (1), 10 of 106 patients with presumed PTC were found to have CSVT, and 4 of those patients were obese women. The question is whether it is cost-effective to order an MRV in all patients, and I fall on the side that it is. Overall, I think this represents a critically important and sensible update to the diagnostic criteria.

—Michael S. Lee, MD

I agree that the diagnostic criteria proposed make sense. Any diagnostic criteria for PTCS are somewhat arbitrary, because there is no biomarker for PTCS. Opening pressure on LP is just one measurement in time, and papilledema is not always present.

I also order MRVs on typical PTC patients who are young and obese, but many patients have already had an MRI without MRV when I initially evaluate them. In these patients, I am comfortable with the authors’ guidelines and often will not order an MRV. Nonetheless, when an MRV has not been performed, it is important that the radiologist has looked for signs of venous sinus thrombosis on the MRI.

The following 2 statements in the article, taken together, were of particular interest to me and raise a controversial question, deserving of study

1. “Notably, LP is always required in the workup of a patient considered to have PTC.”
2. “The occasional patient with a significant tonsillar descent and an otherwise typical presentation of PTCS may be at high risk for herniation with LP and therefore can be diagnosed with PTCS presumptively.”

If some patients can presumptively be diagnosed with PTCS, then perhaps others can as well. The study that I think needs to be performed is looking at all the CSF examination in typical PTC patients, who are young obese women with a typical history and normal MRI and MRV. We need to know in what percent of these typical patients a diagnosis other than PTC was made and whether there are clinical clues in those patients suggesting an alternative diagnosis. That will help determine if our current rule that all patients receive an LP will “hold water” (that is, cm H2O).

—Mark L. Moster, MD


Aims: To evaluate retrospectively the prevalence of positive IgG4-immunostaining in orbital tissue of patients with idiopathic orbital inflammation and to compare the clinical, radiographic, and pathologic features among patients with and without IgG4-positive cells.

Patients and Methods: Twenty-five patients with biopsy-proven idiopathic orbital inflammation examined from January 2006 through December 2011 were included. Immunohistochemistry with IgG and IgG4 immunostaining from biopsy specimens of all patients was performed. Tissue with more than 10 IgG4-positive plasma cells per high-power field and with a ratio of IgG4+/IgG4- plasma cells of more than 40% was scored as positive. Histopathologic features, demographic and clinical data, radiologic findings, and treatment and follow-up information for each patient were analyzed.

Results: Immunohistochemical staining showed 10 cases (40%) were IgG4 positive. The symptoms and signs included eyelid or periocular swelling/mass in all, pain (3/10), extraocular muscle restriction (3/10), proptosis (5/10), and/or decreased vision (4/10). Demographic and clinical findings of these patients did not differ from those with IgG4-negative cells. The presence of positive IgG4-immunostaining in orbital tissue was significantly associated with characteristic pathological features (more background fibrosis, lymphoid hyperplasia, plasma cells, and phlebitis).

Conclusions: Finally, 40% of patients with biopsy-proven orbital inflammation were classified as IgG4-RD, with typical histological features, but without specific clinical or radiological findings.

This article points out that orbital IgG4-related disease (IgG4RD) may present in an identical fashion to idiopathic orbital inflammatory syndrome (IOIS). A problem with interpreting the findings is the lack of a standard definition for IgG4 positivity. This article used the criteria of more than 10 IgG4+ cells per high-power field and a ratio of IgG4+/IgG4- cells of 40%. Although others have used this cutoff in the literature, it is somewhat arbitrary. In fact, if a more stringent cutoff of >100 IgG4+ cells per high-power field had been applied, would have only been one case considered positive. Additionally, in this retrospective series, serum IgG4 levels were not available, which, if obtained, would help support the diagnosis.

We often use pain as a criterion distinguishing IOIS from lymphoma and other infiltrative lesions. It is surprising to see such a low percentage of patients with pain in both the IgG4+ (30%) and IgG4- (33%) groups in this series. It is also surprising to see a similar number of bilateral cases, regardless of IgG4 status. I would have expected more bilateral cases with IgG4 positivity.

This article does not add much definitive knowledge to the literature. However, because IgG4RD has systemic ramifications and the presentation seems identical to IOIS in many cases, this report will decrease my threshold for ordering serum IgG4 levels in future patients with orbital disease.

—Mark L. Moster, MD

So, IgG4RD did not differ clinically from the non-IgG4RD. Regardless of that, I have begun ordering serum IgG4 levels on patients with orbital inflammation. Hopefully, as we move forward in our understanding of the disease, we can identify more targeted ways to manage these patients beyond systemic corticosteroids.

The authors do not indicate whether patients had corticosteroid treatment before the biopsy, which ought to affect the biopsy results. It seems likely that all of the patients had corticosteroids before the biopsy and that many more could have had IgG4RD than reported here.

—Michael S. Lee, MD


Importance: There is a major lack of randomized controlled clinical trials evaluating the efficacy of prismatic treatments for hemianopia. Evidence for their effectiveness is mostly based on anecdotal case reports and open-label evaluations without a control condition.

Objective: To evaluate the efficacy of real relative to sham peripheral prism glasses for patients with complete homonymous hemianopia.

Design, Setting, and Participants: Double-masked randomized crossover trial at 13 study sites, including the Pelli laboratory at Schepens Eye Research Institute, 11 vision rehabilitation clinics in the United States, and 1 in the United Kingdom. Patients were 18 years or older with complete homonymous hemianopia for at least 3 months and without visual neglect or significant cognitive decline.

Intervention: Patients were allocated by minimization into 2 groups. One group received real (57-prism diopters [PD]) oblique and sham (<5-PD) horizontal prisms; the other received real horizontal and sham oblique, in counterbalanced order. Each crossover period was 4 weeks.

Main Outcomes and Measures: The primary outcome was the overall difference, across the 2 periods of the crossover, between the proportion of participants who wanted to
continue with (said yes to) real prisms and the proportion who said yes to sham prisms. The secondary outcome was the difference in perceived mobility improvement between real and sham prisms.

