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J. Lawton Smith, MD (1929–2011)

The end of an era has passed with the death of Joseph Lawton Smith, MD, at age 81. Lawton died on January 10, 2011, in Miami after complications following surgery for a broken hip.

Lawton had many interests in life—jogging, eating (his favorite catch of the day was cow!), and playing the bassoon. But there were 3 things he loved more than anything. One of these was practicing and teaching medicine. Born into a family of physicians, Lawton received his bachelor’s degree from Emory University and his master’s from Duke. He completed his residency training at the Wilmer Eye Institute, and under the tutelage of Dr. Frank Walsh became enthralled with the burgeoning field of neuro-ophthalmology. He did a fellowship with Dr. David Cogan at the Massachusetts Eye and Ear Infirmary, returning to the Wilmer as chief resident, and then joining the ophthalmology faculty at Duke for several years. In 1962, he was recruited by Dr. Ed Norton to join the newly formed Bascom Palmer Eye Institute at the University of Miami. His instructions from Dr. Norton were “I want you to work hard but I don’t care what you do, just so long as you go home tired every day.”

And work hard he did. Lawton was truly a phenomenal doctor. He did the most thorough exams (including 45-minute “doctor-killing” refractions to the 0.12 diopters and single degrees of axis) and made extraordinarily detailed clinical observations. Not infrequently he arrived at diagnoses that were elusive to multiple previous examiners. His fund of knowledge and memory of the literature were phenomenal. His own extensive contribution to medical science included 335 articles, books, and editorials. Along with various notable coauthors, he reported at least 20 completely novel entities or clinical findings, including ischemic optic neuropathy, fundus findings in choroidal hemangiomas and Leber hereditary optic neuropathy, clinical uses of ophthalmodynamometry and OKN testing, fluorescein angiographic findings in retinal artery occlusion and giant cell arteritis, and ophthalmic and neurologic manifestations of Lyme disease and seronegative syphilis. In a field that had few treatments, he strove to find new ones (hemianopic prisms, retrobulbar steroids for optic neuritis, medical treatment for superior oblique myokymia, and radiation therapy for optic nerve sheath meningiomas) and founded the Journal of Clinical Neuro-Ophthalmology in 1981. He also strove to give patients hope for the future and ways to cope despite their illnesses. His motto was to practice “first class medicine in a spirit of love”, and he succeeded every time.

Perhaps, even more than he loved practicing medicine, Lawton loved to teach. For many of us in the field, he was the most amazing teacher we have ever had. He could make the most difficult concepts seem crystal clear and made it all fun. Ed Norton often said that Lawton was the best instructor in the entire University of Miami School of Medicine. I have seen students and house officers absolutely transfixed by his teaching. I have even counseled medical students who could not stand the sight of an eyeball yet tried to pursue ophthalmology simply due to their exposure to Lawton. To truly understand his teaching methods, one needed to learn the particular lexicon that Lawton had developed, all spoken in his distinctive South Carolina twang. For example, to get ready to work hard was to “swing into action totalis”; when he really piqued your interest, he was “working you up to fever pitch”; but if you got too excited and wanted to order too many tests, you were like “a blind dog in a meathouse”; if you incorporated new technology, you were using “twin smitties”; and when he really liked you, you became a “pie.”

Another one of Lawton’s true love was people. He was intensely devoted to his wife of 56 years, Elizabeth, and
greatly loved his 3 children and grandchildren. And Lawton loved his residents and fellows. He mentored more than 50 fellows and hundreds of residents and medical students in his career. He always wanted to get to know them personally and invest in them spiritually. He also loved the Bascom Palmer and his fellow ophthalmologists there and throughout the world. Lawton coupled his love for medicine and his love for people by founding the Christian Ophthalmology Society in 1977 to provide a forum where doctors and their families could learn new advances in ophthalmology and renew their professional and personal lives. Today the group that started with 25 doctors has grown to a group of more than 600 with annual meetings throughout North America.

And finally, most of all, Lawton loved God. In his younger days, Lawton did his fair share of carousing. I have heard many stories from him and from others that make “Animal House” look tame! But his life was dramatically changed when, in 1963, he met one of his old residency classmates, Dr. Jack Cooper, who told Lawton that he had given his life to Christ and since then his practice went better, his friendships were better, and his family life was better. As Lawton would say, this “ate into his brain like a rat” and shortly thereafter he became a Christian. Lawton has said that from that time on, the presence of “Jesus in his heart far eclipsed” every other aspect of his life. His overriding purpose became to know God more intimately and to encourage others to find the overwhelming joy and peace that he had found. Although we shall greatly miss Lawton, we celebrate the tremendous accomplishments of his life.

R. Michael Siatkowski, MD

Equal to his reputation as the consummate clinician, Lawton Smith was an educator par excellence. He possessed the uncanny knack of using examination techniques and “down home” phrases to share his astute clinical observations with fellows, residents, and medical students. He was able to take complicated clinical findings and make them understandable and practical. He described himself as a “treating doc” and wanted his colleagues to always keep the credo of “help the patient” at the forefront of their clinical practice.

Creating the Journal of Neuro-Ophthalmology was a natural extension of Lawton’s teaching zeal. In the early years of publication, many articles were followed by “editorial comment” or “new pearls checklist,” in which he would emphasized the importance of a particular manuscript and highlight how it would help in clinical practice. He cared deeply about his patients and wanted to make sure that readers of the Journal had the latest and best information to deliver that care.

Those who knew Lawton and were fortunate enough to see him “in action” fully realize how lucky they were. Lawton Smith was a unique individual—a great physician, educator, and mentor. We are proud that his legacy lives on in the Journal of Neuro-Ophthalmology!

Lanning B. Kline, MD

To read more about Dr. Smith’s career, see “For J. Lauton Smith” by Joel S. Glaser, MD (J Neuroophthalmol 1996;16:233).
Leber Hereditary Optic Neuropathy: Some New Observations

Nancy J. Newman, MD

Clinical medical science classically progresses from the single case report, to multiple case series, to molecular diagnosis, to an expanded phenotype. Such has been the case with Leber hereditary optic neuropathy (LHON), a disorder first described in the mid-19th century by astute German clinical ophthalmologists as a syndrome of bilateral subacute optic neuropathies in otherwise healthy young men, often with a characteristic funduscopic appearance (1,2). Subsequent large case series in the premolecular era better defined the hereditary nature of the disorder and expanded the clinical phenotype (3–5). With the discovery of the causal LHON mitochondrial DNA point mutations at the end of the 20th century came further expansion of the demographic and clinical profile of this disease, sometimes with unusual and unexpected observations (6–9).

In this issue of the Journal, 2 such interesting observations are reported (10,11). In the Photo Essay by van Westen et al (10), MRI performed several months after visual loss in 2 male members of the same molecularly confirmed 11778 LHON pedigree showed enlargement of the anterior visual pathways without enhancement, and increased T2 signal, not only in the optic nerves and chiasm but also in the optic tracts, extending to the lateral geniculate bodies. Follow-up MRIs months later showed persistent bright T2 signal in normal-sized or atrophied anterior visual pathways. Although most MRIs are reportedly normal in the acute and chronic phases of LHON (6,7), increased T2 signal of the optic nerves has been previously noted on MRIs of LHON patients months to years after visual loss (12,13), less often in the chiasm (14,15), but never before in the optic tracts. Given that the pathology of LHON ultimately involves the entire length of the retinal ganglion cell axon (16), these findings should not be surprising. The bright T2 signal likely reflects axonal degeneration and ultimately gliosis. Why this has not been previously noted may reflect the usual timing of diagnostic imaging early in the acute phase of visual loss before degeneration can occur, combined with low imaging quality and lack of specific views of the optic tracts. Of course, an alternative explanation is that we just haven’t looked carefully—perhaps now we will!

In the second article in this issue of the Journal dealing with LHON, Mnatsakanyan et al (11) report brachial plexus peripheral nerve abnormalities in a single patient with LHON visual loss associated with the 3460 mitochondrial DNA mutation, and no antemortem symptoms of peripheral neuropathy. Brachial plexus specimens obtained at necropsy and evaluated by light and electron microscopy showed various stages of extensive axonal degeneration of the large heavily myelinated fibers, clearly abnormal when compared to similar specimens from age-matched controls without known neurologic disease. Histopathology of muscle samples showed variable fiber size consistent with a neurogenic myopathy. Although it is possible that the patient had an unrecognized alternative cause for brachial plexopathy (such as cervical disc disease), good clinical documentation in this patient did not suggest prior neurologic disease. Additionally, although only one brachial plexus and no other peripheral nerves were sampled from the patient, the extent of neurodegeneration as demonstrated in both the brachial plexus and the muscles innervated suggested a widespread phenomenon. Morphometric analysis failed to
demonstrate a preferential vulnerability of smaller axons, which has been previously suggested to occur in the optic nerves of LHON patients (17).

Although never previously demonstrated histopathologically, clinical peripheral nerve involvement in LHON has been rarely reported, as have other nonophthalmologic neurologic manifestations, usually designated within the so-called Leber’s plus phenotype (18–20). Other syndromic disorders resulting from mitochondrial DNA mutations, such as mitochondrial encéphalopathy with lactic acidosis and stroke-like episodes (MELAS), mitochondrial neurogastrointestinal encéphalopathy (MNGIE), and chronic progressive external ophthalmoplegia (CPEO), have peripheral neuropathy more commonly demonstrated, both clinically and histopathologically. Similarly, other optic neuropathies in which mitochondrial dysfunction has been proposed as a causal mechanism have had peripheral neuropathy as a more consistent clinical feature, such as the Cuban epidemic neuropathy in which more patients had clinically manifest peripheral neuropathy than optic neuropathy (21). Dominant optic atrophy patients have also recently been shown to manifest other neurologic features, including both clinical and subclinical peripheral neuropathy (22). Additionally, various forms of the hereditary peripheral neuropathies, including some forms of Charcot-Marie-Tooth disease linked to mitochondrial dysfunction, also include optic neuropathy in their clinical phenotype (23).

It should not be so surprising that a mitochondrial DNA mutation that is present in every cell and in every tissue in the body should have more consequences than just optic neuropathy. Indeed, one of the paradoxes in LHON is that the sole tissue to be clinically affected in the vast majority of patients is specifically the optic nerve. As the authors suggest (11), the answer may lie in variable tissue reliance on mitochondrial function and the different regenerative capability of tissues. Studies such as this single case report should help further our understanding of the tissue-specific pathophysiology of LHON.

Clinical observation has always been the cornerstone of neuro-ophthalmologic practice. It is fitting that in a genetically defined disorder, such as LHON, astute clinical, radiographic, and histopathologic observation of single cases, still plays an important role in the advancement of knowledge of this disease. These new observations should help us better understand the pathophysiology of LHON and other similar disorders, hopefully with the ultimate goal of generating targeted therapeutic options.

REFERENCES


Axonal Degeneration in Peripheral Nerves in a Case of Leber Hereditary Optic Neuropathy

Lilit Mnatsakanyan, MD, Fred N. Ross-Cisneros, BA, Valerio Carelli, MD, PhD, Michelle Y. Wang, MD, Alfredo A. Sadun, MD, PhD

Background: Leber hereditary optic neuropathy (LHON) is a mitochondrial DNA (mtDNA) genetic disorder characterized by profound bilateral loss of central vision due to selective loss of retinal ganglion cells. Most patients with LHON do not have complaints related to the peripheral nervous system. We investigated possible qualitative and quantitative histological changes in the peripheral nerve of a patient with LHON as compared to normal controls.

Methods: Brachial plexus specimens were obtained at necropsy from a patient with LHON carrying the 3460/ND1 mtDNA mutation and age-matched controls without known history of neurological disease. The nerves were evaluated by light microscope coupled to a digital camera-based morphometric analysis and electron microscopy.

Results: Extensive axonal degeneration of the large heavily myelinated fibers was found in the brachial plexus from the patient with LHON. In LHON nerve fascicles, we counted over 10 times as many degenerated profiles as found in the control nerve fascicles.

Conclusions: Microscopic examination of the brachial plexus in the patient with LHON clearly demonstrated a significant pattern of neurodegeneration. Our study suggests that peripheral neuropathy may be a subclinical feature associated with LHON.

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Leber hereditary optic neuropathy (LHON) is a maternally inherited form of bilateral subacute loss of central vision affecting predominantly young adults. Three pathogenic mitochondrial DNA (mtDNA) point mutations, at positions 11778/ND4, 3460/ND1, and 14484/ND6, account for more than 90% of cases (1). Optic atrophy with permanent and severe loss of central vision is the usual end point of the disease (1,2). Extensive efforts have been made to further elucidate the pathology and pathophysiology of LHON. It has been found that within the optic nerve, there is a predominant involvement of the papillomacular bundle (PMB), represented by small caliber parvocellular axons (3). The disease is characterized by symmetrical dropout of retinal ganglion cell axons in the PMB in the absence of inflammation on fundus examination (4). Larger axons in the optic nerve are selectively spared. Dramatic loss of the retinal ganglion cells and the axons that compose the nerve fiber layer are the main histopathological findings in LHON (1–3).

Biochemical evidence in patients with LHON indicates that all 3 pathogenic mitochondrial mutations involving different subunits of complex I affect the respiratory function by decreasing the complex I–driven adenosine triphosphate (ATP) synthesis (5). This in combination with an increase in the reactive oxygen species (ROS) production may lead to tissue damage. It has been suggested that environmental factors, such as smoking and alcohol consumption, might influence the penetrance of the LHON mtDNA homoplasmic mutation (1,2). An extensive investigation of a large Brazilian pedigree of 11778/ND4 on haplogroup J was conducted on 328 living family members; this study found a statistically significant association with drinking alcohol and especially tobacco use in LHON-affected members as compared to asymptomatic carriers (6). Among the patients affected with LHON, smokers also had poorer visual acuity (6,7). Most recently, an extensive study on many LHON pedigrees confirmed the risk factor of smoking on the conversion of carriers to the affected members (8).

LHON has been classically thought to only affect the optic nerve. This tissue specificity is intriguing.

Doheny Eye Institute, Department of Ophthalmology (LM, FNR-C, MYW, AAS), University of Southern California, Los Angeles, California; and Dipartimento di Scienze Neurologiche (VC), Universita di Bologna, Bologna, Italy.

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Address correspondence to Alfredo A. Sadun, MD, PhD, Doheny Eye Institute, Department of Ophthalmology, University of Southern California, 1450 San Pablo Street, Los Angeles, CA 90033; E-mail: asadun@usc.edu

Original Contribution

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Mitochondrial dysfunction might be expected to involve other systems since it plays a central role in all cellular functions through impaired oxidative phosphorylation (9). Indeed, evidence of some systemic involvement in LHON has been previously recognized. Rare nonophthalmologic manifestations have been reported including defective cardiac conduction, spinal cord disease, brainstem and basal ganglia involvement, dementia, tremor, parkinsonism, migraine, epilepsy, myoclonus, dystonia, a multiple sclerosis–like disorder, Charcot-Marie-Tooth disease, progressive auditory neuropathy, and peripheral nerve involvement (10–18). All these cases have been characterized as the “Leber plus” clinical phenotype. The fact that other metabolic mitochondrial optic neuropathies, like Cuban epidemic optic neuropathy, also involve the peripheral nerves (19) prompts the question as to whether patients with LHON may also have subclinical or histopathological evidence of a peripheral neuropathy. There have been associations of peripheral neuropathy with LHON (18,20), but none of these have provided strong evidence for a common etiology.

There are excellent reasons, however, to expect peripheral nerve involvement in LHON. The peripheral nerves are the longest axons in the body. Long (and unmyelinated) axons might be vulnerable in LHON as they have a higher energy demand (9). To test this hypothesis, we examined the brachial plexus obtained at necropsy from a patient with LHON with the 3460/ND1 mtDNA mutation, looking for morphological changes, fiber loss, degeneration, and morphometric changes.