**Results:** Of 73 patients randomized, 61 completed the crossover. A significantly higher proportion said yes to real than sham prisms (64% vs 36%; odds ratio, 5.3; 95% confidence interval, 1.8–21.0). Participants who continued wear after 6 months reported greater improvement in mobility with real than sham prisms at crossover end (P = 0.002); participants who discontinued wear reported no difference.

**Conclusions and Relevance:** Real peripheral prism glasses were more helpful for obstacle avoidance when walking than sham glasses, with no differences between the horizontal and oblique designs. Peripheral prism glasses provide a simple and inexpensive mobility rehabilitation intervention for hemianopia.

This was a prospective, multicentered, double-masked randomized crossover trial comparing patient satisfaction using sector, high-power, peripheral prism glasses vs sham among patients with complete homonymous hemianopia. The real prisms were 57-prism diopters (PD) oriented either base out or obliquely on the spectacle lens ipsilateral to the hemianopia. The sham prism was 5-PD and coated to mimic the blurring from the 57-PD prism. Subjects wore either real or sham prisms for 4 weeks, and then crossed over to the opposite prism for 4 weeks. At the end of each period, the subjects were asked to assess mobility and interest in continuing prisms.

When forced to choose, 60% chose the real prism, but more than 1/3 chose the sham prism, which highlights the effects of placebo and the need for a control group. In this study, only limited training was provided and 12 patients (16%) withdrew from the study and 35 (48%) discontinued prism use at the end of the study. This could represent lack of training vs lack of efficacy. I have had some success with the 57-PD oblique prisms in patients with complete homonymous hemianopia. There is definitely a learning curve to using them, and I have patients visit with an occupational therapist to provide extensive training. To me, patient training seems to make a big difference, but obviously this factor needs to be studied.

—Michael S. Lee, MD

Surprisingly after the first period, when some had only sham prism and some real prism—58% endorsed a desire to continue wearing the real prism and 46% the sham prism—not a significant or a whole lot of difference. However, by the end of the second period, when the patients had experience with both a real and a sham prism, 71% wanted to continue the real prism and only 27% the sham prism.

The main outcome of the study was whether patients self-reported a desire to continue wearing prism and the secondary outcome was a self-reported benefit in mobility. With that goal, this study does demonstrate that prisms do benefit, but follow-up should reveal how much benefit and what kind of difference it makes in daily activities.

The authors acknowledged that “we were unable to ensure total masking of data collectors” which is of concern.

—Mark L. Moster, MD

**Objective:** To determine whether the association between MS and Leber hereditary optic neuropathy (LHON) (known as “Harding disease”) is a chance finding, or the 2 disorders are mechanistically linked.

**Methods:** We performed a United Kingdom–wide prospective cohort study of prevalent cases of MS with LHON mitochondrial DNA (mtDNA) mutations. The new cases were compared with published cases, enabling a comprehensive clinical description. We also performed a meta-analysis of studies screening patients with MS for LHON mtDNA mutations to find evidence of a genetic association.

**Results:** Twelve new patients were identified from 11 pedigrees, and 44 cases were identified in the literature. The combined cohort had the following characteristics: multiple episodes of visual loss, predominance for women, and lengthy time interval before the fellow eye is affected (average 1.66 years), which is very atypical of LHON; conversely, most patients presented without eye pain and had a poor visual prognosis, which is unusual for optic neuritis associated with MS. The number of UK cases of LHON-MS fell well within the range predicted by the chance occurrence of MS and the mtDNA mutations known to cause LHON. There was no association between LHON mtDNA mutations and MS in the meta-analysis of the published data.

**Conclusions:** Although the co-occurrence of MS and LHON mtDNA mutations is likely to be due to chance, the resulting disorder has a distinct phenotype, implicating a mechanistic interaction. Patients with LHON-MS have a more aggressive course, and prognostication and treatment should be guarded.

This study has limitations of being based on a survey of neurologists voluntarily responding with reports of both LHON and MS in the same patient. Therefore, it may underestimate the number of cases. Nonetheless, based on the rarity of the association, it provides support to the notion that LHON does not cause an MS-like illness, but rather that the relatively common illness of MS occurs in some patients who also have LHON.

Intriguing are the phenotypic features that are different from either MS or LHON and in some ways an average of both. For instance, the ratio of women to men 2:1/1 is much greater than in LHON but less than in MS. The visual loss had features of both LHON and MS but not typical for either. Four of 12 patients had pain, 5 patients...
had more than 2 episodes of visual decline, and 4 patients had some degree of recovery. Half the patients ended with visual acuity less than 20/400. One patient had bilateral simultaneous visual loss. When sequential visual loss occurred, the interval was more than 1 year in 7 patients and up to 17 years in 1 patient.

The authors concluded that the LHON-MS phenotype, which is distinct from either disorder, may have several possible causes. One possibility is that having the mtDNA mutation modifies the MS phenotype. The other is that the genetic and environmental factors that predispose to MS precipitates acute LHON in carriers, mostly women, who would have otherwise remained asymptomatic.

—Mark L. Moster, MD

Despite the suggested reasonable proposals for the atypical phenotype, the authors do not describe the orbital MRI findings, which could separate out these possibilities. Optic nerve enhancement on the MRI would strongly suggest optic neuritis, and lack of enhancement would more likely indicate LHON. This may help us understand why these patients lose vision, but it does not change the fact that patients with LHON and concomitant MS tend to be young women with painless sequential visual loss sometimes separated by years and they have a poor visual prognosis.

—Michael S. Lee, MD

It is often quoted that approximately 50% of patients with Graves’ disease will develop ocular involvement. In this relatively large prospective cohort of patients with newly diagnosed Graves’ disease at a nontertiary care facility, the authors found moderately smaller numbers. At presentation, 26% of patients had evidence of thyroid eye disease (TED). Of these, 21 patients (6%) had moderate-to-severe TED. Of the patients without TED at baseline, 13% developed TED over 18 months of follow-up. Of the patients who completed follow-up, 6 (3%) developed moderate-to-severe disease. Interestingly, 58% of those with mild TED at baseline experience remission.