**METHODS**

We obtained at necropsy a specimen of 1 brachial plexus nerve from a previously reported female patient with LHON (3) carrying the homoplasmic 3460/ND1 mutation, who died of cardiac failure at 75 years of age. Her well-documented history did not include the clinical features of peripheral neuropathy. She had lost her vision in both eyes at the age of 22. Her right and left eyes were affected within a 1-month interval from each other. At about the time of her visual loss, her neurological examination revealed extrapyramidal signs. Furthermore, the last 10 years of her life were characterized by a slowly progressive cognitive decline.

The tissue was formalin-fixed within 24 hours postmortem. The peripheral nerves were separated from the surrounding adipose tissue and remnants of the skeletal muscles, then cut in cross-sections. The nerves were postfixed in a buffered aldehyde solution (2% paraformaldehyde and 2% glutaraldehyde in 0.1 M phosphate-buffered saline [PBS]) and then processed for embedding into plastic blocks. This process involved further fixation of the nerves in 2% osmium tetroxide (OsO₄) in 0.1 M PBS for 3–4 hours for lipid stabilization, then rinsing first with PBS, then with 0.1 M sodium acetate buffer. Enblock staining was performed with 1.0% uranyl acetate in 50 mM sodium acetate overnight. The tissues were then dehydrated with increasing concentrations of ethanol to 100%, then propylene oxide.

Following dehydration, each specimen was infiltrated with a 1:1, then a 2:1 epon:propylene oxide mixture. Next, the nerves were placed in 100% epon in vacuum overnight. Finally, the tissue was placed in freshly made 100% epon, oriented in an embedding mold, labeled, and placed in an oven at 60°C for 2 days to allow for complete polymerization of the epon into tissue blocks.

For light microscopic examination, semithin (1 μm) cross-sections of nerves embedded in epon were obtained using a diamond histoknife on an ultramicrotome. Tissue sections were then dried on glass microscope slides and stained with p-phenylenediamine (PPD) in absolute methanol (21). The slides were then cleared in xylene, mounted with a permanent mounting media, and then coverslipped. The brachial nerves were evaluated using a Zeiss Axioskop light microscope (Carl Zeiss, Inc, Thornwood, NY) coupled to a Spot RTk4e digital camera (Diagnostic Instruments, Inc, Sterling Heights, MI) that allowed for capturing and saving of the images onto a computer. Approximately, 8–10 areas were sampled from the nerve cross-sections at ×630 magnification. Degenerated fibers were recognized as dark, opaque, solid profiles. The average number of thin (<2 μm), highly myelinated, thick (>2 μm), and degenerated axonal profiles were calculated per 1 mm² manually.

We counted and measured the calibers of normal appearing axons per square millimeter of the LHON and control brachial nerves using computer-assisted image analysis from a morphometry software program called Aphelion (Amerinex Applied Imaging, Inc, Monroe Township, NJ). For examination, using transmission electron microscopy, ultrathin sections of nerves were cut using a diamond knife on an ultramicrotome from selected areas chosen using a light microscope. The sections were placed on copper grids and stained with uranyl acetate and lead citrate for examination on a JEOL transmission electron microscope (JEOL USA, Peabody, MA). PPD stains lipid aggregates and membranes (22). We used the appearance of homogeneously opaque, thick, dark brown, individual fibers and, less commonly, larger singular profiles consisting of elements from many degenerated axons often surrounded by additional myelin (21,22) as defining degenerated axons. We defined the normal myelinated axon as containing a clear axoplasm surrounded by an intensely stained annulus of myelin. The qualitative changes, average density of thin and thick myelinated fibers...
per 1 mm², and percentage of fibers undergoing axonal degeneration were then estimated from our calculations.

RESULTS

We estimated the qualitative changes, average density of thin and thick myelinated fibers per square millimeter, and percentage of fibers undergoing axonal degeneration in a sample of brachial plexus nerve from a patient with LHON. We found extensive axonal degeneration at various stages in cross-sectional profiles of nerves. The typical spectrum of this degeneration appeared to range from axonal swelling to increasing levels of condensation of axoplasm and myelin thickening (Figs. 1B, 3C). There were focal areas within the fascicles demonstrating higher densities of axonal degeneration. In the control peripheral nerves, a few degenerated profiles were also observed. Figure 1 compares cross-sections from normal and LHON brachial nerves.

The magnitude of axonal degeneration was calculated as a ratio of degenerated profiles to normal axons. We previously demonstrated that in later stages of axonal degeneration, a single large profile can consist of elements from many degenerated axons (Fig. 3B) (21,22). However, most of the degenerated axons in our counts were observed to be at an early 1-axon stage (Fig. 3C). We manually counted an average of 7,000 normal appearing axons per square millimeter in the peripheral nerves of controls and about 6,000 in the LHON nerve. However, the number of degenerated profiles in LHON was increased by a factor of 13. Approximately 20% of the profiles were degenerated in the LHON nerve, compared to only 1%–3% in the controls (Fig. 2).

Computer-assisted image analysis of the nerve fiber spectra showed that the mean axonal diameter was similar in patients with LHON and in controls. Although the computerized study may mistakenly identify the same axon twice for external and internal diameter or overlook the smallest fibers, we manually corrected for these issues before counting.

The degeneration in the nerve of the LHON case was seen slightly more frequently in axons with medium to large diameters (not shown). Examination by electron microscopy permitted better qualitative assessment of normal and degenerated profiles in normal control and LHON peripheral nerves (Fig. 3). The brachial plexus axons from the controls demonstrated a wide variety of axon calibers, most of which had medium thick myelin sheaths. The axoplasm was not electron dense and contained a normal distribution of neurofilaments and other axoplasmic constituents (Fig. 3A). In contrast, the brachial plexus from the patient with LHON displayed numerous individual axonal profiles that possessed thick electron dense myelin with a condensed axon (Fig. 3C) and, less often, a large degenerated profile consisting of globular subelements, each representing the degeneration of a separate axon (Fig. 3B). These larger single profiles consisted of remnants from 4 to 8 axons (21,22). In addition to the extensive axonal degeneration, muscle histopathology showed wide variability of muscle fiber caliber, hypotrophic fibers, and angulated fibers.

DISCUSSION

This is the first qualitative histologic and quantitative morphometric description of degeneration in peripheral nerves from a patient with LHON. Extensive neurodegenerative morphological changes affecting many fibers in the peripheral nerve were seen in this case of 3460/ND1 mutation but not in controls. Calculations quantitated this degeneration to be at a rate approximately 13 times higher than the age-matched controls. This finding suggests that LHON does affect the peripheral nerves at a subclinical level probably as a part of a common pathogenetic mechanism. The fact that the total number of fibers in the LHON brachial plexus was not significantly reduced suggests that compensatory regeneration may maintain fiber number, leading to a steady state and subclinical condition.
Nonspecific axonal degeneration (up to 3%) and segmental demyelination were seen in the peripheral nerves of our controls, and this has been observed with normal aging as a part of other morphological changes (23,24). Limited morphological degenerative changes in the fibers of peripheral nerves have been reported as being due to repeated microtraumas, pressure on the nerve, but also simply as age related (23). Indeed, the number of myelinated axons in the peripheral nerves decreases with age in normals, especially in the distal regions, but overall, fiber morphology abnormalities are mild (24).

We observed larger scale degeneration in the LHON brachial plexus specimen that greatly exceeded the expected age-related changes. The peripheral nerves in the present LHON case demonstrated pathological features of neurodegeneration. Mitochondrial dysfunction from LHON might have at least 2 deleterious consequences for neurons. The first is a reduction in ATP production.

Cybrid studies have shown that LHON mutations can impair complex I–driven ATP synthesis, but total cellular ATP content is not significantly affected (5,25). This explains why, even in symptomatic patients, most tissues do not manifest pathology (1). A second consequence of LHON mutations concerns the complex I–driven increase of ROS. ROS may act as an intracellular messenger and lead to changes in the membrane potential of mitochondria, predisposing to the opening of the mitochondrial permeability transition pore, releasing cytochrome C, and thus activating the apoptotic cascade (26–29). Neurons consume ATP at the highest rate, and most of this energy requirement is for axonal membrane polarization and axonal transport. Hence, neurons are sensitive to mitochondrial dysfunction, particularly those with long axonal segments and less myelin. This includes the retinal nerve fiber layer and optic nerve (1) and perhaps other neuronal systems with long axons, including peripheral nerves.

At least 4 LHON patients with the 11778/ND4 mutation have been reported with diminished or absent sensation (ie, light touch and vibration sense), and reflexes in their extremities and nerve conduction velocities were slightly attenuated (18). Fiber loss and chronic axonal degeneration were noted in peroneal nerve biopsies from patients with mitochondrial disorders other than LNON such as mitochondrial encephalomyopathy lactic acidosis stroke, myoclonic epilepsy ragged red fibers, and mitochondrial neurogastrointestinal encephalopathy (20). One further patient with 11778/ND4 LHON has been described with progressive sensory complaints and electrophysiological evidence of sensorimotor demyelinating polyneuropathy but without peripheral nerve biopsy (30). Hence, to date, there has not been strong evidence for LHON-associated peripheral neuropathy. The present study, in showing marked degeneration of fibers in LHON

![Axonal count in control and LHON periperal nerves](image)

**FIG. 2.** Average counts of the thin (<2 μm), thick (>2 μm), and degenerated axons per 1 mm² of the brachial plexus nerve in control and LHON are shown. The degenerated fibers only account for 0.8%–2.8% of the control nerves as compared to approximately 20% of the LHON nerve.

![Plastic-embedded thin sections of human brachial plexi, cross-sectional profiles, transmission electron microscopy](image)

**FIG. 3.** Plastic-embedded thin sections of human brachial plexi, cross-sectional profiles, transmission electron microscopy. A. Example of a typical myelinated fiber from a normal control. B. Example of a degenerated profile consisting of a cluster of electron-dense material representing multiple individual degenerated axons such as those seen in C. C. Note small condensed axons (arrows) in 2 of these degenerated fibers with thickening of electron-dense myelin. (scale bar in A, 0.5 μm; in B, 1 μm; and in C, 3 μm).
peripheral nerve, provides further support for the notion that long axons of peripheral nerve may also be vulnerable to the same pathophysiological mechanism (1).

We observed extensive degeneration in the peripheral nerve (brachial plexus) from a patient with 3460/ND1 LHON, not seen in controls. Although not previously described, this finding was predicted by the pathophysiological mechanisms that our group has previously proposed (1). Long and less myelinated axons, such as the retinal nerve fiber anterior to the optic disc, may be vulnerable to mitochondrial dysfunction. However, while the clinical manifestation of blindness is common in LHON, clinical evidence of peripheral neuropathy is not. The difference is probably due to the capacity of the peripheral nerve system to regenerate.

Many processes can cause peripheral neuropathy and brachial plexus damage. However, based on the well-documented history, there were no motor or sensory symptoms or signs suggesting the presence of other neurological conditions. There was no history of compression, transection, or ischemia of the brachial plexus. No risk factors, such as radiation therapy, were noted. Cervical disc disease is a common condition affecting the elderly. Since this is a retrospective study, we cannot completely rule out cervical disc disease. There was no history of pain, sensory loss, or weakness involving the shoulder, arm, or hand, and cervical disc disease was not likely present. LHON, confirmed by genetic analysis, was the only neurological condition that could be supported. Furthermore, postmortem histopathology of muscle samples demonstrated variable fiber size most consistent with a neurogenic myopathy. All our findings suggest that the basis of the peripheral neuropathy in our patient is due to axonal damage.

Although our histopathological sampling was extensive, we only studied 1 LHON and 4 control cases. Such limitations often occur in conditions as rare as LHON. We look forward to confirmation in other cases of molecularly characterized LHON, as well as other mitochondrial optic neuropathies.

REFERENCES


Neuroretinitis With Retrobulbar Involvement

Michael S. Vaphiades, DO, Eric H. Wigton, MD, Hossein Ameri, MD, Andrew G. Lee, MD

Abstract: Two patients with neuroretinitis are presented, both having MRI abnormalities of the orbital portion of the optic nerve. We review previous reports of CT and MRI findings in patients with neuroretinitis and propose a spectrum of neuroimaging abnormalities in these patients.

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Neuroretinitis is an inflammatory optic neuropathy characterized by optic disc edema associated with a macular star. Using fluorescein angiography, Gass (1) demonstrated that the macular exudates arise from leakage of proteinaceous material from vessels on the surface of the optic disc. This pathogenic mechanism has been confirmed using optical coherence tomography (OCT) (2).

There are few reports of neuroimaging studies in patients with neuroretinitis (3–5). In general, such studies are normal (6). We report 2 patients with neuroretinitis in which MRI demonstrated abnormalities of the orbital optic nerve and propose that patients with neuroretinitis have a spectrum of neuroimaging findings.

CASE 1

A 6-year-old girl presented with a 4-day history of painless visual loss in the left eye. Three years previously she suffered a decrease in vision in the right eye due to neuroretinitis.

At that time, testing for Bartonella, Lyme, and syphilis was negative and the patient was not treated. In addition, contrast-enhanced MRI of the brain and orbits without fat suppression was found to be normal.

Examination showed normal vital signs, a visual acuity of no light perception in the right eye and 20/400 in the left eye. Color vision was diminished in the left eye, and the right pupil was amaurotic. The right optic nerve was pale with pigmented changes in the macula, while the left fundus showed optic disc edema and a macular star (Fig. 1).

Laboratory studies for Bartonella, angiotensin-converting enzyme, Lyme, Toxoplasma, Toxocara, syphilis, and neuromyelitis optica antibodies were all negative. A contrast-enhanced fat-suppressed orbital MRI revealed diffuse enhancement of the left optic nerve and sheath (Fig. 2). Lumbar puncture showed a normal formula and was negative for oligoclonal bands.

The patient was treated with 250 mg oral azithromycin daily for 5 days, and 5 days of high-dose intravenous methylprednisolone (500 mg/day). Eight weeks later, her vision had improved to 20/20 in the left eye. The patient now correctly identified the Ishihara color plates, and the left fundus showed mild optic disc pallor and a resolving macular star.

CASE 2

A 23-year-old man developed sudden onset of a headache and pain with eye movement associated with visual loss in the left eye. His medical and ocular histories were unremarkable. He was scratched by a 3-month-old kitten 2 weeks previously and developed fever, which resolved spontaneously.

Examination showed normal vital signs, visual acuity of 20/20 in the right eye and counting fingers in the left eye. His pupils were isocoric with a left relative afferent pupillary defect. Automated visual field testing was normal in the right eye and demonstrated an inferior arcuate defect in the left eye. Extraocular movements, slit-lamp examination, and the right fundus were normal. The left optic disc was swollen with subretinal fluid and striae in the macula and dot hemorrhages in the peripheral retina (Fig. 3A).
Complete blood count, anti-HIV-1 and HIV-2 antibodies, syphilis, and Bartonella studies were negative. Given the history of contact with a cat, the patient was treated for presumed cat scratch disease with 500 mg oral azithromycin on day 1, followed by 250 mg daily for 4 days.

Because vision failed to improve over the ensuing 1 week, MRI was performed. There was enhancement of the left optic nerve head and contiguous 3-mm orbital portion of the left optic nerve (Fig. 4). An OCT of the left eye confirmed the presence of subretinal fluid causing macular thickening at 976 μm versus normal right macular thickness of 339 μm.

One week later, the patient developed a macular star in the left eye (Fig. 3B), and he was treated with a 10-day course of tetracycline. Serology for Lyme, Toxoplasma, angiotensin-converting enzyme, and a chest radiograph were normal. Repeat serology for Bartonella henselae showed a positive IgG titer (1:128). The patient showed progressive improvement in his vision, and 2 months later, he had an acuity of 20/40 in the left eye, with a less prominent macular star (Fig. 3C).

**DISCUSSION**

Our patients had neuroretinitis, one due to Bartonella henselae and the other of unknown cause, and in both patients, neuroimaging demonstrated involvement of the orbital portion of the optic nerve. Although classically the macular star figure is the hallmark of neuroretinitis, the star figure is a late sign following the optic disc edema phase and peripapillary subretinal fluid accumulation by 1–3 weeks (7). The subretinal fluid in the macula can be detected on OCT before the development of the star (2).

Neuroimaging abnormalities in patients with neuroretinitis have been infrequently reported. Zhang et al (3) reported a case of idiopathic neuroretinitis in which CT revealed “tubular enlargement of the optic nerve and postcontrast enhancement.” Histopathologic examination was consistent with optic perineuritis. Wals et al (4) reported a similar case of neuroretinitis of unknown cause associated with optic perineuritis. The MRI demonstrated enhancement and thickening of the involved optic nerve sheath with sparing of the nerve. Fat suppression of the
orbital soft tissue further supported the diagnosis of optic perineuritis. Schmalfuss et al (5) evaluated the MRI characteristics of patients with optic neuropathy of all types. Nine of their 82 patients were diagnosed with cat scratch disease. In 5 of the 9, optic nerve enhancement was present on contrasted orbital MRI at the optic nerve-globe junction with extension of up to 4 mm within the orbital segment of the nerve. At the time of MRI scanning, only 1 of these 5 patients had the macular findings of neuroretinitis.

Neuroimaging findings in our 2 patients add further evidence that orbital optic nerve enhancement may be seen in neuroretinitis. No specific cause was found for neuroretinitis in our first patient despite extensive evaluation. Clinically, this case fits the category of recurrent neuroretinitis as reported by Purvin and Chioran (6). Seven such cases were described, all of unknown etiology and, in general, a poor visual outcome. Radiologic studies were reported to be normal, but it was not specified if these scans

FIG. 3. Case 2. Evolution of neuroretinitis in the left eye. A. At initial presentation, there is swelling of the optic disc and retina. B. One week later, macular star formation is evident. C. Two months later, mild optic disc pallor is present with a resolving macular star.
included fat-suppressed orbital views. Our second patient was found to have cat scratch disease as the cause of neuroretinitis. Short-segment MRI enhancement localized to the optic nerve-globe junction has been reported as a highly specific sign for cat scratch neuroretinitis (5). Our case is consistent with this observation.

The neuroimaging results in our 2 patients support the fact that a macular star does not exclude retrobulbar pathology. Perhaps, in some cases of neuroretinitis, the inflammation is so severe and widespread that it extends posteriorly from the optic disc to include the retrobulbar optic nerve. Blood-brain barrier breakdown, similar to what occurs at the level of the optic disc, may produce retrobulbar optic nerve enhancement on contrast-enhanced fat-suppressed T1 orbital MRI. The fundus findings in some cases of neuroretinitis may not reflect the extent of the disease.

In summary, there appears to be a spectrum of neuroimaging findings in neuroretinitis:

1. Normal optic nerve.
2. Intraocular optic disc enhancement at the nerve-globe junction.
3. Optic nerve sheath enhancement (optic perineuritis).
4. Optic nerve and optic sheath enhancement.

REFERENCES

Neuromyelitis Optica Antibodies in Patients With Severe Optic Neuritis in China

Chuntao Lai, MD, Guohong Tian, MD, PhD, Toshiyuki Takahashi, MD, PhD, Wu Liu, MD, PhD, Ling Yang, PhD, Xiaojun Zhang, MD, PhD

Background: Severe visual loss is seen in both multiple sclerosis–associated optic neuritis (ON) and neuromyelitis optica (NMO)–associated ON. NMO (aquaporin 4) antibodies have been reported to have diagnostic and prognostic value for visual and neurological outcomes of recurrent ON. We performed this study to investigate the frequency of NMO antibodies and its prognostic value for visual and neurological outcomes in Chinese patients with severe ON.

Methods: Single-center prospective cohort study. Detection of NMO antibodies was by indirect immunofluorescence method using human aquaporin 4–transfected cells. Severe ON was defined as visual acuity of 20/200 or worse in at least 1 eye at the nadir of the patients’ course. Clinical features at baseline, visual outcome, and sequential neurological events were compared between seropositive and seronegative groups.

Results: NMO antibodies were detected in 11 of 34 patients (32.4%) with severe ON. Five seropositive patients with recurrent ON had significantly higher titers (range: 1:512 to 1:65,536; median: 1:512) than those of 6 seropositive patients with only 1 episode (range: 1:16 to 1:512; median: 1:32) ($P = 0.021$). Female to male ratio (10:1) and antinuclear autoantibody positivity in seropositive patients (3 of 9, 33.3%) were statistically higher than those of the seronegative group (12:11; 0 of 19; $P = 0.026$). The seropositive patients had significantly poorer visual outcomes than seronegative patients ($P = 0.025$). During the averaged 32-month follow-up, 2 of 11 seropositive patients (18.2%) developed clinically incomplete transverse myelitis, while no similar symptoms were reported in the seronegative group.

Conclusion: NMO antibody positivity is relatively high in Chinese patients with severe ON and suggests a poorer visual outcome, probably higher risk of developing spinal cord lesions and a closer association with systemic autoimmune disorders.

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patients had complete medical history, ophthalmological and neurological examinations, brain and orbital MRI with short T₁ inversion recovery sequences, laboratory testing for fluorescent treponemal antibody absorption, and mitochondrial DNA sequencing to rule out other possible causes of optic neuropathy. The majority of patients had a lumbar puncture and testing for autoimmune diseases including antineutrophil cytoplasmic antibody (ANCA), extractable nuclear antigen, and antineuropil epitope cytoplasmic antibody (ANCA).

After the protocol was approved by the Institutional Review Board of Beijing Tongren Hospital, Capital Medical University, patients gave informed consent and blood was obtained for NMO antibody within 1 month of onset of visual loss. The serum samples were sent to the Department of Neurology, Tohoku University Graduate School of Medicine, and the antibody was detected by the indirect immunofluorescence method using human AQP4-transfected cells. The cutoff value for positivity (minimal dilution of serum) was 1:4.

Demographic and clinical data were recorded together with the NMO antibody results. Visual acuity of each eye was scaled as follows: 0 = 20/20; 1 = better than 20/30; 2 = 20/30 to 20/59; 3 = 20/60 to 20/199; 4 = 20/200 to 20/800; 5 = count fingers only; 6 = light perception; and 7 = no light perception. Patients were followed up clinically or by phone if the patient could not come to the clinic. We compared the demographic and clinical features at baseline, the visual and neurological outcomes of the NMO antibody seropositive and seronegative groups, using Fisher exact test for frequency data, t test for continuous data, and Mann–Whitney U test for non-normally distributed data.

RESULTS

NMO Antibody Test
NMO antibody testing was performed in 34 patients with severe ON. Patients ranged in age from 16 to 54 years (average: 31.1 years). There were 22 women and 12 men. NMO antibody was positive in 11 of 34 patients (32.4%) with severe ON. While 6 of 23 patients (26.1%) with 1 episode of ON were seropositive, the rate was higher (5 of 11, 45.5%) in patients with recurrent ON but did not reach statistical significance (Fisher exact test, P = 0.434). The overall range of antibody titers was from 1:16 to 1:65,536. The 5 seropositive patients with recurrent ON had significantly higher titers (range: 1:512 to 1:65,536; median: 1:512) than those of the 6 seropositive patients with isolated ON (1:16 to 1:512; median, 1:32) (P = 0.021).

Comparison of Seropositive and Seronegative Patients
Clinical features, MRI findings, blood and cerebrospinal fluid results at baseline, and follow-up data were compared between the seropositive and seronegative groups.

Baseline Data
No statistically significant differences were found between the 2 groups regarding the age of onset, number of attacks, visual acuity at nadir, and bilateral or subsequent involvement of both optic nerves (Table 1). Mild and sparse white matter lesions on brain MRI were reported in 7 of 23 seronegative patients (30.4%) and 3 of 11 seropositive patients (27.3%). No difference was found with respect to the number or location of white matter lesions between the 2 groups. The female gender ratio was much higher in the seropositive group (female:male = 10:1) than in the seronegative group (female:male = 12:11), but the difference did not reach statistical significance (P = 0.053). ANA was tested in 9 seropositive patients, 3 of which (33.3%) were positive at over 1:320 level, while none of the 19 seronegative patients were ANA positive (P = 0.026). At the time of testing, no patient with ANA positivity met the diagnostic criteria for Sjogren syndrome, systemic lupus erythematosus, or any other autoimmune disease.

Follow-up Data
Follow-up information was available in 10 of 11 seropositive patients (91.0%) and 19 of 23 seronegative patients (82.6%). Follow-up time was similar between the 2 groups (Table 1). Two of 10 seropositive ON cases and 1 of 19 seronegative ON cases had at least 1 additional episode of ON (P = 0.239). Final visual scores of the seropositive group were worse than those of the seronegative group (P = 0.025) (Table 1). At the last follow-up examination, 8 of 10 seropositive patients (80%) had visual acuity worse than 20/200 in at least 1 eye, while this poor visual outcome was present in only 3 of 20 seronegative patients (15%). During follow-up, while none of the seronegative patients reported symptoms due to lesions other than the optic nerve, 2 seropositive patients developed incomplete transverse myelitis.

DISCUSSION
Lennon et al (4) initially reported that 25% of patients with recurrent ON (simultaneous or sequential) were seropositive for NMO antibodies and noted a similar result (5 of 25, 20%) in a more recent study (5). Chan et al (6), in the first report dealing with NMO antibody in Chinese patients, found that 2 of 9 patients (22%) with recurrent ON were seropositive and 1 of 11 patients (9.1%) with isolated ON. Our study showed that 11 of 34 Chinese patients (32.4%) with severe ON were seropositive, and there was an even higher rate (45.5%) of positivity in the group with recurrent ON. Compared to the previous reports in both white (3,5,7) and Asian (6) patients, our rate of seropositivity is
higher. Because these studies identified patients with both mild and severe ON, our results suggest that NMO antibodies are more likely to be found in cases of severe ON.

Our results are similar to those of Matiello et al (5) in finding no significant difference between seropositive and seronegative groups regarding age, bilaterally simultaneous or subsequent onset of visual loss, and the number of recurrent attacks. No difference was found in the brain MRI findings between the 2 groups. The only statistically significant difference we found was the frequency of a positive ANA test. Of these seropositive patients we were ANA positive, while none of the seronegative patients were ANA positive. It has been reported that NMO is often associated with clinical or serological markers of systemic autoimmune disorders such as ANA and Sjögren syndrome A antibodies (1,8), although the basis of coexisting NMO and systemic autoimmune disorders is unknown.

The comparison of follow-up data in our study documented that seropositive patients had much worse visual scores at the last follow-up than seronegative patients. This confirms that Chinese patients with severe ON have poorer visual outcome if they have NMO antibodies. Matiello et al (5) showed that during an average 8-year follow-up period, only 1 seronegative patient (6.6%) but 6 of 12 seropositive patients (50%) developed transverse myelitis ($P = 0.03$). Similarly, 2 of our seropositive patients with ON developed myelitis during the average 8-year months follow-up, while none of the seronegative patients reported myelitis episode. Yet, the number of patients is small and the length of follow-up is limited in both our report and that of Matiello et al (5), and further study is warranted to better define these seropositive patients with ON and subsequent development of spinal cord lesions. The findings of such investigation might also clarify the controversy regarding classification of NMO and optical–spinal MS (9–11).

There were limitations to our study. Not all patients with ON were studied, only those admitted to hospital. Follow-up time was relatively short (Table 1). Due to financial reasons, we could not perform brain or spinal MRI on all patients during follow-up.

In conclusion, we have shown that Chinese patients with severe ON have a higher frequency of NMO antibodies, which increase with recurrence of the optic neuropathy. Seropositive patients are more likely women with a greater likelihood of having autoimmune serological markers. Finally, seropositive patients have a poor visual prognosis, and

### TABLE 1. Demographic, clinical, and outcome data stratified by NMO-immunoglobulin G (IgG) antibody status

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Seronegative (n = 23)</th>
<th>Seropositive (n = 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, years, median (IQR)</td>
<td>35 (17–54)</td>
<td>28 (16–48)</td>
<td>0.164*</td>
</tr>
<tr>
<td>Sex, F:M</td>
<td>12:11</td>
<td>10:1</td>
<td>0.053†</td>
</tr>
<tr>
<td>No. patients with bilateral episodes</td>
<td></td>
<td></td>
<td>1.0000</td>
</tr>
<tr>
<td>(simultaneously and subsequently) of ON</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. patients with recurrent ON</td>
<td>6</td>
<td>5</td>
<td>0.240†</td>
</tr>
<tr>
<td>Visual score at nadir, median (IQR)</td>
<td>5 (4–7)</td>
<td>5 (4–7)</td>
<td>0.976‡</td>
</tr>
<tr>
<td>Abnormal brain MRI (n, %)</td>
<td>7/23 (30.4)</td>
<td>3/11 (27.3)</td>
<td>1.000*t</td>
</tr>
<tr>
<td><strong>Blood test</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accelerated ESR (n, %)</td>
<td>1/20 (5)</td>
<td>1/10 (10)</td>
<td>1.000†</td>
</tr>
<tr>
<td>Increased CRP (n%,)</td>
<td>1/22 (4.5)</td>
<td>0/11</td>
<td>1.000†</td>
</tr>
<tr>
<td>ANCA positive (n, %)</td>
<td>0/19</td>
<td>0/8</td>
<td>—</td>
</tr>
<tr>
<td>ANA (≥1:320, %)</td>
<td>0/19</td>
<td>3/9 (33.3)</td>
<td>0.026‡</td>
</tr>
<tr>
<td><strong>CSF analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (≥10/mm$^3$, n, %)</td>
<td>0/23</td>
<td>0/11</td>
<td>—</td>
</tr>
<tr>
<td>OB of CSF (n, %)</td>
<td>2/11 (18.2)</td>
<td>2/11 (18.2)</td>
<td>1.000†</td>
</tr>
<tr>
<td>IgG synthesis rate of CSF (n, %)</td>
<td>4/16 (25)</td>
<td>3/11 (27.3)</td>
<td>1.000†</td>
</tr>
<tr>
<td><strong>Follow-up data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. cases</td>
<td>19</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>Time (mean ± SD, months)</td>
<td>31.6 ± 13.1</td>
<td>33.7 ± 8.2</td>
<td>0.741*</td>
</tr>
<tr>
<td>Visual score at the last follow-up</td>
<td>1 (0–6)</td>
<td>4 (0–7)</td>
<td>0.01‡</td>
</tr>
<tr>
<td>of visual loss, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. cases with final VA &lt; 20/200</td>
<td>3</td>
<td>8</td>
<td>0.001†</td>
</tr>
<tr>
<td>No. cases with recurrent ON</td>
<td>1</td>
<td>2</td>
<td>0.239†</td>
</tr>
<tr>
<td>Cases with myelitis episodes (n, %)</td>
<td>0 (0)</td>
<td>2 (18.2)</td>
<td>0.111†</td>
</tr>
</tbody>
</table>

* t test. † Fisher exact test. ‡ Mann–Whitney U test.

ANCA, antineutrophil cytoplasmic antibody; CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; F, female; M, male; IQR, interquartile range; VA, visual acuity; WBC, white blood cell.
our data suggests a greater chance of ultimately developing spinal cord involvement.

REFERENCES

Novel Ophthalmic Pathology in an Autopsy Case of Autosomal Dominant Retinal Vasculopathy With Cerebral Leukodystrophy

Aaron M. Gruver, MD, PhD, Lynn Schoenfield, MD, Joshua F. Coleman, MD, Rula Hajj-Ali, MD, E Rene Rodriguez, MD, Carmela D. Tan, MD

Abstract: Autosomal dominant retinocerebral vasculopathy with cerebral leukodystrophy (RVCL) is a rare neurovascular syndrome causing retinal and central nervous system vasculopathy often recognized as contrast-enhancing white matter changes or pseudotumors on imaging. Heterozygous frameshift mutations in the 3-prime repair exonuclease 1 gene have been identified in families affected by RVCL. Variable light microscopic findings and a characteristic ultrastructural appearance of the vasculature in the brain have been reported. Description of the ophthalmic histopathology is exceedingly rare. Here, we report previously undescribed bilateral eye findings in a patient diagnosed with RVCL. The ophthalmic pathology includes thickening and reduplication of the retinal capillary basal lamina demonstrated by electron microscopy. These findings expand what is known about this disease and help further delineate its phenotype.