I believe these data are helpful when counseling patients with Graves’ disease, because we often do not get to see these patients unless they develop eye findings. We can tell our patients that less than 15% of those without TED at baseline go on to develop it and less than 5% develop moderate-to-severe disease in the first 18 months. If one has mild TED at baseline, there may be a fair chance that it might resolve spontaneously.

—Michael S. Lee, MD
Editor’s Note: There are a number of clinical entities in neuro-ophthalmology having eponymous designations that are frequently discussed but rarely seen. One example is Argyll Robertson pupils. With the advent of improved methods to diagnose syphilis and effective antibiotic treatment, it is rare to detect this pupillary abnormality. Similarly, Foster Kennedy syndrome is well ensconced in the literature, and a topic we might use to test the fund of knowledge of our residents and fellows. Yet, this syndrome also is rarely seen clinically. No doubt that advances in neuroimaging have contributed to its infrequent appearance, with earlier detection of an intracranial mass lesion. What you will read here is a well-illustrated case of Foster Kennedy syndrome by Lai et al, and historical background of this neuro-ophthalmic syndrome by our esteemed British colleague, Michael Sanders. Being the purist, he prefers the term "sign" yet "syndrome" is more frequently used in the literature. In this article, the terms are used interchangeably.

CASE REPORT

A 36-year-old man reported blurring of vision in his left eye for 1 month and headache for 1 week. The headache was intermittent in the left frontal region and was not worsened by coughing, straining, or changing positions. It was not throbbing and was not associated with any aura. The patient did not have a history of headache or head trauma, and his medical and family histories were unremarkable. He denied anosmia.

Visual acuity was 20/20, right eye, and 20/40, left eye. Color vision was intact, and there was a left relative afferent pupillary defect. The patient had normal eye movements. Visual fields showed an enlarged blind spot in the right eye and nasal field loss in the left eye. Slit-lamp examination was normal with normal intraocular pressures. Funduscopic examination demonstrated right optic disc edema and left optic disc pallor (Fig. 1).

Magnetic resonance imaging of the brain revealed a left sphenoid wing meningioma, with compression of the left optic nerve (Fig. 2). The patient was treated with preoperative embolization of the tumor via the left middle meningeal artery, followed by a left frontotemporal craniotomy. Histopathologic examination of the tumor was consistent with a transitional meningioma (WHO grade I).

The patient made an uneventful postoperative recovery and, at 6 months of follow-up, his visual acuity remained unchanged. His right optic disc edema and headache resolved.

DISCUSSION

Neurologists have always embellished the medical establishment, and Foster Kennedy was no exception. He apparently traveled round New York from patient to patient wearing a flowing brown coat and a black homburg in a handsome carriage with fine horses. An engaging, charming, and humorous person, he loved and excelled in his chosen specialty and mixed with the rich and distinguished both as friends and patients.

Robert Foster Kennedy was born in Belfast, educated at Queens College, and qualified in medicine in 1906. He joined the junior staff of the National Hospital for the paralyzed and epileptic in 1907. The Hospital, founded in 1860, was one of the earliest neurological institutes and rapidly established a global reputation on account of its outstanding medical staff. Foster Kennedy worked with Sir William Gowers, Henry Head, and Sir Victor Horsley. He attended the Neurological Meeting where he met Sir William Osler (Regius Professor of Medicine at Oxford) and younger neurologists such as Gordon Holmes and Kinnier Wilson. During his 4-year tenure as medical officer, he gained immense experience, sometimes having to write daily notes on 85 patients, and caring for 13 cases of cerebral tumor. He debated with his seniors on diagnostic
accuracy, and when he correctly diagnosed a cerebral abscess, he left Horsley humbled. On one occasion, he wrote to his fiancée on Horsley, “the operation was mechanically exquisite and most thoroughly unjustified after full consideration of the facts.” Even at an early stage of his medical career, he showed a strong independence of mind accompanied by sound judgment.

Kennedy met Royalty when King Edward VII visited the Hospital, and he managed to knock over a bowl of flowers on the King’s boots. “Don’t worry” proclaimed the monarch, “they are cleaned almost every day.” He wrote frequent letters to Isabel McCann, his fiancée, and signed them off with “your boy.” They provide a vivid picture of life and medicine at the turn of the 20th century and have been published by his daughter who married a distinguished British medical academic (1).

In 1910, Kennedy left the National, and despite the endeavors of his eminent teachers, he failed to find a post in the United Kingdom. He accepted an appointment at the recently formed Neurological Institute in New York. This institute, the first of its kind in America, floundered initially but then became part of the Columbia—Presbyterian medical complex. In 1911, he published an article that was to establish his international reputation (2). This will be discussed later.

The rumblings of war erupted in 1914, and Kennedy offered his services. As a Lieutenant in the Royal Army Medical Corps, he was asked to set up a hospital in France. During this period, he also joined the Harvard Surgical Unit, which had been established by Harvey Cushing. His war experiences, including the battles of the Somme and Ypres, left a deep impression on him.

Returning to New York in 1919, he was appointed as professor of neurology at the Bellevue Hospital, which was the first public hospital in the United States and linked to Cornell and Columbia Universities. As time progressed, he reached the apex of his career with patients and friends from the heights of business and the arts, and a serene domestic environment (Fig. 3). He examined Winston Churchill after he had been hit by a taxi on Fifth Avenue and remained in contact with him. A dinner at his home with Churchill and one other started with Liebfraumilch at 8:30 PM and finished with stronger “ingredients” at 4:00 AM He also treated and knew the President, Franklin Delano Roosevelt.

In the early 20th century, 50 years after the advent of the ophthalmoscope, clinicians were attempting to relate visual acuity and optic disc appearances to etiology and, in the process, to construct meaningful diagnostic terminology. Therefore, the article Kennedy published in 1911, in which a patient had optic disc swelling on one side with optic atrophy, on the other in association with a frontal tumor provided a good diagnostic platform (2).