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The retinocerebral vasculopathies are a group of small vessel diseases that involve the cerebral and retinal arteries and, in some disorders, the vessels of the inner ear (1). One such type is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (1). Characteristic manifestations are recurrent strokes, dementia, and migraine in the fifth and sixth decades. CADASIL is related to mutations in the Notch homolog 3 (NOTCH3) gene that encodes a cell surface receptor expressed in the vascular smooth muscle cells. The most recently designated of the retinocerebral vasculopathies is the autosomal dominant retinocerebral vasculopathy with cerebral leukodystrophy (RVCL) (2). It encompasses 3 previously described syndromes: cerebroretinal vasculopathy; hereditary vascular retinopathy; and hereditary endotheliopathy, retinopathy, nephropathy, and stroke (2–5). These syndromes map to chromosome 3p21.1-p21.3, and heterozygous frameshift mutations of the gene encoding the 3-prime repair exonuclease 1 (TREX1) have been documented in 9 families to date (2,6). Affected individuals usually present in middle age with a progressive loss of vision due to retinal vasculopathy. The extent of neurological disease varies and includes dementia, stroke, and migraine. Some kindred display systemic involvement that includes Raynaud phenomenon, micronodular cirrhosis, and renal dysfunction. The typical length of survival from the onset of symptoms is between 5 and 10 years.

We report the pathological findings in a patient with RVCL with particular attention to previously undescribed ocular histopathologic and retinovascular abnormalities.

CASE REPORT

A 55-year-old white man presented with a 1-year history of gradual bilateral visual loss that eventually worsened to the point that he was unable to work. His medical history included a 10-year history of elevated liver enzymes, proteinuria, and a possible stroke. He was receiving oral prednisone for presumed bilateral retinal vasculitis and referred to rheumatology and neurology for further evaluation.

An extensive workup failed to show evidence of systemic vasculitis. Neurological evaluation revealed mild cognitive impairment with thought-processing and word-finding difficulty. MRI of the brain demonstrated mildly progressive
white matter changes in the paramedian right precentral gyrus and subcortical white matter of the left superior frontal gyrus. Prominent hyperintensity was noted along the genu of the corpus callosum, body of the corpus callosum, and periatrial region (Fig. 1). These changes raised the question of demyelinating disease. A cerebral angiogram demonstrated a small anterior communicating artery aneurysm without evidence of vasculitis. Workup for an infectious process yielded no positive results.

Ten months after initial presentation, systemic steroids were discontinued. After undergoing bilateral cataract surgery, the patient’s vision was stable for approximately 2 years. Three years following initial presentation, he experienced exacerbation of his visual disturbance. Fundus findings and fluorescein angiography during this time are shown (Fig. 2). An open brain biopsy of the right temporal lobe revealed no definitive abnormality. Superficial temporal artery biopsy showed intimal fibroplasia. Genetic testing for mutations of the NOTCH3 gene, implicated in CADASIL, was negative. The differential diagnosis included a central nervous system vasculitis or multiple sclerosis, and the patient was started on cyclophosphamide.

Visual acuity stabilized at 20/100, right eye, and 20/60, left eye. However, musculoskeletal strength, gait, and memory did not improve. Additional family history revealed blindness and kidney failure in the patient’s father and a history of “brain tumor” in a cousin. This family history, poor response to cyclophosphamide, and lack of vasculitic changes on brain biopsy led to testing for RVCL. This proved positive for a mutation in the TREX1 gene (2). Several months later, his condition continued to decline, and the patient expired approximately 5 years after initial presentation.

A complete autopsy, including examination of the eyes, was performed 12 hours after death. Tissues obtained were fixed in 10% buffered formalin and processed routinely for hematoxylin–eosin staining. The eyes were sectioned in the horizontal plane. Additional sections from brain and eye were fixed in a 3.75% glutaraldehyde solution, embedded in epoxy resin, cut into thin sections, and stained with uranyl acetate and lead citrate for examination with a Philips CM-12 transmission electron microscope.

Gross examination of the brain showed a soft cavitary lesion (5.8 × 2.5 cm) in the right temporal lobe and an area of softening in the left lateral cerebellum (2.3 × 1.4 cm). Histologic examination of the brain demonstrated a microscopic acute infarct of the left frontal cortex, dystrophic calcification of the pons and left parietal lobe, and multiple small foci of myelin loss in the frontal, temporal, parietal, and occipital lobes (Fig. 3). The small vessels showed vascular sclerosis. No senile plaques, neurofibrillary tangles, or amyloid deposition were identified.

Intraocular lenses were present in both eyes. Microscopic examination demonstrated thickened retinal vessels and small telangiectasias. Some vessels contained fibrin thrombi (Fig. 4). Amyloid was not present, and no evidence of vasculitis was identified in either eye. Electron microscopy of the retina demonstrated thickening and reduplication of the capillary basal lamina, and similar findings were observed in the right temporal lobe (Fig. 5). No vascular pathology or demyelination was identified in the optic nerves.

There were no specific pathologic changes noted in the microscopic study of the liver and kidneys. No reduplication of the basal lamina in the kidneys or liver was identified by electron microscopy. No fibrin thrombi were identified in any of the other organs.

DNA was extracted from frozen brain tissue for resequencing of TREX1 (NM_016381) to confirm the previously reported mutation. Polymerase chain reaction was performed using published primers (2). Bidirectional sequencing using a BigDye Terminator cycle sequencing kit v3.1 (Applied Biosystems, Foster City, CA) was carried on an ABI 3730 automated DNA sequencer. A heterozygous “GTCA” duplication (g.907_910dupGTCA) in the coding region of TREX1 was reconfirmed by direct sequencing. This frameshift mutation changes the amino acids starting at codon 304 and culminates in a stop codon resulting in a truncated protein (Fig. 6).

FIG. 1. Fluid attenuated inversion recovery (FLAIR) MRI of the brain shows periventricular white matter changes.

DISCUSSION

While RVCL has been recently classified based on the presence of mutations in TREX1, variations in its phenotype...
resulted in the syndromes being viewed as separate entities in the past (2). Brain pathology previously reported in cases is variable and includes foci of coagulation necrosis, subacute cerebral infarction, spongiosis, and white matter astrocytic gliosis (7,8). Vascular changes include fibrinoid necrosis, variable thickening of the media in small to medium sized white matter vessels, obliterative fibrosis of the vessel wall, and vascular proliferation and telangiectasia (3,7,8). A

FIG 2. A. Fundus photograph of the right eye demonstrating pallor of the optic disc with overlying telangiectasias and an area of adjacent hemorrhage (arrow). B. Fluorescein angiogram of the right eye shows perivascular leakage of dye and vessel wall staining (arrows) as well as telangiectatic vascular changes (arrowheads) in the macula.

FIG 3. Representative section taken from the frontal lobe demonstrates small patches of absent blue staining of myelin in the white matter (Luxol fast blue, ×200).

FIG 4. A. Light microscopy of the retina shows that some of the vessels contain fibrin thrombi (arrow) (hematoxylin and eosin, ×400). B. Vascular telangiectasia (arrow) is evident in a longitudinally oriented vessel (periodic acid-Schiff, ×400). C. Vascular wall thickening (arrow) is demonstrated in a cross-section of a retinal vessel (periodic acid-Schiff, ×400).
characteristic thickening and reduplication of the capillary basement membranes in the brain has been reported in 3 studies to date (7–9). Jen et al (7) also described similar ultrastructural findings in reprocessed samples of kidney, stomach, appendix, omentum, and skin. Neuropathology observed in the present case, on both biopsy and autopsy samples, is concordant with published findings. Additionally, the scattered areas of white matter demyelination identified histologically correlate with neuroimaging findings.

Retinal capillary obliteration and telangiectasia have been demonstrated by fluorescein angiography; however, documentation of ophthalmic histopathology in RVCL is exceedingly rare (3,7,10). In 1988, Grand et al (3) reported that cornea, trabecular meshwork, ciliary body, ciliary process, anterior chamber, and iris were found to be normal. Microinfarctions and changes due to cytomegalovirus retinitis were identified. Although ultrastructural investigations revealed atrophy of ganglion cells and inner nuclear layer cells in areas of microinfarction, the vasculature was reportedly normal. The observation of significant vascular changes by light microscopy, including telangiectasias and fibrin thrombi, is unique to the present case. Furthermore, thickening and reduplication of the retinal capillary basal lamina was demonstrated on electron microscopy. Fluorescein angiography in our study, and in reported cases, demonstrates findings consistent with retinal vasculitis (9,11). Despite this, no histological evidence of retinal vasculitis has been described.

While patients with RVCL share a group of mutations resulting in carboxy-terminal truncations in TREX1, the pathogenesis of this disorder remains to be elucidated. Richards et al have shown that the mutations in TREX1 associated with RVCL do not alter the catalytic activity of the enzyme. Rather, the truncated protein loses its normal intracellular localization (2). This has led to the hypothesis that TREX1 in patients with RVCL does not participate in the repair of oxidative DNA damage because of its abnormal location within the cell. It has been proposed that the misplaced TREX1 may accumulate to cause a detrimental effect on endothelial cells (2). It remains to be determined how the manifestations of disease show a predilection for vessels of the brain and eye.

Further study of RVCL may allow for subclassification based on precise mutations in TREX1 producing specific histopathologic and clinical findings. This could partially account for the observed phenotypic variation. The severity of disease present at autopsy may simply reflect the extent of accumulated endothelial damage present in target organs.

The findings presented here provide further insight into a newly designated and rare neuro-ophthalmic syndrome. Additional studies of RVCL will provide a better understanding of the molecular basis of small vessel diseases

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**FIG. 5.** A. Electron micrograph reveals thickening and reduplication (white arrowheads) of the capillary basal lamina within the eye (×5000). B. Similar changes (white arrowheads) are noted in the vessels of the right temporal lobe (×3000).

**FIG. 6.** A. Electropherogram demonstrates the presence of a heterozygous GTCA duplication of base pairs 907–910 as indicated by the arrows in the coding region of the TREX1 gene. B. The amino acid sequence is shown with the frameshift mutation in bold letters eventually resulting in a carboxy-terminal truncation of the TREX1 protein.
affecting the brain and eye leading to improvements in
diagnostic studies and therapeutic options.

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Endoscopic Orbital Roof Fenestration as an Alternative Treatment Option for Idiopathic Intracranial Hypertension: A Cadaveric Anatomical Study

Asem Salma, MD, Martin Lubow, MD, Ashley Scheffer, BS, Mario Ammirati, MD, MBA

Background: We investigated a new minimally invasive surgical technique for the treatment of idiopathic intracranial hypertension in a cadaveric model. This technique aims at establishing a communication between the intraorbital and intracranial compartments by creating a bone, dural, and periorbital window in the anterior cranial fossa. This procedure is predicated on intraorbital absorptive capability that has been demonstrated in animals and discussed in humans.

Methods: Three fresh cadaver heads were fixed in a head holder so as to mimic the hyperextended supine position. The procedure was conducted bilaterally in each specimen. Our technique is as follows: 1) An incision is made in the eyebrow medial to the supraorbital notch; 2) using an endoscope and a periosteal elevator, the intraorbital surface of the orbital roof is separated from the periorbita in an anteroposterior direction for a length of 1.5–2.5 cm; 3) a 1 cm² of the exposed orbital roof is removed, and the dura and arachnoid are opened; and 4) slits are made in the exposed periorbita.

Results: We were able to create a communication between the intracranial and the intraorbital compartments in all specimens.

Conclusion: Our technique is new and does not require any foreign body implantation. Its applicability in humans needs to be evaluated in a clinical context.

and, in sequence, 2 rigid endoscopes 4 mm 0° angle and 4 mm 30° angle (Aesculap, Tuttlingen, Germany). This dissection was continued in an anteroposterior direction, just lateral to the medial wall of the orbital cavity, for a length of approximately 1.5–2.5 cm depending on the posterior extension of the frontal sinus.

Computer-aided surgery (Stryker Instruments, Kalamazoo, MI) was then used to make certain that the exposed orbital roof was beyond any ethmoidal air cells or frontal sinus extension (Fig. 1). The exposed bone was fenestrated using a curette and high-speed drill creating a 0.5 cm² opening (Fig. 2).

FIG. 1. Computer-aided surgery. The precise location of the surgical instruments (A), indicated by the blue line (arrow), is seen in the axial (B), coronal (C), and sagittal (D) projections.

FIG. 2. Stepwise endoscopic views showing the fenestration of the orbital roof (A, B) and the overlying dura (C, D).
The dura was then exposed with a dura hook and incised. Arachnoid was entered using a blunt micro hook, and multiple small 3–4 mm fenestrations were made in the adjacent periorbita with microscissors (Fig. 3). This procedure was performed in both orbits of each specimen.

RESULTS

We were able to successfully create a window in the roof of the orbit in all of our specimens (Fig. 4). We were able to create this window without using a high-speed drill in 4 of the 6 orbits.

DISCUSSION

IIH primarily affects obese women of 20–44 years with an estimated prevalence of 13 per 100,000 (1,15). It is much less common in the pediatric and male populations (1,16–19). Goals of therapy include relieving headache and preventing visual failure (1–3,6,20,21). The first line of treatment is medical, consisting of weight loss, carbonic anhydrase inhibitors and furosemide (1,20,22). It has been reported that 40% of patients fail medical therapy within a 10-year period (1). Patients who fail medical therapy are treated with CSF diversion procedures and/or ONSF (1,19,23,24).

CSF diversion procedures for IIH have failure rates from 48% to 55%, resulting in multiple operations in most cases (25,26). In one series, 56% of patients with IIH required shunt revision and over a 31-month period with the average number of revisions per patient being 2.4 (27).

With progressive visual loss, ONSF has become a popular surgical option. Using this technique, improvement of visual acuity and visual fields has been reported in 50% and 72% of patients, respectively (28). Yet, visual acuity and visual fields may worsen after the procedure in up to 11% of patients, and postprocedural blindness has been reported in 1.5%–2.6% of patients (22,28,29). Reoperation has been reported within 3–5 years in as many as 32% of patients who had an initial favorable response (30). More recently, the need for reoperation after ONSF has been estimated at 6% (28), with periopic nerve fibrosis being a likely cause for failure of the initial procedure. Clearly, there is a need for improved surgical alternatives for patients with IIH.

An increasing number of physiological and morphological studies indicate that CSF drains via nonarachnoidal pathways in several mammalian species (4,8,10–13). In animal models, the orbital route is one such nonarachnoidal pathway (4,8,10,11,13). A connection between the subarachnoid space of the orbital optic nerve and orbital contents through a putative lymphatic system has been proposed to explain the observation of the transitory intraorbital presence of radioactive material following injections into the ventricular system or cisterna magna (4,8,10,11,13). Additional evidence supporting the existence of an orbital lymphatic system in an animal model has recently emerged (31) including the report by Beden et al (32) demonstrating that the intraorbital space has the capability of quickly clearing large molecules into the systemic circulation that cannot pass through blood vessel walls.

Our proposed technique would rely on the CSF absorptive capacity of the orbit. Although not yet proven in

FIG. 3. Multiple fenestrations are created in the exposed periorbita using microscissors.

FIG. 4. Following removal of the orbital contents, the location of the bone window between the orbit and anterior cranial fossa is visible.
humans, this mechanism has been postulated to explain the relief of headache following ONSF (1,2,14,29). With our surgical procedure, CSF drainage should be facilitated by the pressure gradient between the elevated ICP (>20 cm of H$_2$O) in patients with IIH compared to lower intraorbital pressure (4.1–8.2 cm of H$_2$O) (33).

Our study has a number of limitations. First, it was performed in cadavers. Second, the rationale for this procedure in humans is currently speculative. Additional evaluation of our surgical technique in the animal model is essential to further test and validate this procedure.

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Pupil-Involving Third Nerve Palsy as a Manifestation of Anti-Myelin–Associated Glycoprotein Neuropathy

Madhura A. Tamhankar, MD, Steven L. Galetta, MD, Mina Massaro, MD, Laura J. Balcer, MD, MSCE, Edward A. Stadtmauer, MD, Mark J. Brown, MD

Abstract: A 56-year-old man developed a pupil-involving left third nerve palsy. Imaging studies of the brain and intracranial vessels were normal. Neurological examination demonstrated a sensory polyneuropathy and mild distal weakness. Nerve conduction studies showed prolonged distal motor latencies. An enzyme-linked immunosorbent assay test detected high titers of anti-myelin–associated glycoprotein (MAG) antibodies. The patient improved with prednisone and rituximab treatment. Anti-MAG neuropathy should be considered when evaluating a patient with an undiagnosed cranial neuropathy, especially in the setting of a sensory neuropathy.

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Paraproteinemic neuropathies are a heterogeneous group of peripheral nerve disorders characterized by the presence of a monoclonal M protein (1). Although all classes of immunoglobulins have been reported in this condition, IgM antibodies are found in 60% of patients (2). The prevalence of neuropathy in patients with IgM monoclonal gammopathy has been reported to be between 5% and 31% (3,4). The most common type is a demyelinating neuropathy with IgM antibodies directed against myelin-associated glycoprotein (MAG) and sulfoglucuronyl paragloboside (SGPG). Anti-MAG antibody neuropathy differs from the classic chronic inflammatory demyelinating polyneuropathy (CIDP) by the clinical, electrophysiological, and pathological features; response to treatment; and prognosis (5–11). Cranial nerve involvement is occasionally observed in patients with CIDP, but cranial nerve involvement with anti-MAG neuropathy is rare (3).

CASE REPORT

A 56-year-old man presented with sudden onset of diplopia and left ptosis. He also complained of a mild headache. He reported left facial weakness a month before onset and right facial weakness 6 months earlier that resolved after treatment with acyclovir and corticosteroids. He reported a self-limited episode of bilateral leg pain and numbness 4 years prior. He had type 2 diabetes, hyperlipidemia, and depression.

Physical examination revealed an alert, awake, and oriented man in no acute distress. Visual acuities were 20/20 in the right eye and 20/25 in the left eye with normal color vision. He had complete left upper lid ptosis. Pupils measured 2 mm on the right with a brisk reaction to direct light and 6 mm on the left with no reaction to light. Extraocular motility in the right eye was full. In the left eye, there was absence of up gaze, down gaze, and adduction. Left superior oblique and lateral rectus functions were intact. Ophthalmoscopic examination revealed healthy optic nerves and maculae. The patient was diagnosed with pupil-involving left third nerve palsy.

Neurological examination revealed mild left lower facial weakness. Arm and leg strength was normal aside from mild weakness of toe dorsiflexion bilaterally. Temperature and vibration sensation were decreased below the elbows and thighs. Reflexes were normal aside from depressed ankle jerks.

MRI and MRA of the brain and cerebral angiography were normal. Laboratory testing revealed a normal complete blood count, erythrocyte sedimentation rate, hemoglobin A1C, rapid plasma reagin, angiotensin-converting enzyme, antineutrophil cytoplasmic antibodies, anti-double–stranded DNA, and Sjogren syndrome A and Sjogren syndrome B.
antibodies. Tests for hepatitis B and C viruses, Lyme disease, and HIV were negative. Lumbar puncture revealed an elevated cerebrospinal protein (148 mg/dL, normal: 15–55 mg/dL), a slightly elevated glucose (77 mg/dL, normal: 40–70 mg/dL), zero white blood cells, and negative cytology. MRI of the spine showed enhancement of the nerve roots from L2 to L5 (Fig. 1). The radiologic differential diagnosis included infectious and inflammatory disorders including sarcoidosis, carcinomatous meningitis, and lympho-proliferative diseases. CT of the chest, abdomen, and pelvis and a whole body positron emission tomographic scan were normal. A repeat lumbar puncture revealed an elevated cerebrospinal protein of 128 mg/dL and normal cytology.

Nerve conduction studies demonstrated markedly decreased sensory amplitudes in the upper and lower extremities. Motor conduction velocities were slowed in the arms and legs and unobtainable from the feet. Distal motor latencies were markedly prolonged. The diagnosis was moderate, chronic, predominantly sensory, axonal polyneuropathy with multifocal demyelinating features, most likely an anti-MAG neuropathy.

Serum protein electrophoresis showed a monoclonal IgM spike at 470 mg/dL (normal: 40–270 mg/dL). An enzyme-linked immunosorbent assay test revealed a high-titer anti-MAG antibodies (16,525 units, normal <1000 titer units). Urine protein electrophoresis was negative for Bence Jones proteins. Serum cryoglobulins were undetectable. A bone scan was normal. The final diagnosis was pupil-involving left third nerve palsy in association with an anti-MAG antibody neuropathy.

The patient was initially treated with high-dose oral prednisone (60 mg/day and tapered over 8 weeks), and within 2 days, diplopia improved (Fig. 2). However, leg weakness, numbness, and imbalance progressed. Prednisone was tapered, and rituximab treatment was initiated (375 mg/m^2 given weekly for 4 weeks) and then given in 3 monthly cycles. There was complete resolution of the third nerve palsy after 4 months and anisocoria completely resolved at 1-year follow-up examination (Fig. 3). His strength, sensation, and gait improved. He has been followed for more than 2 years since his initial presentation. The neuropathy has continued to get better with decrease in anti-MAG antibody titers on serial examinations.

**DISCUSSION**

Anti-MAG antibody–associated neuropathy is a distinct subset of demyelinating polyneuropathy characterized by prominent sensory loss and ataxia (11–14). The typical clinical course of anti-MAG antibody neuropathy is that of slow progression without relapsing and remitting episodes, increasing numbness and paresthesias, and declining proprioception with legs being more involved than the arms (11,15,16). Distal lower extremity weakness is a common late finding (17). Monoclonal IgM antibodies directed against MAG and SGPG are believed to be pathogenic (18).

MAG is a cell adhesion molecule that is found in periaxonal myelin. Anti-MAG activity leads to alterations of myelin morphology and loss of peripheral and central axon–myelin stability causing segmental demyelination and axonal atrophy (19–25).

The pathogenesis of cranial nerve involvement in anti-MAG antibody neuropathy is unknown. It is not clear how the antibody crosses the blood-brain barrier. Anti-MAG antibodies can be detected in the cerebrospinal fluid, and therefore intrathecal production of anti-MAG antibody may be a factor in the occurrence of cranial polyneuropathy in this condition (26).

The diagnosis of anti-MAG antibody neuropathy is established by the presence of both IgM paraproteinemia and anti-MAG antibody titers in association with the specific neuropathy phenotype (27,28). It has been proposed that the occurrence of anti-MAG antibody titers greater than 1:12,800 in the presence of a demyelinating polyneuropathy provides conclusive evidence that the antibodies are pathogenic (27).

Electrophysiological studies of anti-MAG antibody neuropathy show demyelinating features with varying degrees of axonal loss. Disproportionately prolonged distal

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**FIG. 1.** Contrast-enhanced T1 sagittal MRI image of the lumbar spine reveals enhancement of L2–L5 nerve roots (arrows).
motor latencies are a characteristic nerve conduction finding in anti-MAG neuropathy that indicates distal demyelination. This feature is less commonly seen in CIDP (6,8,9,11,29). In contrast to CIDP, conduction block seldom occurs in neuropathy associated with anti-MAG antibody (7).

Cranial nerve involvement, especially facial neuropathies, is an occasional feature in CIDP (9,30–33). Oculomotor nerve involvement is rarely reported in CIDP, and in many of the reported cases, thickening and enhancement of multiple cranial nerves has been observed (34–38). Involvement of cranial nerves in anti-MAG neuropathy is

**FIG. 2.** One month after initial presentation, examination showed resolution of left ptosis, but with persistent adduction, elevation, and depression deficit of the left eye and anisocoria.

**FIG. 3.** Four months after initial visit, there was significant improvement in the motility of the left eye with minimal anisocoria.
even rarer. In a study of 14 patients with anti-MAG–
associated neuropathy, one had associated facial nerve
paralysis (9). Yoshida et al reported 1 patient with anti-MAG
antibody neuropathy, facial palsy, and bilateral sluggish pu-
illary light reflexes without external ophthalmoplegia (39).
Mailiot et al reported a 79-year-old patient with anti-MAG
antibody neuropathy and B-cell lymphoma who presented
with bilateral third nerve palsies (40). Aside from our case, we
are not aware of another patient without lymphoma who had
pupil-involving third nerve palsy as a manifestation of anti-
MAG–associated peripheral neuropathy.

The possibility of diabetic microvascular third nerve palsy
was also considered in our patient. Pupillary involvement in
diabetic microvascular third nerve palsy reportedly occurs in
14%–38% of patients (41–46). The degree of anisocoria when
present is almost always 1 mm or less and the pupil is reactive
(46). In our patient, the anisocoria was 4 mm and the pupil
was nonreactive to light. In addition, the presence of con-
current facial weakness and the immediate improvement of
the motility disturbance after initiation of corticosteroids made
a microvascular etiology for the oculomotor palsy less likely.

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Abducens Neuromyotonia as the Presenting Sign of an Intracranial Tumor

Daniel J. Salchow, MD, Thomas K. Wermund, MD

Abstract: In this case series and review of the literature, we describe 2 cases of abducens neuromyotonia (ANM) as the presenting sign of an intracranial tumor (meningioma). Review of the literature suggests that the pathophysiology of ocular neuromyotonia is incompletely understood. Most patients with ANM have a history of radiation therapy. The diagnosis of ANM is made on the basis of clinical findings and can be supported by electrophysiological studies. A complete neurologic examination is mandatory for patients with ANM. Treatment consists of eliminating the underlying cause; carbamazepine is effective in alleviating the symptoms of ANM. Neuroimaging should be performed if patients with ANM lack the typical history of radiation therapy, as ANM may be the presenting sign of an intracranial mass.

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Ocular neuromyotonia (ONM) is a rare eye movement disorder. It consists of paroxysmal contraction of 1 or more extraocular muscle(s) innervated by an affected oculomotor cranial nerve. The activated muscle does not relax until the paroxysm subsides, which may take seconds to several minutes. The third (oculomotor) nerve is most commonly affected in ONM, followed by fourth (abducens) and sixth (trochlear) nerves.

The vast majority of patients with ONM have a history of radiation therapy (1–13). The time from radiation therapy to clinical manifestation of ONM ranges from 2 months to 18 years (7). Some of the reported patients had intracranial or nasopharyngeal masses, but ONM usually did not present until after radiation therapy. In a few cases, nerve compression caused by intracranial aneurysms has been associated with ONM (5,12,14–16). Moreover, ONM has been described after myelography with thorium (13), after a stroke (17), in patients with thyroid-related orbitopathy (18) and with cavernous sinus thrombosis due to mucormycosis (19). In some, no cause for ONM can be found (20–25).

Neuromyotonia affecting the abducens nerve (ANM) leads to paroxysmal contraction of the ipsilateral lateral rectus muscle, causing abduction of the eye. To our knowledge, no case of ANM as the presenting sign of an intracranial tumor has been described. We present 2 cases where ANM was the first sign of an intracranial tumor. In both cases, consent to publish was granted.

CASE REPORTS

Case 1

A 48-year-old woman complained of episodic binocular horizontal diplopia, which she first noted approximately 1 year before presentation. The episodes lasted from a few seconds to 1 minute and occurred several times per day. During the episodes, the patient noted a “pulling sensation” around the left eye, she felt nauseated and had a mild left frontal headache, which was not present between episodes. Her medical history was significant for excision of a benign breast cyst at the age of 18 years; there was no history of an intracranial mass or radiation therapy. Social history was significant for smoking (half pack-year). She denied alcohol use and did not take any medications.
Best corrected visual acuity was 20/20 in each eye. External and anterior segment exams were unremarkable except for mild nuclear sclerotic cataracts. Stereopsis and color vision were normal, and visual fields were full to confrontation in both eyes. Pupils reacted equally to light, there was no afferent pupillary defect, and the fundi were normal. The patient was orthophoric in primary gaze at distance and near, and ocular versions were full. There was no strabismus in any gaze position except for esotropia of 14° on left gaze. After maintaining left gaze for 20–30 seconds, the left eye assumed a maximally abducted position and could not be adducted beyond midline. Attempted adduction during the attack resulted in retraction of the left globe (Fig. 1; see also Video, Supplemental Digital Content 1, http://links.lww.com/WNO/A13). On further questioning, the patient reported mild tingling over the left cheek, although sensation to touch in this area was intact and not different from the right cheek. All other cranial nerve functions were intact.

MRI of the brain showed a large homogenously enhancing mass originating from the preoptic cistern, compatible with a meningioma (Fig. 2). Neurosurgical removal of the tumor was undertaken, and pathological evaluation confirmed the diagnosis of meningioma. Post-operatively, the patient had paresis of the third through seventh cranial nerves. ANM did not recur, but the patient was left with a mild left sixth nerve palsy.

Case 2
A 49-year-old woman complained of transient diplopia associated with a sensation of pressure around the right eye lasting seconds to 1 minute and occurring 10–15 times per day. Visual acuity was 20/20 in each eye, and ocular exam was normal. Ocular motility testing revealed paroxysmal abduction of the right eye after right gaze, lasting approximately 30 seconds (Fig. 3). At other times, ocular alignment and motility were completely normal. Electromyography (EMG) of the right lateral rectus muscle during the
The patient was started on 600 mg/day carbamazepine, and the paroxysmal ocular deviation disappeared. Stereotactic conformal radiation therapy (total dose: 56 Gy) was given, and carbamazepine was tapered and discontinued. Brain MRI 2.5 years later showed considerable reduction in the size of the tumor, and the patient remained free of diplopia.

DISCUSSION

The term ONM was introduced by Ricker and Mertens (26) to describe a peculiar disturbance of ocular motility, consisting of paroxysmal contraction of an extraocular muscle, causing the eye to deviate with resultant diplopia. The muscle does not relax until the paroxysm subsides, which may take minutes. A pulling sensation around the involved eye and headaches may be reported. The majority of cases with ANM have a history of previous radiation therapy. Only 1 reported case had resection of an intracranial tumor (clivus chordoma) without radiation therapy before developing ANM (27).

We could not find any published cases of ANM as the presenting sign of an intracranial mass. Oculomotor neuromyotonia associated with compressive lesions without radiotherapy has been reported (5,12,14,16). One patient with oculomotor neuromyotonia secondary to a cavernous sinus meningioma also had “paroxysmal electrical discharges in the ophthalmic division of the left trigeminal nerve,” indicating involvement of the fifth cranial nerve (28). One of our patients (Case 1) complained of paresthesias in the distribution of the maxillary division of the left trigeminal nerve, emphasizing the importance of a complete cranial nerve exam in patients with ONM.

ONM has to be distinguished from oculomotor paresis with cyclic spasm, which is characterized by a cycle of paresis and spasm of muscle(s) innervated by the third nerve.

FIG. 3. Case 2. A. The eyes are aligned in primary position. B. Ocular versions are full. C. Occasionally, the right eye persists in abduction after right gaze or spontaneously deviates to the right for 30–60 seconds.

FIG. 4. Case 2. Contrast-enhanced T1 MRI of the brain. Axial (A) and coronal (B) scans show a mass (arrow) (1.9 × 1.3 × 1.6 cm) within the right cavernous sinus extending dorsally toward the tentorium and encircling the right internal carotid artery.
The spasms are neither induced nor altered by eccentric gaze (29). In ONM, the deviation can often be induced by looking in the direction of action of the involved extracocular muscle. Another differential diagnostic consideration is myokymia. Although rare, superior oblique myokymia is more common than trochlear neuromyotonia. Myokymia consists of an ocular microtremor that is not present in neuromyotonia. EMG shows phasic contractions in myokymia in contrast to tonic contractions in ONM (7).