Miss Cameron, a 37-year-old Scottish woman, was referred to Foster Kennedy when he was Medical Officer to Sir William Gowers by the ophthalmologist, Marcus Gunn. She had a long history of progressive headaches, fainting attacks, and ultimately vomiting. She had obscurations of

**FIG. 2.** Precontrast T1 axial (A) and coronal (B) magnetic resonance imaging shows a large tumor mass causing left to right shift with ventricular obstruction and compression of the prechiasmal portion of the left optic nerve (arrow). C. Postcontrast T1 axial scan reveals tumor enhancement and left optic nerve compression (arrow).
vision in the eye with better visual acuity, described in the right eye by Gowers as “paroxysm of dimness,” although Foster Kennedy attributed this to the left eye. Vision was perception of light in the left eye with a pale disc, and 6/6 in the right eye with papilledema (measured as 1.5 mm by Gunn). There was an afferent pupillary defect on the left with a central scotoma. Anosmia was present in the left nostril, and although initially normal on the right, developed later.

On October 13, 1908, Sir Victor Horsley loosened the frontal bone and then replaced it, and although the patient briefly regained consciousness, she swiftly passed away. Postmortem examination showed a large olfactory groove meningioma more on the left than on the right. The optic nerve sheath was distended distally on the right side but was normal on the left side, which showed a greater degree of compression. The olfactory nerve on the left had “almost disappeared.”

The clinicians were pleased with their localization, and Sir William Gowers had never seen such a case. This led him to give a lecture on this case at the University College Hospital, and this was published 8 months later in the Lancet with a photograph (Fig. 4) and discussion of the pathology (3). Gowers used the term optic neuritis for the swollen disc and entitled the article “A case of unilateral optic neuritis from intracranial tumour.”

Foster Kennedy used the same case in his publication (2) but added 5 similar cases of frontal lesions and indicated that these clinical features were a “sign” of a frontal lesion. His series could be divided into 3 groups:

Type 1: optic atrophy on one side with contralateral papilledema
Type 2: bilateral papilledema developing unilateral optic atrophy
Type 3: bilateral papilledema developing bilateral optic atrophy.

In only 2 eyes was good vision retained, and in the remaining 10 eyes, vision was 3/36 or worse. Anosmia was present in 5 cases. Thus, the commonest feature of these large frontal masses was bilateral papilledema, progressing to atrophy on one or both sides.

In contrast, in 1972, I reviewed 6 cases of Foster Kennedy sign and found 3 cases of type 1, and 1 case each of types 2 and 3 (4). This heterogeneous group included no cases of olfactory groove meningioma but consisted of 2 frontal gliomas, 1 falx meningioma, 1 sphenoid ridge meningioma, and 1 cavernous sinus meningioma. The sixth case was caused by a cholesteatoma, which conformed more to the type described by Schultz-Zehden in 1905 (5), in which a mass below the chiasm produces asymmetric compression of the optic nerves. Anosmia was absent in all cases. In a review by Watnick and Trobe (6), the rarity of the “sign” was emphasized: out of 36 cases in the literature, only 8 (22%) had the true Foster Kennedy sign.

Today, any patient complaining of progressive headaches or visual loss would undergo neuroimaging, leading to early detection of intracranial lesions. In part, this may contribute to the rarity of the Foster Kennedy sign. For the purist, the Foster Kennedy sign represents optic atrophy and anosmia on one side, with papilledema caused by raised intracranial pressure on the other. However, the majority of cases with these findings occur without anosmia and are due to a variety of intracranial disorders. In Gowers’ day, the clinician localized the lesion. Today, the neuroradiologist does it for him!

ACKNOWLEDGMENTS

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REFERENCES

We read with interest, the report by Bodanapally et al (1) of using diffusion tensor imaging (DTI) in evaluating patients with traumatic optic neuropathy (TON). The authors concluded that decreased axial diffusivity and mean diffusivity in the posterior segment of the optic nerve might serve as a biomarker of axonal damage in patients with TON.

We describe a patient with right homonymous hemianopia who presented 11 years after a severe closed head trauma with a negative conventional magnetic resonance imaging (MRI) and magnetic resonance angiography in whom left optic tract atrophy was documented with DTI.

A 59-year-old woman complained of transient visual loss. In 1999, she was involved in a motor vehicle accident with loss of consciousness and associated memory loss. Recently, she reported 2 episodes of transient “tunneling of vision,” each lasting 5 minutes. She was not certain if they were monocular or binocular. Her evaluation for these episodes was unremarkable, and they spontaneously resolved with no recurrence.

On examination, the patient was found to have a right homonymous hemianopia, but she was unaware of this visual field loss. MRI of the brain with and without contrast was unremarkable.

Eighteen months later, despite normal intraocular pressures, the patient’s optic discs were believed to have enlarged cup-to-disc ratio, and she was not started on the treatment. Her medical, surgical, social, and family histories were noncontributory, and she was on no medications.

Neuro-ophthalmological testing demonstrated visual acuity 20/25 in the right eye and 20/20 in the left eye. The pupils were isocoric with a right relative afferent papillary defect. Slip-lamp examination showed mild nuclear sclerotic cataracts, and intraocular pressures were 20 mm Hg, right eye, and 19 mm Hg, left eye. Funduscopy showed both optic discs to have enlarged cup-to-disc ratio, and the right disc demonstrated band optic atrophy (Fig. 1). Automated perimetry revealed an incongruous right homonymous hemianopia (Fig. 2). The pattern of retinal nerve fiber layer loss on optical coherence tomography of the right eye confirmed...
band optic atrophy, and there was temporal fiber atrophy in the left eye.

A repeat MRI of the brain showed atrophy of the left optic tract (Fig. 3). This was confirmed using DTI (25 gradient directions, 1.8 mm isotropic spatial resolution, b value 1,000 s/mm$^2$) with fiber tractography of the visual pathways (2–4). MRI DTI fiber tractography (Diffusion Toolkit and TrackVis, Martinos Center for Biomedical Imaging, Massachusetts General Hospital (5); second-order Runge Kutta propagation algorithm, 35° angle threshold, min fractional anisotropy threshold automated by software, same tracking parameters for both right and left sides) of the optic tracts and optic radiations showed marked reduction in reconstructed fibers along the left optic tract (Fig. 4). The atrophic left optic tract had significantly decreased fractional anisotropy and increased mean diffusivity, consistent with chronic degeneration (Fig. 5). The left optic radiation had mildly decreased fractional anisotropy and increased mean diffusivity that were not statistically significant.

FIG. 3. Contiguous, noncontrast T1 coronal magnetic resonance imaging of the anterior visual pathways. Arrows denote optic nerves (A), optic chiasm (B), and optic tracts (C and D). The left optic tract is atrophic.

FIG. 4. Diffusion tensor imaging tractography of optic tracts (red arrows) and optic radiations (green arrows) shown in oblique (A), coronal (B), and axial (C) projections demonstrates atrophy of the left optic tract. The majority of left optic radiation fiber tracts generated from the fiber tracking algorithm have nonanatomical fiber trajectories proximal to the lateral geniculate nucleus (yellow arrows), presumably from dominant crossing fibers secondary to left optic tract atrophy. Fiber tracts were constructed from regions of interest placed at ends of either optic tract (chiasm and lateral geniculate nucleus [LGN]) or optic radiation (LGN and occipital lobe); some of the shorter tracts are specific for optic tract or optic radiation. Nonanatomical tracts were removed, which accounts for the fewer fiber tract on the left side due to crossing fibers dominating at the left LGN secondary to right optic tract atrophy. On the normal right side, the majority of fiber tracts are continuous through the LGN from the optic tract to optic radiation because the fiber tracts are mathematical constructions that follow principal diffusion eigenvector flow lines and do not demonstrate that axons synapse in the LGN.
We believe that the DTI results in this case are consistent with a posttraumatic optic tract lesion. Diffusion of water in tissue is affected by the presence of semipermeable membranes and oriented structures in the intracellular, extracellular, and vascular compartments that result in preferential movement of water parallel to them. Anisotropy describes the directional dependence of diffusion, and white matter (e.g., optic tract) has relatively high anisotropy because longitudinal structures such as myelin, axonal membranes, and subcellular organelles contained in highly organized fiber bundles along white matter tracts contribute as barriers to water movement perpendicular to these structures. Fractional anisotropy is an index of anisotropy measuring the degree of diffusion differences in different directions. Decreased fractional anisotropy along white matter tracts can be from either reduced axial or increased radial diffusivity and should be correlated with mean diffusivity in determining changes in the underlying microstructural architecture. The combination of decreased fractional anisotropy and increased mean diffusivity in this case is likely due to chronic degeneration with membrane disruption, cell lysis, and gliosis.

Atrophy of the optic tract often is difficult to detect with conventional neuroimaging in patients with an unexplained homonymous hemianopia. In our patient, previous MRI had been interpreted as normal, but more detailed analysis including DTI confirmed left optic tract atrophy. Clinicians should be aware of DTI as a diagnostic aid in evaluating patients with optic tract syndrome.

FIG. 5. Diffusion tensor imaging gray scale and color directional fractional anisotropy maps through the levels of the optic tracts (red arrows and regions of interest [ROI] overlay) and optic radiations (green arrows and ROI overlay). The gray scale map shows decreased fractional anisotropy along the left optic tract. The color map shows fiber orientation in 3-dimensional space (red color for the x axis along right–left orientation, green color for the y axis along anterior–posterior orientation, and blue color for the z axis along cranial–caudal orientation).

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Restricted Diffusion in Isolated Superior Ophthalmic Vein Thrombosis

Superior ophthalmic vein (SOV) thrombosis is a rare disease entity characterized by rapidly progressive orbital symptoms, including periorbital edema, chemosis, proptosis, and ophthalmoplegia. It may be isolated or accompanied by cavernous sinus thrombosis. Parmar et al (1) reported the value of diffusion-weighted imaging (DWI) in establishing this diagnosis, and we describe our experience with this disorder.

FIG. 1. Orbital magnetic resonance imaging. Postcontrast T1 axial (A) and coronal (B) scans show diffuse enhancement of preseptal and retrobulbar regions of the left orbit, and absence of normal enhancement within the left superior ophthalmic vein (arrows). Diffusion-weighted imaging (C) reveals hyperintense signal in the left superior ophthalmic vein (arrows) and apparent diffusion coefficient map (D) shows a corresponding hypointense signal (arrow) confirming restricted diffusion.

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Letters to the Editor

A 53-year-old man presented with headache and left eye swelling for 6 days. Examination revealed proptosis, eyelid edema, and weakness of depression in the left eye and a dilated poorly reactive left pupil. Orbital magnetic resonance imaging performed 6 days after symptom onset, showed diffuse left orbital enhancement and an intraluminal filling defect within the left SOV (Fig. 1A, B). There was no abnormal signal or filling defect within the cavernous sinus. DWI disclosed restricted diffusion in the left SOV (Figs. 1C & 1D) consistent with thrombosis. Over the next 7 days, the patient was treated with intravenous broad-spectrum antibiotics. He showed marked improvement of periorbital swelling, and limitation of left eye movement gradually resolved.

Although the utility of orbital DWI is limited due to inhomogeneous tissues that produce susceptibility artifacts, there have been 3 reported cases of restricted diffusion in SOV thrombosis reflecting the presence of intravascular clot (1–3). Restricted diffusion corresponding to the presence of intravascular clots has been described in vertebral artery dissection and cerebral venous thrombosis, but the frequency and evolution of diffusion changes are variable (4–6). Our patient showed high signal intensity on DWI on the 6th day after the onset of symptoms, which corresponds to the early subacute (3–7 days) stage of intraparenchymal hematoma. However, previous case reports described restricted diffusion of the thrombosed SOV in patients with different time periods of acute (1–3 days) or chronic (>14 days) stages (1,2). These findings suggest that the diffusion changes of intravascular clots differ from that of intraparenchymal hematoma that mainly shows hyperintense signal at the hyperacute (<1 day) stage (7).