The pathophysiology of ONM is not well understood. Potential mechanisms include 1) ephaptic transmission along the affected nerve, 2) disturbances of potassium channels in the neuronal cell membrane, and 3) central neural reorganization. In most published cases of ONM, an extra-axial lesion is present, but Banks et al (17) indicated that a brainstem lesion may lead to the eye movement disorder. A more detailed discussion on pathogenesis of ONM has been published elsewhere (30).

In summary, ANM should prompt a complete neurologic exam of the patient, with special attention to the cranial nerves. Most often, it is associated with previous radiation therapy. Neuroimaging should be performed in patients with ANM who lack such a history because it may be the presenting sign of an intracranial mass.

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Unusual Monocular Pendular Nystagmus in Multiple Sclerosis

Laurence Jasse, Alain Vighetto, MD, Sandra Vukusic, MD, PhD, Denis Pelisson, PhD, Caroline Tilikete, MD, PhD

Abstract: Two unusual cases of monocular pendular nystagmus in patients with multiple sclerosis are reported. One patient showed regular horizontal oscillations of the right eye in abduction, associated with right abduction paresis. The second patient had a similar abnormal eye movement of the left eye in adduction, with partial left internuclear ophthalmoplegia. Such eye position–dependent monocular pendular nystagmus provides new insights into pathogenic mechanism for acquired pendular nystagmus. Different mechanisms are discussed such as the combination of paresis and commonly accepted hypothesis of dysfunction of visual and/or motor feedback loops in the ocular motor neural network.

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The most frequently reported eye movement disorders in multiple sclerosis (MS) are internuclear ophthalmoplegia, isolated ocular motor palsy, gaze-evoked nystagmus, and pendular nystagmus (1). Pendular nystagmus is characterized by quasi-sinusoidal oscillations of the eyes along a horizontal, vertical, or torsional direction. Pendular nystagmus in MS may be asymmetrical and in this case, most frequently of greater amplitude in the eye with poorer vision (2). Strictly, monocular forms of pendular nystagmus in MS have been reported, either associated with chronic visual deficit following optic neuropathy (2,3) or observed during convergence (4). We report 2 patients with MS with monocular horizontal pendular nystagmus, which was specifically triggered in eccentric gaze.

CASE REPORTS

Case 1

A 40-year-old woman was evaluated with a 5-year history of relapsing-remitting MS. The first manifestation of the demyelinating disease was a right sixth nerve paresis, and since then, she complained of diplopia in right gaze. Due to recurrent episodes of left lower limb paresthesia, she was treated with azathioprine. She was referred to the neuro-ophthalmology unit for daily episodes of paroxysmal oscillopsia in her right eye.

Her expanded disability status scale (EDSS) score was 2 (minimal disability). Visual acuity was 20/20 in each eye, with no relative afferent pupillary defect and normal fundi. Automated perimetry, static contrast sensitivity values, and scores for the Farnsworth-Munsell D-15 Hue test and Ishihara color plates for each eye were normal. Visual evoked potentials were normal bilaterally. Ocular motor examination showed right esotropia with abduction paresis of the right eye. Horizontal pendular nystagmus of the right eye was observed during right gaze. The nystagmus persisted as long as the eccentric gaze was maintained and ceased when the patient directed her eyes to primary position or left gaze. Pendular nystagmus was dampened at near fixation, convergence, and with a 4-diopter base-out prism placed in front of the right eye. Gabapentin (up to 900 mg/d for 2 months), carbamazepine (up to 600 mg/d for 2 months), or clonazepam (up to 1 mg/d for 2 months) yielded no benefit.

Case 2

A 42-year-old woman with a 5-year history of relapsing-remitting MS was referred to the neuro-ophthalmology unit...
for monocular oscillopsia. This occurred due to the development of pendular nystagmus in the left eye during adduction of that eye. There was no improvement following a course of systemic steroids. Two months later, the patient complained of decreased vision. Visual acuity was found to be 20/50 in each eye, and visual field testing disclosed centrocecal scotoma in the right eye and central scotoma in her left eye. Felt to have bilateral optic neuritis, a course of steroids was prescribed and interferon therapy was started.

Her most recent EDSS score was 1 (no disability). Visual acuity was 20/25, right eye, and 20/32, left eye. Static central visual field (Metrovision®, Pérenchies, France) disclosed decreased macular threshold of the right eye and a mild global defect on the left. Static contrast sensitivity was subnormal for the left eye with 2 of the 6 tested spatial frequencies. Scores of Farnsworth-Munsell D-15 Hue test and Ishihara color plates test showed numerous errors for her left eye. Visual evoked potentials showed bilateral increase of latency with P100 value at 168 millisecond, right eye, and 176 millisecond, left eye. Ocular motor examination disclosed bilateral horizontal gaze-evoked nystagmus. In far right gaze, a monocular horizontal pendular nystagmus of her left adducting eye was observed, persisting as long as the adduction was maintained. Left adducting saccadic velocity was diminished, consistent with left internuclear ophthalmoplegia.

**DISCUSSION**

We describe 2 patients with MS complaining of chronic monocular oscillopsia brought about by an unusual form of monocular pendular nystagmus. Both patients presented some clinical features consistent with the common forms of pendular nystagmus observed in MS in terms of frequency (4–5 Hz), small amplitude (5), and for Case 2, in association with optic neuropathy (2–4,6). It may also be seen in the setting of normal optic nerve function (7,8) as in our Case 1. Our 2 cases are unusual in that their monocular pendular nystagmus was observed only in eccentric horizontal gaze. While monocular nystagmus of the abducting eye is observed with internuclear ophthalmoplegia in MS, it is of jerk and not pendular form. Monocular adduction pendular nystagmus can be observed in MS but has only been reported with convergence (4).

Explanations for pendular nystagmus in patients with MS involve abnormal delays in feedback loops that control eye stability. First, a role of a persistent delay of visual
FIG. 2. Case 2. Horizontal eye position recording in primary gaze, eccentric right gaze, and during convergence. A monocular pendular nystagmus of the adducting left eye occurs in right gaze, and a binocular pendular nystagmus is triggered with convergence. The nystagmus is of 3.5 Hz frequency and 2° mean amplitude. Binocular gaze-evoked nystagmus is also seen on right gaze. Positive values: gaze right; negative values: gaze left.
feedback secondary to demyelination of the optic nerve has been proposed (2). This hypothesis is supported by the previous reports of large oscillations occurring in an eye having a severe optic neuropathy (2,4). This could explain the monocular nystagmus in our Case 2 but does not account for the nystagmus being triggered by eccentric gaze. Moreover, this proposal has been challenged by experimental data in patients showing persistence of the nystagmus in darkness (9), and in patients with MS, there is no change in the nystagmus even with prolongation in latency of visually guided eye movements (10). A second hypothesis involves a role of abnormal delay in the ocular motor feedback loops secondary to demyelination of central neurons. Instability in motor feedback could involve the ocular motor neural integrator, as suggested by transient suppression of the nystagmus following saccades (8). Our data did not allow us to evaluate the effect of saccades on pendular nystagmus. However, the theory of an unstable neural integrator could lead to triggering of nystagmus with eccentric gaze. The onset of nystagmus during convergence, such as observed in our Case 2, also supports the concept of instability in motor feedback loops involving the vergence system (4).

Finally, there may be a role for ocular motor paresis in precipitating monocular pendular nystagmus. In Case 1, demyelination involved the sixth nerve fascicle and in Case 2, the left medial longitudinal fasciculus. It is well known that peripheral motor paresis can trigger central adaptive changes (9). This consists of detecting visual errors due to ocular motor paresis and increasing the innervation to the paretic eye through central feedback loops (11). In our 2 patients, these adaptive changes took place in a neural network affected by demyelination, and instability in these feedback loops might have triggered monocular eye position–dependent pendular nystagmus.

REFERENCES

Congenital Myasthenic Syndrome Due to Homozygous CHRNE Mutations: Report of Patients in Arabia

Mustafa A. Salih, MD, Darren T. Oystreck, MMedSci, OC(C), Yasser H. Al-Faky, MD, FRCS, Mohammed Kabiraj, MD, Mohamed I. A. Omer, FRCP, Elamin M. Subahi, FRCP, David Beeson, PhD, Khaled K. Abu-Amero, PhD, Thomas M. Bosley, MD

Abstract: We describe the clinical characteristics of 3 siblings from 1 family with congenital myasthenic syndrome due to homozygous mutations of the gene coding for the epsilon subunit of the acetylcholine receptor (CHRNE). Onset of symptoms occurred in the first few months of life with ptosis, restricted ocular motility, mild proximal weakness, and difficulty swallowing. Multiple hospital admissions were required due to recurrent pulmonary infections. There was no decremental conduction on repetitive nerve stimulation, but jitter was increased on single fiber electromyographic. Since early childhood, our patients have done well without pulmonary or bulbar symptoms and with partial improvement on pyridostigmine therapy. Response of ptosis to diagnostic ice pack test was striking. Although these siblings have a clinical history and examination findings typical of homozygous CHRNE mutations, the clinical presentation of congenital myasthenia subtypes is variable, and accurate genotyping is essential in choosing the appropriate treatment.

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CASE REPORT

Three siblings from a consanguineous family with 5 children were the product of normal pregnancies (with normal in utero movement) and were asymptomatic in the immediate postpartum period. However, by the age of 2–3 months, the oldest boy (Patient 1) developed bilateral ptosis, decreased feeding, choking, and failure to thrive. He had several hospital admissions and on 4 occasions was admitted to the neonatal intensive care unit because of respiratory failure. The middle brother (Patient 2) and the younger brother (Patient 3) had less severe symptoms beginning at approximately 4 months of age, although they
also had hospital admissions for respiratory problems during the first year of life. Pulmonary function testing showed modest reductions of peak flow in all 3 (Patient 1, 497 L/min with predicted value 600 ± 50 L/min; Patient 2, 427 L/min, predicted 570 ± 50 L/min; and Patient 3, 317 L/min, predicted 475 ± 50 L/min).

All subjects had complete neurologic, neuro-ophthalmologic, oculoplastic, and ear, nose, and throat examinations. Orthoptic evaluation included near and distance visual acuity, accommodation, ocular alignment, eye movements, and fusional status. All patients had pulmonary function tests using the Wright peak flow meter, EMG with repetitive stimulation, and single fiber EMG (SFEMG). All 3 had the ice pack test to see if ptosis responded to a transient cold environment (7,8). Direct sequencing of CHRNE was performed by bidirectional sequencing of polymerase chain reaction–amplified products containing the 12 exons and the promoter region of CHRNE (9).

All 3 siblings had normal developmental milestones. Each began taking pyridostigmine at approximately 5 months of age. Respiratory function and extremity weakness improved, but ptosis improved only minimally. Substantial restriction of ocular motility persisted in all fields of gaze with occasional complaints of diplopia. At times, this occurred with near vision as convergence was slow and markedly reduced. An exotropia developed at near fixation distances of 30 cm (Patient 1), 20 cm (Patient 2), and 15 cm (Patient 3).

At the last examination, they were aged 21 years (Patient 1), 17 years (Patient 2), and 13 years (Patient 3) each taking 30–60 mg of pyridostigmine 3 times per day. They were all of normal height and weight with intact cognitive function. Mild, diffuse, proximal muscle weakness was present with mild facial involvement but no apparent bulbar weakness. Gait was normal, and Gower sign was absent.

Ophthalmologic testing revealed normal visual acuity in each patient with intact pupillary responses and accommodative range. All 3 had reduced eye movements in all directions of gaze (Fig. 1). Smooth pursuit was deficient in all directions, and saccades were extremely slow and hypometric. No patient had a manifest strabismus in the primary position, and all had normal stereopsis (40 seconds of arc).

The orbicularis ocular muscle was weak in all 3 patients. Ptosis was present bilaterally and occluded the visual axis in all 3 when the frontalis was at rest. Each had Cogan lid twitch sign. Ice pack test markedly improved ptosis in all 3 individuals (Fig. 2).

In all 3 patients, EMG revealed a normal action potential and no significant decrement in amplitude or area (<10%) after repetitive stimulation of the ulnar nerve. SFEMG of the extensor digitorum communis had increased jitter (range: Patient 1, 56–96 μs; Patient 2, 66–95 μs; and Patient 3, 36–52 μs). All 3 patients had homozygous duplication mutations 123_127dupCTCAC in exon 2 of the CHRNE gene, while their parents were heterozygous for this mutation (Fig. 3).

**DISCUSSION**

These siblings have CMS with moderate to severe ptosis and restriction of ocular motility, mild facial and proximal muscle weakness, and partial improvement with
pyridostigmine. Symptoms were static since childhood with manifestations slightly more severe in Patient 1 compared to Patients 2 and 3 despite genetic uniformity.

Currently, mutations in at least 12 genes are known to cause CMS (Table 1) (4). There are 91 CHRNE mutation entries reported in the human gene mutation database (http://www.hgmd.cf.ac.uk), including 35 missense/ nonsense mutations, 14 splicing mutations, 17 small deletions, 18 small insertions, 3 regulatory mutations, 3 large deletions, and 1 large insertion. CHRNE mutations have been identified in people from North Africa (10) but to our knowledge, not previously in the Arabian Peninsula.

This genetic mutation in our patient has been previously described in heterozygous status (in a compound heterozygous patient) (11) and homozygous status (10) and is felt to lead to a frameshift, resulting in the conversion of Leu–Asn–Glu codons to Pro–His–Stop at positions 43–45 followed by a truncation of the epsilon subunit in its extracellular domain with resulting severe AChR deficiency for the adult form of the receptor (9,11). The mutation was not detected in 50 individuals (100 chromosomes) from similar ethnicity.

Our patients’ clinical course is similar to other patients with mutations of the CHRNE gene (1,5,12–14), including a family history of consanguinity, a brief asymptomatic interval between birth and onset of ptosis, pulmonary symptoms early in life with gradual improvement, prominent early bulbar involvement, and profound ophthalmoplegia (12). They differ from previous published cases that reported nonconsanguinity (14), decreased movements in utero (11), and worsening during adult life (14).

Our patients’ clinical history is not diagnostic of CHRNE mutations because similar clinical findings may be due to other genetic defects (Table 2). Patients with symptoms and signs similar to our patients could be mistaken for chronic progressive external ophthalmoplegia or autoimmune myasthenia gravis if evaluated later in life without careful attention to the clinical history. Diagnostic tools beyond clinical examination are only partially helpful. While repetitive stimulation was normal, SFEMG revealed increased jitter. The ice pack test, which is commonly used in the diagnosis of autoimmune myasthenia gravis, led to dramatic improvement in ptosis of our patients and may prove to be a valuable diagnostic test in patients with CHRNE mutations.

Given the limitations of clinical tools and the variable phenotypic characteristics of CMS, a genetic diagnosis is the most accurate method to confirm the CMS subtype and select the most appropriate treatment (3). For example, pyridostigmine is effective in CHRNE mutations and certain other CMS variants. Pyridostigmine is contraindicated in patients with CMS with COLQ or DOK7 mutations or with slow channel defects (3,4), while ephedrine has good long-term effectiveness in patients with COLQ or DOK7 mutations (4,15,16). A molecular approach to diagnosis will likely become more frequent as more genes responsible for CMS are identified and as the ease and availability of genetic testing improves (12).