Since SOV thrombosis is a potentially life-threatening condition, prompt recognition is important for effective treatment. DWI may provide an important clue as to the presence of intravascular clots according to the stage of thrombus formation in SOV thrombosis.

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The Immunopathology of Giant Cell Arteritis: Diagnostic and Therapeutic Implications

We read with great interest the article “The immunopathology of giant cell arteritis: diagnostic and therapeutic implications” by Weyand et al (1) and commend the authors on their comprehensive review of giant cell arteritis (GCA) immunopathogenesis and excellent discussion of potential new therapeutic targets. Due to the adverse effects of steroids and lack of therapeutic response in some patients with GCA, clinicians have investigated the use of steroid-sparing agents, including anti-tumor necrosis factor (anti-TNF)-α agents, for GCA treatment. Case reports on the use of anti-TNF-α antibodies for GCA and one small placebo-controlled trial investigating the use of etanercept in GCA patients have been promising (2–7). However, occurrences of GCA despite use of anti-TNF-α antibodies have been reported in the literature (8,9). We add to these reports with a patient who developed arteritic anterior ischemic optic neuropathy secondary to biopsy-proven GCA despite use of etanercept, an anti-TNF agent.

A 59-year-old Caucasian woman with rheumatoid arthritis treated with etanercept and leflunomide was referred for evaluation of sudden peripheral vision loss in her right eye. She reported a 2-week history of intermittent bilateral blurred vision and transient binocular vertical diplopia. She noted transient obscurations of vision during the week before her loss of vision. She also reported a 1-month history of bilateral jaw claudication, low-grade fevers and malaise, a 3-week history of daily global headaches, and weight loss of 15 lbs over the previous 6 weeks. She had been taking leflunomide for 2.5 years and etanercept for 1.5 years. Etanercept was discontinued for 3 weeks due to her low-grade fever and malaise and was restarted 1 week before her vision loss. On examination, her best-corrected visual acuity was 20/25 in each eye. Her color vision was slightly decreased in the right eye and full in the left eye (13/14 and 14/14 Hardy-Hand-Rittler plates, respectively). A right afferent pupillary defect was present. Automated visual field 24-2 SITA Standard testing demonstrated dense superior altitudinal and inferior arcuate defects in her right eye. Her left visual field was normal. Fundus examination revealed pallid optic disc edema with associated peripapillary hemorrhage in the right eye and a normal appearing disc in the left eye (Fig. 1). The right superficial temporal artery pulse was not palpable. Laboratory workup was notable for an erythrocyte sedimentation rate of 106 mm/hr and a C-reactive protein of 55.1 mg/L (normal: 0–10 mg/L). The patient was immediately treated with 100 mg of prednisone and a right temporal artery biopsy performed the same day demonstrated active GCA. She was subsequently admitted and treated with methylprednisolone (250 mg intravenously 4 times a day) for 3 days and aspirin (81 mg) daily. At 1-month follow-up, her best-corrected

FIG. 1. Right optic disc demonstrates pallid edema while the left disc is normal.
visual acuity was 20/20 in each eye, and repeat Humphrey visual field was stable. Her right optic disc was diffusely pale with minimal residual edema.

Given the paucity of cases, the potential role of TNF-α antagonists in the treatment of GCA is unclear. Interestingly, vasculitis has been reported to occur with use of TNF antagonists, mainly in the form of leukocytoclastic vasculitis (10–12). One postulated mechanism for the development of vasculitis during the use of anti-TNF agents is direct drug toxicity to the vasculature. Other mechanisms include deposition of anti-TNF/TNF immune complexes in the vessel wall with induction of a type III hypersensitivity reaction, reaction of autoantibodies with endothelial cells, paradoxical increased vulnerability to granulomatous vasculitis due to TNF deficiency, and a TNF antagonist–induced switch from a Th1 to a Th2 T-lymphocyte response (11). Whether any of these proposed mechanisms of vascular destruction underlie the development of GCA during use of TNF-α antagonists is unknown. While on long-term treatment with etanercept except for a 3-week drug holiday, our patient developed symptoms that, in retrospect, were most likely due to GCA. Although we cannot exclude the gap in therapy as a precipitating event of the patient’s ischemic optic neuritis, we believe this most likely was due to natural evolution of her disease process.

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The authors report no conflicts of interest.

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REFERENCES


Radiation Optic Neuropathy After Proton Beam Therapy for Optic Nerve Sheath Meningioma

I enjoyed reading the recent article regarding radiation optic neuropathy after proton beam therapy for optic nerve sheath meningioma by Siddiqui et al (1). The authors state “magnetic resonance imaging revealed enhancement of the right optic nerve consistent with radiation optic neuropathy.” It is my experience that the optic nerve enhancement, as pictured in Figure 3B, also can result from a multitude of etiologies including extension of optic nerve sheath meningioma (2). Often it is difficult to differentiate the 2 on the fat-suppressed gadolinium-enhanced orbital magnetic resonance imaging. So, how do we know that the optic nerve enhancement was indeed from the radiation and not from progression of the optic nerve sheath meningioma?

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Response

We thank Dr. Vaphiades for his interest in our article and agree that the etiology of optic nerve enhancement may be difficult to distinguish based on magnetic resonance imaging (MRI) findings alone. With an optic nerve sheath meningioma (ONSM), the tumor typically shows gadolinium enhancement rather than the nerve itself, giving rise to the typical tram-track sign, while with radiation optic neuropathy (RON), the optic nerve itself enhances and may therefore be indistinguishable from the enhancement of the surrounding ONSM.

In our patient, we noted several features that supported the diagnosis of RON. Radiographically, the area of new optic nerve enhancement corresponded to the exact location of the highest proton beam radiation dose. Although the optic nerve showed normal short T1 inversion recovery signal at the time of the initial ONSM diagnosis, it showed increased signal with proximal enhancement at the time the patient presented with visual loss, which began 27 months after completion of radiation therapy. Diffuse enhancement of the nerve was noted such that it could not be separated from the surrounding sheath, as opposed to clear tram-track enhancement of the remaining distal nerve. Clinically, it would be unusual for an ONSM to grow rapidly, causing progressive visual loss over a period of days to weeks, and then remain stable for the next year, as in our patient. The onset of symptoms in our patient likewise fell within the typical time course for RON.

We hope that these details help to further clarify the diagnosis of RON in our patient. The above findings were included in our original submission but were then omitted through the editing process.

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Recurrent Third Nerve Palsy as the Presenting Feature of Neurofibromatosis 2

We read with interest the case report (1) describing recurrent third nerve palsy as the presenting feature of neurofibromatosis type 2 (NF2). We evaluated a child with similar clinical findings.

Our patient, whose mother has NF2, presented at age 5 years with painless, right-sided ptosis, and upgaze palsy, with normal pupils that evolved over several days. There was no history of preceding illness or trauma. The remainder of the general and neurological examinations was normal. Hematological and biochemical screening as well as inflammatory markers were negative. Magnetic resonance imaging (MRI) of the brain with contrast was normal. The child remained otherwise well and his findings completely resolved over 6 weeks.

Over the next 3 years, he had 3 identical spontaneous episodes all involving the same eye, with good but incomplete recovery, in that mild ptosis (1–2 mm) and diplopia on upgaze persisted. Repeat contrast-enhanced brain MRI with each episode was normal, as were blood studies including acetylcholine receptor antibodies for myasthenia gravis.
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At the age of 7 years, left hand weakness developed due to nerve sheath tumors affecting the roots of C8 and T1. Genetic testing confirmed the diagnosis of NF2. We agree with Barrett et al that there is no clear explanation for the recurrent third nerve palsy, but that it can be a presenting symptom of NF2 in children.

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REFERENCE

Utilizing Optical Coherence Tomography in Diagnosing a Unique Presentation of Chiasmal Hypoplasia Variant of Septo-Optic Dysplasia

We evaluated a patient whose findings relate to 2 recent reviews in the Journal, that of Borchert (1) on optic nerve hypoplasia and Fraser et al (2) dealing with nonglaucomatous optic disc cupping.

A 13-year-old adopted boy was referred for abnormal optic nerve appearance. On examination, the visual acuity was 20/20 in each eye and intraocular pressure was 13 mm Hg, right eye, and 14 mm Hg, left eye. Funduscopy revealed bilateral excavated and pale optic nerves (Fig. 1). Retinal nerve fiber layer (RNFL) analysis by spectral-domain optical coherence tomography showed a pattern consistent with bow-tie atrophy in each eye (Fig. 2). Automated visual field testing revealed bitemporal hemianopia. Magnetic resonance imaging (MRI) of the brain was remarkable for absence of septum pellucidum and chiasmal atrophy (Fig. 3). Based on these findings, the diagnosis of chiasmal hypoplasia-variant septo-optic dysplasia (SOD) was made.

Our patient presented with optic nerve cupping, raising suspicion for juvenile open-angle glaucoma. However, the RNFL analysis revealed thinning of nasal and temporal quadrants, unlike glaucomatous damage, which typically involves thinning of the superior and inferior quadrants. The relatively preserved superior and inferior RNFL bundles on optical coherence tomographic analysis correlated well with the findings of bitemporal hemianopia and the MRI findings of chiasmal hypoplasia.

To our knowledge, this is the first description of RNFL analysis in the chiasmal hypoplasia variant of SOD. This

FIG. 1. Optic discs show thinning of the nasal and temporal rims, consistent with bow-tie optic atrophy.
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analysis was instrumental in differentiating nonglaucomatous from glaucomatous optic nerve cupping and established correlation between structure and function.

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REFERENCES
Obituary: Melvin G. Alper, MD (1921 – 2013)

It’s my impression that our specialty could be characterized as lacking the large egos often seen dominating other medical fields. Characters, yes, and many, egos, less so. Perhaps it is due to the lack of seemingly simple and miraculous fixes that protect neuro-ophthalmologists from the delusion that doctors actually heal. More likely, however, is that this tone of humility has been set by the founders of our specialty, over its few generations of mentors.

One of those founders, Mel Alper, passed away in February, 2013. He was a driving force in the ophthalmic medical community of the mid-Atlantic area, including Philadelphia, Baltimore and Washington DC. Dr Alper, or “Mel” as he always insisted on being addressed, was one of the early pioneers of orbital surgery and the use of orbital imaging including ultrasound, computed tomography and magnetic resonance imaging. Even more than his publications, his ability to bring doctors together to exchange ideas inspired and encouraged many and sparked several notable careers. His was a prime example of how one’s contribution to a field cannot be measured merely by the number of publications in a CV.

Dr Alper was born in Baltimore in 1921, grew up in Wytheville Virginia and received his undergraduate and medical degrees from the University of Virginia. He trained in ophthalmology at the University of Pennsylvania and subsequently came to Washington DC where he was on the faculty of both the Washington Hospital Center (now part of Georgetown University) and the George Washington University Departments of Ophthalmology. He would ultimately become the chairman of the former, and acting chairman and an emeritus professor of the latter. He was a founding member of the Orbit Society, the International Neuro Ophthalmology Society and the Cogan Ophthalmic History Society. The front row of seats at the regular neuro-ophthalmology case presentations at Washington Hospital Center were predictably occupied by Drs. Alper, David Cogan, Lorenz Zimmerman and Marshall Parks – all of whom would be actively taking notes and asking questions of the presenter. That lecture series now bears Dr Alper’s name and is the longest continuing neuro-ophthalmology series in the country.