CMS due to mutations in CHRND have been reported in patients from Arabia (17), and this report of an Arabian family with CHRNE mutations confirms another CMS genetic variant within this population. In world regions with limited scientific resources, determining the ethnic frequency for CMS genetic variants ensures that the most appropriate candidate genes can be screened first. CHRNE mutations are the most common form of CMS, and a common mutation c.1293insG has been identified in North African populations (10), but further studies will be required to determine if similar founder effects occur in Arabia.
## TABLE 1. Genetically defined CMS variants

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Gene Location</th>
<th>Protein Name</th>
<th>Function</th>
<th>Defect Site</th>
<th>Neuromuscular Transmission Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAT</td>
<td>10q11.2</td>
<td>Choline-O-acetyltransferase</td>
<td>Catalyzes reversible synthesis of ACh from acetyl CoA and choline</td>
<td>Presyn</td>
<td>Choline acetyltransferase deficiency/reduced catalytic activity</td>
</tr>
<tr>
<td>COLQ</td>
<td>3p25</td>
<td>AChE collagentic tail peptide</td>
<td>Anchors catalytic subunits of asymmetric AChE to synaptic basal lamina</td>
<td>Synaptic</td>
<td>Synaptic AChE deficiency</td>
</tr>
<tr>
<td>CHRNA1</td>
<td>2q24-q32</td>
<td>AChR receptor subunit alpha</td>
<td>Opening of ion-conducting channel</td>
<td>Postsyn</td>
<td>AChR deficiency, FCS and SCS:kinetic abnormalities of AChR</td>
</tr>
<tr>
<td>CHRN1</td>
<td>17p13.1</td>
<td>AChR receptor subunit beta</td>
<td>Opening of ion-conducting channel</td>
<td>Postsyn</td>
<td>AChR deficiency, FCS and SCS:kinetic abnormalities of AChR</td>
</tr>
<tr>
<td>CHRND</td>
<td>2q33-q34</td>
<td>AChR receptor subunit delta</td>
<td>Opening of ion-conducting channel</td>
<td>Postsyn</td>
<td>AChR deficiency, FCS and SCS:kinetic abnormalities of AChR</td>
</tr>
<tr>
<td>CHRNE</td>
<td>17p13-p12</td>
<td>AChR receptor subunit epsilon</td>
<td>Opening of ion-conducting channel</td>
<td>Postsyn</td>
<td>AChR deficiency, FCS and SCS:kinetic abnormalities of AChR</td>
</tr>
<tr>
<td>CHRNG</td>
<td>2q33-q34</td>
<td>AChR receptor subunit (fetal form)</td>
<td>Opening of ion-conducting channel</td>
<td>Postsyn</td>
<td>AChR deficiency</td>
</tr>
<tr>
<td>RAPSN</td>
<td>11p11.2-p11.1</td>
<td>43 kDa receptor-associated protein of the synapse</td>
<td>Anchors AChR to postsynaptic cytoskeleton</td>
<td>Postsyn</td>
<td>Affects clustering of AChR at the end plate</td>
</tr>
<tr>
<td>MUSK</td>
<td>9q31.3-q32</td>
<td>Muscle, skeletal receptor tyrosine protein kinase</td>
<td>NMJ organization</td>
<td>Postsyn</td>
<td>Decreased agrin-dependent AChR aggregation leading to defect of NMJ formation</td>
</tr>
<tr>
<td>AGRN</td>
<td>1p36.33</td>
<td>Proteoglycan agrin</td>
<td>NMJ development and AChR clustering</td>
<td>Presynaptic/postsynaptic</td>
<td>Unstable and constant reforming of NMJ</td>
</tr>
<tr>
<td>DOK7</td>
<td>4p16.2</td>
<td>Protein Dok-7</td>
<td>Encodes MuSK-interacting cytoplasmic protein Dok-7</td>
<td>Postsyn</td>
<td>Small, simplified NMJ; normal AChR and AChE function</td>
</tr>
<tr>
<td>SCN4A</td>
<td>17p13-p12</td>
<td>Sodium channel protein type 4 subunit alpha</td>
<td>Mediates voltage-dependent sodium ion permeability</td>
<td>Postsyn</td>
<td>Decreased safety margin of NMT by increasing the size of the endplate potential to reach threshold for MAP generation</td>
</tr>
</tbody>
</table>

ACh, acetylcholine; AChE, acetylcholinesterase; FCS, fast channel syndrome, resulting in fewer and/or shorter AChR channel opening episodes; MAP, muscle action potential; NMJ, neuromuscular junction; NMT, neuromuscular transmission; postsyn, postsynaptic defect; presyn, presynaptic defect; SCS, slow channel syndrome, resulting in prolonged opening of AChR channels; synaptic, synaptic defect (basal lamina).

Adapted from the Protein Knowledgebase (UniProtKB; http://www.uniprot.org) and Ohno et al (11) and Harper (17).
<table>
<thead>
<tr>
<th>Syndrome/ Gene</th>
<th>Symptom Onset</th>
<th>Respiratory Problems</th>
<th>Neuro-ophthalmological Features</th>
<th>Other Salient Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChAT deficiency/CHAT</td>
<td>First year of life</td>
<td>Respiratory crisis common</td>
<td>Generally full eye movements</td>
<td>Severe respiratory crises in early life tend to resolve with age</td>
</tr>
<tr>
<td>EAD/COLQ</td>
<td>Birth; first year; occasionally childhood</td>
<td>—</td>
<td>Common: ophthalmoparesis, ptosis; rare: slow pupil response to light; full eye movements</td>
<td>Muscle weakness, poor head control, ptosis, poor cry and suck, respiratory insufficiency</td>
</tr>
<tr>
<td>FCS/CHRNA, CHRND, CHRNE</td>
<td>Birth</td>
<td>Respiratory crises common</td>
<td>Common: ophthalmoparesis, ptosis</td>
<td>Homozygous nonsense mutations cause stillbirth and fetal akinesia sequence</td>
</tr>
<tr>
<td>SCS/CHRNA, CHRNA, CHRNB, CHRND, CHRN</td>
<td>Variable: birth to adulthood</td>
<td>—</td>
<td>Variable</td>
<td>Only CMS that shows dominant inheritance</td>
</tr>
<tr>
<td>AChR deficiency/CHRNE</td>
<td>Birth; occasionally in childhood</td>
<td>—</td>
<td>Common: ophthalmoparesis and ptosis</td>
<td>CHRNE mutations common (compensation by expression for fetal AChR γ subunit); CHRNA, CHRNA, CHRND: rare and tend to be more severe</td>
</tr>
<tr>
<td>FADS/CHRNG</td>
<td>Fetus</td>
<td>N/A</td>
<td>N/A</td>
<td>Reduced fetal movement, arthrogryposis, multiple pterygium</td>
</tr>
<tr>
<td>AChR deficiency/RAPSN</td>
<td>Birth: first year of life; rare late onset reported</td>
<td>Respiratory crisis common</td>
<td>Usually normal eye movements; strabismus common</td>
<td>Muscle weakness, contractures, and arthrogryposis common; weakness and respiratory crises tends to improve with age</td>
</tr>
<tr>
<td>DOK7</td>
<td>Variable from birth to adulthood but usually second year of life</td>
<td>—</td>
<td>Usually normal eye movements</td>
<td>Proximal muscle weakness predominates; stridor</td>
</tr>
</tbody>
</table>

ChAT, choline acetyl transferase; EAD, endplate acetylcholinesterase deficiency; FADS, fetal akinesia deformation sequence; FCS, fast channel syndrome; NA, not applicable; SCS, slow channel syndrome.

Adapted from Mihaylova et al (4), Beeson et al (12), and Harper (17), Mihaylova et al (18), Michalk et al (19), Palace et al (20), and Engel et al (21).
REFERENCES


Magnetic Resonance Findings in the Pregeniculate Visual Pathways in Leber Hereditary Optic Neuropathy

Danielle van Westen, MD, PhD, Björn Hammar, MD, PhD, Gunnel Bynke, MD, PhD

FIG. 1. Case 1. T2 axial (A, D) and coronal (B, E, C, F) MRI of the optic tracts (arrows). On the initial study, an increased signal is seen (B, C) and the tracts are mildly swollen. The signal abnormality remains in the follow-up study (E, F), and the tracts are now atrophic.
Abstract: Two relatives, a 61-year-old man and the 21-year-old grandson of his sister, suffered from bilateral visual loss and were diagnosed with Leber hereditary optic neuropathy. In both cases, the diagnosis was molecularly confirmed with the 11778 mitochondrial mutation. MRI showed increased T2 signal not only in the optic nerves and chiasm but also in the optic tracts, extending to the lateral geniculate bodies. To our knowledge, the latter finding has not been described previously.

Case 1: A 61-year-old man, complained of painless decline in vision in both eyes. Three months later, visual acuity was counting fingers (CF) at 1 m bilaterally, kinetic perimetry revealed large central scotomas, and funduscopy was normal. Genetic analysis revealed the mitochondrial DNA 11778 mutation consistent with the diagnosis of Leber hereditary optic neuropathy (LHON). MRI of the brain and orbits performed 1 month later demonstrated increased T2 signal centrally in moderately enlarged prechiasmal optic nerves, optic chiasm, and optic tracts (Figs. 1, 2). Similar signal increase was found on the short time inversion recovery sequence (STIR). No contrast enhancement was present. Repeat MRI examination 9 months later revealed persistent high T2 signal in atrophic retrobulbar optic nerves, chiasm, and optic tracts (Figs. 1, 2). His final visual acuity remained at CF in both eyes.

Case 2: A 21-year-old man is the maternal grandson of the sister of Case 1. He experienced decreased vision in his right eye with visual acuity of CF at 1.5 m, loss of color vision, and a central scotoma on visual field testing. Three months later, the visual acuity in his left eye decreased to CF. Six months after the initial visual loss, MRI of the brain and orbits demonstrated increased T2 signal centrally in the prechiasmal optic nerves, optic chiasm, and optic tracts.

FIG. 2. Case 1. Coronal T2 MRI of retrobulbar (A, D) and prechiasmal (B, E) optic nerves and optic chiasm (C, F). The retrobulbar optic nerves are normal. Arrows indicate increased signal in prechiasmal nerves (B) and chiasm (C), which are slightly swollen. The signal abnormality is present (E, F) in the follow-up examination, although the structures are shrunken.
There was no contrast enhancement. Repeat MRI 6 months later revealed that the signal abnormality was still present (Figs. 3, 4). His final visual acuity was CF 1 m in both eyes.

To the best of our knowledge, this is the first report of signal changes detected on MRI in the optic tracts of patients with LHON. Anatomic changes in LHON include reduction of the optic nerve diameter, central axonal loss, and sometimes minimal inflammatory changes (1–3). In a whole brain specimen from a patient with the classical clinical profile of LHON, severe loss of retinal ganglion cells and axons was present as well as central demyelination in the optic nerves chiasm and optic tracts (4). Thus, LHON seems to affect the retinal ganglion cells along the whole length of the axon. In our patients, signal changes in the optic tracts (arrows) (Figs. 3, 4). Initial study (A, B, C) reveals increased signal within slightly swollen optic tracts. Follow-up images (D, E, F) show that the signal abnormality persists, and the tracts are now smaller in size.

FIG. 3. Case 2. T2 sagittal (A, D) and coronal (B, E, C, F) MRI of the optic tracts (arrows). Initial study (A, B, C) reveals increased signal within slightly swollen optic tracts. Follow-up images (D, E, F) show that the signal abnormality persists, and the tracts are now smaller in size.

Considering that histopathologic studies have shown involvement of the retinal ganglion cell axon along its entire length, it is remarkable that MRI demonstration of the optic tract involvement in LHON has not been reported previously. Generally, no abnormalities are seen on MRI of the brain and orbits in patients with LHON (5–7). A few reports document T2 and STIR signal abnormalities several months to years after the onset of visual loss (6–10). Signal changes in the optic chiasm have been reported twice (11,12). We reviewed the findings in these reports, but adequate imaging of the optic tracts was not performed.

Failure to detect optic tract involvement in LHON may be due to lack of awareness and failure to use an examination designed to image the optic tracts. In case 1, such images were accidentally obtained because the patient was evaluated with a combined orbit and pituitary protocol. Case 2 was subsequently examined with the same protocol. The frequency of our finding can be established only when dedicated imaging of the optic tracts is performed routinely in patients with LHON.
REFERENCES


FIG. 4. Case 2. T2 sagittal MRI of the prechiasmal optic nerves (A, D) and optic chiasm (B, E) and coronal view of the optic chiasm (C, F). Arrows indicate increased signal in mildly swollen optic nerves (A) and chiasm (B, C) in the initial study, which persists (D, E, F) 6 months later.
Dorsolateral Midbrain MRI Abnormalities and Ocular Motor Deficits Following Cytarabine-Based Chemotherapy for Acute Myelogenous Leukemia

Thuy Doan, MD, PhD, Norman Lacayo, MD, Paul G. Fisher, MD, Yaping Joyce Liao, MD, PhD

Cytarabine-based chemotherapy is a mainstay in the treatment of hematologic malignancies despite its known neurologic toxicities, including cerebellar ataxia, diplopia, locked-in syndrome, myelopathy, cognitive decline, encephalitis, headache, and papilledema (1–8). We report a case of ocular motor deficits with striking midbrain MRI abnormalities.

A 12-year-old boy with acute myelogenous leukemia (AML) was treated with induction chemotherapy, which included intrathecal (IT) cytarabine (60 mg) and intravenous (IV) cytarabine (3,000 mg/m², 6 times), daunomycin (50 mg/m², 3 times), and etoposide (100 mg/m², 5 times). Induction continued with 36 mg IT cytarabine, 12 mg methotrexate, and 24 mg hydrocortisone (triple therapy) in addition to IV cytarabine, daunomycin, and etoposide.

Following the first round of consolidation therapy, which consisted of IT triple therapy and IV cytarabine and etoposide, the patient developed right-sided appendicular ataxia, instability of gait, and nystagmus. Brain CT was negative, and the ataxia gradually improved.

For the second consolidation round, the IT cytarabine was withheld, and the IV cytarabine dose was reduced by 66%. Even so, ataxia, diplopia, and slurred speech occurred. For the third consolidation round, IT and IV cytarabine were withheld, and no further clinical deficits developed.

Neuro-ophthalmologic examination 2 months following the third consolidation round revealed prominent hyperintensities on FLAIR sequences in the dorsal midbrain, including the periaqueductal gray, superior colliculi, and superficial lateral tegmentum (Fig. 1). There were 2 punctate T2 hyperintensities in the right cerebrum. There was no pathologic contrast enhancement. Brain MRI performed 7 months later showed that all MRI abnormalities had largely disappeared (Fig. 1). The patient’s ocular motor deficits, hearing loss, and subtle ataxia never improved.

This is the first case to document ocular motor deficits in conjunction with midbrain MRI signal abnormalities as a result of chemotherapy in the treatment of AML. The clinical findings and MRI abnormalities appeared following multiple exposures to cytarabine, consistent with a cumulative effect (1). Acute infusion-induced neurotoxicity was preventable by withholding cytarabine.

Cytarabine therapy has been associated with cerebellar atrophy and, rarely, signal abnormalities in the spinal cord (5–8) and cerebellum (9–12). Midbrain signal abnormalities have not previously been reported. Close surveillance of neuro-ophthalmologic findings, prompt readjustment of medications and treatment routes, and timely serial MRI
studies are essential in reducing central nervous system toxicity while still allowing for lifesaving treatment of hematologic cancers.

REFERENCES


FIG. 1. Axial FLAIR MRI performed 2 months after the third consolidation round of cytarabine-based chemotherapy for acute myelogenous leukemia (A, B) discloses focal high-signal areas in the midbrain (arrows). Axial FLAIR MRI performed 7 months later (C, D) shows that these signal abnormalities have largely disappeared, although clinical abnormalities persisted.
Horner Syndrome Following a Selective Cervical Nerve Root Block

Kevin Kaplowitz, MD, Andrew G. Lee, MD

Abstract: A 31-year-old man with cervical degenerative disc disease was seen at an outside institution for a right selective cervical nerve root block at C7. Following the procedure, he had right ptosis and miosis. Pharmacologic testing confirmed a right Horner syndrome. MRI and MRA showed no arterial dissection. This report documents the unusual occurrence of permanent Horner syndrome following a selective cervical nerve root block.