Here are comments from some of his colleagues:

“Mel Alper, my mentor, esteemed colleague, and friend was one of the most influential people in my life. He welcomed my efforts to integrate orbital surgery into neuro-ophthalmology.” – Jack Kennerdell, Pittsburgh, PA

“A gentle giant.”- Neil Miller, Baltimore MD

“His leadership in ophthalmology was renowned in our field but his daily example was a powerful influence on me and many of those who followed.” – David Berler, Washington DC

Lastly, other than the concern about how our future obituaries will read, why memorialize our predecessors, some of whom many of us have never met? Although there are deep historical roots from the days when neuro-ophthalmologic problems were considered every eye doctor’s concern, the specialty as an independent group is still young enough to acknowledge a relatively short lineage. We can’t help but be aware of the profound influence of these mentors, as if they are looking over our shoulder as we go about our daily clinical work.

Dr Alper is survived by his wife, 2 children and 4 grandchildren. Our society owes Mel, and his family, a great debt of gratitude.

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The 6th Congress of the Korean Society of Neuro-Ophthalmology, Seoul, Korea

The 6th Congress of the Korean Society of Neuro-ophthalmology was held at Seoul National University Hospital, Seoul, Korea, on October 5, 2013. It was hosted by Professor Seong-Ho Park, the president of the Korean Society of Neuro-Ophthalmology. The society has held a nationwide congress biannually since its inception in 2011. This year, the meeting consisted of keynote lectures, an invited lecture, and discussions of interesting cases in the field of neuro-ophthalmology. There were approximately 150 attendees from all regions of South Korea (Fig. 1).

One main theme of the meeting was “the differential diagnosis of ophthalmoplegia,” covering supranuclear, nuclear, and infranuclear lesions that cause ophthalmoplegia and diplopia. There were 5 keynote lectures:
1. General approach to the patients with diplopia—Young Eun Huh (Seoul National University)
2. Ocular motor nerve palsies—Jae-Hwan Choi (Pusan National University)
3. Anti-GQ1b antibody syndrome—Dong Uk Kim (Chosun University)
4. Neuromuscular junction disorder including ocular myasthenia—Hyun Seok Song (Kyungpook National University)
5. Ocular myopathies—Seong-Hae Jeong (Chungnam National University)

The other major theme was “common symptoms and signs in neuro-ophthalmology.” These presentations included
1. Visual loss—Sun-Young Oh (Chonbuk Nation University)
2. Anisocoria—Hyun Ah Kim (Keimyung University)
3. Oscillopsia—Kwang-Dong Choi (Pusan National University)
4. Cortical visual symptoms—Seo Young Choi (Chungbuk National University)

The invited speaker was Lanning B. Kline (UAB School of Medicine, Birmingham, AL) who lectured on “Cavernous Sinus Syndrome.” In addition, as the Editor-in-Chief of the Journal of Neuro-Ophthalmology, he discussed the journal and encouraged submissions from the neuro-ophthalmic community of Korea.

Finally, there were interesting case reports with a discussion session. Topics included pendular see-saw nystagmus as a delayed complication of traumatic brain injury (Jae Han Park), myopic strabismus fixus presenting as intermittent strabismus (Kyung-Ha Noh), monoculcar pendular nystagmus in a patient with sporadic cerebellar ataxia (Sung Min Woo), superior ophthalmic vein thrombosis presenting with painful ophthalmoplegia and proptosis (Hak Seung Lee), and pupil-sparing oculomotor nerve palsy in herpes zoster ophthalmicus (Yun-Ju Choi).

On the evening of the meeting, a special dinner included all the society executive members, speakers, and the guest speaker, Dr Kline, and Mrs Kline. Fresh fish and many kinds of delicious Korean food were served.

The next congress of the Korean Society of Neuro-Ophthalmology will be held in Seoul, Korea, in the spring of 2014.

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FIG. 1. Ji-Soo Kim and Lanning Kline (center, left, and right) with members of the Korean Society of Neuro-Ophthalmology.
The 25th Reunion of CLAN, the Latin American Neuro-Ophthalmology Club

Since 1988, a group of Latin-American neuro-ophthalmologists has met annually in various cities, primarily on the continent of South America. The 25th reunion of CLAN was held on the 6th and 7th of September 2013 in Santiago, Chile, at Hotel Neruda.

Thirty-four members participated in this meeting, including ophthalmologists, neurologists, and radiologists. All were united by a common interest in neuro-ophthalmology, creating a stimulating professional conference dealing with the complexity of neuro-ophthalmic patients.

The annual conference of CLAN allows colleagues in the region to review topics of interest, discuss clinical cases, and compare management options and outcomes. This year we had participants from Argentina, Brazil, Columbia, Cuba, Mexico, the USA, and Chile (Fig. 1). Dr. Veronica Fernandez-Salgado, the General Secretary of CLAN, organized the meeting, which was both educational and entertaining. In addition to the usual members of CLAN, there were several fellows in training in neuro-ophthalmology, especially from Chile and Argentina. The meeting was open to all colleagues interested in neuro-ophthalmology, including residents in training. One hundred twenty additional professionals apart from the CLAN group attended.

The sessions for the meeting were organized to update attendees on the management of inflammatory diseases, including infectious diseases, demyelinating disorders, and vascular and infiltrative diseases especially involving the optic nerve. Neuro-ophthalmic pathology of pregnancy, neuro-rehabilitation and ocular motor disorders also were presented. There was ample time for lively discussion and comments especially regarding the clinical cases.

CLAN has led to creation of strong friendships among members including couples and families constituting the so-called Ami-CLAN or friends of CLAN who help and actively participate in events involving the social program. This year we had dinner at the home of Dr. Fernandez with musical entertainment, and there was a closing lunch in a vineyard nearby Santiago, which allowed for camaraderie in a relaxed atmosphere.

We successfully concluded another of many wonderful CLAN meetings as we shared and learned with input from everyone to advance the development of neuro-ophthalmology in Latin America.

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Tufts University, Boston, MA


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Anthony Arnold
Robert Avery
Asim Bag
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Jason Barton
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Steven Bernstein
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Sophia Chung
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