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A 31-year-old man with a history of pain from cervical degenerative disc disease was seen at an outside institution for a right selective cervical nerve root block at C7. He reported intermittent stabbing pain in the back and right side of his neck, and 4 years earlier he had undergone the same procedure without complication. During the current cervical procedure, he received a 6-mL injection consisting of 40 mg Kenalog in 0.25% Marcaine. On awakening from anesthesia his radicular pain had resolved, but he noted a droopy right upper eyelid. Two months later, he was seen in The Methodist Hospital neuro-ophthalmology clinic. Vision was 20/20 in each eye, and the remainder of the examination was normal except for pupil size and eyelid position. In darkness, pupils measured 3 mm on the right eye and 4 mm on the left eye (Fig. 1), and the right pupil showed dilation lag. There was 1 mm of right ptosis. Topical apraclonidine drops confirmed the diagnosis of a right Horner syndrome (Fig. 2). Contrast-enhanced MRI of the head and neck was normal, and MRA of the neck showed no evidence of carotid or vertebral dissection.

Selective nerve root block (SNRB) is an increasingly utilized procedure for both confirmation of diagnosis and treatment of radicular pain (1). It is being used to empirically help define the etiology of pain in patients and to deliver local therapeutics. The procedure typically involves injecting 1–2 mL of a combination of a local anesthetic and steroid. Fluoroscopic guidance is used first to achieve appropriate positioning, and then contrast is injected to anticipate where the medication will be delivered.

In a review of 4,612 patients undergoing a cervical SNRB, the only neurological complication involved one patient who had a seizure (2). In a prospective review of 799 SNRBs, 5 patients had transient sympathetic blockade leading to ptosis and miosis, but these all resolved (3). There are 3 reported cases of vertebral artery dissection following fluoroscopically guided cervical SNRB, but Horner syndrome was not noted in any of these cases (4,5).

Other reported complications of SNRB include direct damage to the nerve or the nearby radicular artery; transient extremity paresis; cerebral, cerebellar, or spinal cord infarction; cardiac arrhythmia; meningitis; syncope; dural puncture; and death (4). Some may be due to the physical trauma of the injection, others from particulate emboli of the injected steroid preparation, and yet others from the inadvertent injection of the anesthetic agent into the radicular artery, which usually results in motor weakness (6).

In our patient, the cause of Horner syndrome was most likely damage to the second-order neuron of the oculosympathetic pathway. The operative record noted that a 22-gauge needle was inserted near the right seventh cervical nerve root under fluoroscopic guidance. While transient sympathetic blockade is possible from local absorption of

FIG. 1. Patient examination reveals right ptosis and miosis, 2 months after a selective cervical nerve root block.
the injected anesthetic, our patient’s symptoms were present 2 months following SNRB, arguing against a medication-related neuropathy. The needle could have perforated the vertebral artery. The MRI and MRA revealed no such pathology; however, a dissection could potentially have already healed. The most likely possibility is direct damage from the needle to the second-order sympathetic neurons as they ascend to the superior cervical ganglion.

Although Horner syndrome is well recognized following stellate ganglion block, we found no other reports of a permanent Horner syndrome following a selective cervical nerve root block. Physicians involved with selective nerve blocks should be aware of this potential complication and consider including this during discussion of informed consent with the patient.

REFERENCES

Monocular Elevation Deficiency (“Double Elevator” Palsy): A Cautionary Note

Michael C. Brodsky, MD, Virginia Karlsson, CO

Abstract: Monocular elevation deficiency (or “double elevator” palsy) is a descriptive term denoting a congenital deficiency of monocular elevation that is equal in abduction and adduction. We describe a child with monocular elevation deficiency who displayed tethering and buckling of the central lower eyelid in downgaze. We caution that this manifestation of inferior rectus contracture can simulate impaired infraduction in the involved eye.

CASE REPORT

A 4-year-old boy was referred to us for evaluation of an inability to elevate the right eye since birth. He was born prematurely at 28.5 weeks gestation, weighing 2 lb 13 oz, and required hospitalization for 3 months. He was currently meeting his developmental milestones.

On examination, visual acuity was 20/25, right eye, and 20/20, left eye, using Allen cards. He maintained fixation with the left eye but did not do so with the right eye. Extraocular movements showed absent elevation of the right eye in primary position and right and left gaze. Mild right upper eyelid pseudoptosis was noted, which resolved with fixation of the right eye. An enhanced right lower eyelid fold was present. Titmus stereoacuity was 60 seconds of arc. Fixing at near, he had 5 prism diopter right hypotropia, which was horizontally comitant but increased to 25 prism diopter in upgaze and resolved in downgaze. Upward saccades from infraduction to primary position were brisk in the right eye. Bielschowsky head tilt testing produced no detectable change, and Bell phenomenon was diminished in the right eye. The patient maintained a slight chin-up head position when viewing objects of interest. There was no associated jaw winking, and retinal examination showed mild extorsion in both eyes. Cycloplegic refraction was +1.75 +2.00 × 15° in the right eye, and +1.25 +0.50 × 175° in the left eye. He was prescribed glasses and treated with part-time occlusion therapy of the left eye.

On his follow-up visit, his findings were unchanged except that version testing showed what appeared to be deficient downward rotation of the right eye compared to the left eye (Fig. 1). However, prism and alternate cover testing showed no hyperdeviation in downgaze. On closer examination, it became apparent that the mid portion of the right lower eyelid had tethered and buckled in downgaze, producing retraction of the right lower eyelid. The greater visibility of the right lower iris created the appearance of an infraduction deficit of the right eye (Fig. 1). This focal...
eyelid retraction was attributed to contracture of the right inferior rectus muscle.

**DISCUSSION**

In 1977, Scott and Jackson (4) described an accentuated lower eyelid fold that became more prominent in attempted upgaze as a sign of inferior rectus contracture in children with monocular elevation deficiency or “double elevator palsy.” In our patient, an accentuated lower eyelid fold in upgaze was accompanied by focal tethering and buckling of the lower eyelid in downgaze, creating the appearance of an infraduction deficit in the involved eye. If not recognized as a correlative sign of inferior rectus contracture, this unusual clinical manifestation could lead to unnecessary neurodiagnostic evaluation.

**REFERENCES**


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**FIG. 1.** Vertical gaze positions showing absent supraduction with enhanced right lower eyelid fold in the right eye (A), vertical alignment near primary position (B), and focal tethering and retraction of the midportion of the right lower eyelid in downgaze (C). Note the greater visibility of the lower right iris, which creates the appearance of an infraduction deficit in the right eye (C).
Neuroretinitis: Review of the Literature and New Observations

Valerie Purvin, MD, Seema Sundaram, MD, Aki Kawasaki, MD

Abstract: Neuroretinitis (NR) is an inflammatory disorder characterized by optic disc edema and subsequent formation of a macular star figure. The underlying pathophysiology involves increased permeability of disc vasculature, but the etiology is not fully defined. In some cases, NR is probably due to an infectious process involving the disc; in others, a postviral or autoimmune mechanism is more likely. Cases can be divided into those in which a specific infectious agent has been identified, those considered idiopathic, and those with recurrent attacks. Some reports have not distinguished among these subgroups, and it is unclear if their clinical features vary. We reviewed the literature and our own patients looking particularly at features that might better distinguish these subtypes. Features common to all 3 groups included age, absence of pain, and fundus appearance. Preceding systemic symptoms were more common in patients with cat scratch disease (CSD) and uncommon in those with recurrence. The pattern and magnitude of visual field loss differed, more commonly confined to the central field in CSD cases and more severe in recurrent cases. Recovery of visual acuity and field was less substantial in recurrent cases even after the initial episode. MRI was usually normal in all 3 groups. Enhancement confined to the optic disc was found in all 3 groups, but enhancement of the retrobulbar optic nerve was seen only in recurrent cases. Findings that are strongly suggestive of CSD include very young age, preceding systemic symptoms, and poor visual acuity but with a small or absent relative afferent pupil defect (RAPD). In contrast, the following are suggestive of idiopathic NR with a high risk of recurrence: absence of systemic symptoms, visual field defect outside the central field, preserved visual acuity with a large RAPD, and poor recovery of vision. Decisions regarding evaluation and treatment should be made with these features in mind.

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OVERVIEW

Our understanding of neuroretinitis (NR) has continued to evolve since its first description by Theodor Leber in 1916 (1). Leber reported a patient with acute unilateral visual loss with disc edema and macular exudates arranged in a star pattern and used the term "stellate maculopathy." This localization was challenged by Gass in 1977 (2), who noted that disc edema precedes the formation of exudates in this condition. Using fluorescein angiography (FA), he demonstrated that the site of the leakage is, in fact, not the macula but the optic disc and suggested the term "neuroretinitis." In recent years, the concept that NR is caused by an increased permeability of optic disc vasculature with secondary leakage into the surrounding retina has been confirmed and further delineated using retinal and optic nerve imaging (3–5).

The series by Dreyer et al (6) and by Maitland and Miller (7) furnished a description of the typical clinical features of this disorder. Since that time, a number of articles have reported additional cases of NR due to a wide range of infections (see below). Nomenclature has varied including stellate retinopathy (1), NR (2), Leber idiopathic stellate NR (8), and optic disc edema with a macular star (ODEMS) (9). Brazis and Lee have suggested using the term ODEMS for idiopathic cases and the term "neuroretinitis." In recent years, the concept that NR is caused by an increased permeability of optic disc vasculature with secondary leakage into the surrounding retina has been confirmed and further delineated using retinal and optic nerve imaging (3–5).

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Pathophysiology

The primary process in NR involves inflammation of optic disc vasculature causing exudation of fluid into the peripapillary retina. An elegant study by Kitamei et al (5) using FA and indocyanine green angiography coupled with optical coherence tomography (OCT) in a patient with idiopathic NR demonstrated massive leakage of dye from a single arteriole on the disc surface, rather than widespread leakage from optic disc capillaries. Lipid-rich fluid flowed directly into the outer nuclear-plexiform space but only the aqueous phase then passed through the external limiting membrane to accumulate beneath the neurosensory retina. Due to the loose, radial configuration of the outer plexiform layer, the lipid-rich exudates form a star pattern (10).

The mechanism of disc vasculitis in NR is unclear. The presence of a flu-like prodrome in many cases has been taken as evidence of a viral etiology, either due to direct invasion of the nerve or a virally induced autoimmune response (7). The former mechanism was supported by the autopsy findings in 1 case of NR associated with herpes simplex encephalitis in which intranuclear viral inclusion particles were identified in the optic nerve and retina (11). Alternatively, NR may be due to an actual focal infectious process induced by an agent with a predilection for vasculature, notably cat scratch disease (CSD). A variety of posterior segment manifestations of CSD have been described and a common feature in these cases is vascular leakage due to retinal vasculitis (12). Evidence for a blood-borne agent as the cause of NR includes the presence of chorioretinal white spots, occasional bilateral involvement, and the segmental nature of the disc staining in symptomatic and asymptomatic eyes consistent with access to the optic nerve via the ciliary or central arterial system (6). In cases of NR with recurrent attacks, local invasion via hematogenous spread is highly unlikely, and in these cases, an autoimmune vasculitis seems more likely, although reactivation of a localized infectious organism, as seen in toxoplasmosis, remains a possibility.

Differential Diagnosis

Not all cases of ODEMS are due to NR, and it is important for the clinician to be alert to these other disorders that might be mistaken for NR (Table 1). In cases of hypertensive retinopathy and in most cases of papilledema (increased intracranial pressure [ICP]), fundus abnormalities are bilateral, whereas most cases of NR are unilateral. Another helpful feature is the presence of cotton wool spots scattered throughout the posterior pole in hypertensive retinopathy. These should be distinguished from the deep chorioretinal white spots that are sometimes seen in NR (17). Macular exudates are occasionally seen with papilledema and the presence of symptoms and other signs of increased ICP should lead to the correct diagnosis. Brain neuroimaging and lumbar puncture may be needed for confirmation. Rarely, a macular star is observed in nonarteritic anterior ischemic optic neuropathy (NAION), causing potential confusion with NR. The exudation in such cases is typically less robust, and the star often incomplete. The presence of vitreous cells would be consistent with NR rather than with NAION. In such cases, distinction between NAION and NR is made on the basis of other clinical findings, such as age and vascular risk factors. Patients with diabetic papillopathy may also exhibit a macular star, and some of these cases are bilateral.

Etiology

Cases of NR have been reported in association with a wide variety of infectious agents (Table 2). The single most common of these is CSD, which accounted for two thirds of cases in one series (33). Because the prevalence of CSD varies widely with climate and geography (84), this percentage may vary in different locations. The introduction of an indirect fluorescent antibody test for Bartonella henselae, the causative organism of CSD, has facilitated the accurate diagnosis of this disease (85). In retrospect, some cases previously designated as idiopathic NR may in fact have been due to CSD. For idiopathic cases, a viral etiology has been assumed, but this has never been proven.

NR has also been described as a part of other retinal inflammatory disorders, including idiopathic retinal vasculitis, aneurysms and NR (IRVAN) syndrome (82,83) and diffuse unilateral subacute neuroretinitis (DUSN), the latter caused by a nematode (75). Occasional cases of NR are due to noninfectious forms of uveitis, such as sarcoidosis (78) and periarteritis nodosa (81). In addition, there have been 3 reported cases of NR associated with inflammatory bowel disease (33,79,80). One of our patients with recurrent NR was diagnosed with ulcerative colitis 9 years after the second attack of NR (86). Because of the long interval between the 2 conditions, it is difficult to be certain of a causal relationship.

Relationship to Multiple Sclerosis

Individuals with demyelinating optic neuritis (retrobulbar or papillitis) are at an increased risk for the future development of multiple sclerosis (MS). Since NR is a form of papillitis, one might assume that patients with this condition would be
NR can be classified on the basis of etiology (idiopathic vs specific infectious agent), although this classification is not always clear-cut. The large series reported by Dreyer et al (6) was designated as idiopathic. However, the authors acknowledged that 3 of their cases were strongly suspected to have CSD. In the series of Maitland and Miller (7), one patient had a preceding varicella infection. With further advances in serologic testing, more cases may be moved out of the idiopathic category and into that of a specific cause.

Idiopathic cases can be further subdivided into those with a single episode of NR and those with recurrent attacks. Some case reports, case series, and reviews have not clearly distinguished among these different forms of NR, and it is unclear if the clinical features vary among these subsets. This distinction is of interest for several reasons. First, since the basis for idiopathic NR is unknown, it would be helpful to know if the clinical features more closely resemble CSD-NR due to an infectious agent, or if the disorder is more similar to recurrent idiopathic NR, which is thought to be due to an autoimmune process. Second, it would be helpful to know how aggressively to pursue a workup for a specific etiologic agent in an individual patient. Finally, management decisions may differ in these subgroups.

To better characterize these features, we reviewed the literature and our own experience with the 3 most common forms of NR: idiopathic NR, cat scratch NR, and recurrent idiopathic NR. We identified publications using the Ovid search engine from 1950 to June 2010 using the subject heading neuroretinitis and limiting the search to articles in English and involving humans. Additional cases were collected from articles on CSD.

Idiopathic Neuroretinitis

The clinical features of idiopathic NR have been described in several case series and single case reports (6,7,9,17,21,33,89,90) and summarized in a number of reviews (8,9,91). NR usually affects young adults (average age, 28 years), but the age range is broad (8–55 years). In published cases, more than half experienced a preceding flu-like illness, usually affecting the upper respiratory tract. Visual loss is usually painless, although occasional patients experience a mild retrobulbar discomfort.

Most cases are unilateral, but bilateral cases have been described. Some of these are characterized by bilateral visual loss, whereas in others, asymptomatic disc edema is observed in the fellow eye. Visual acuity is usually between 20/50 and 20/200 but can range from 20/20 to light perception. The most common pattern of visual field loss, found in 24 of 29 eyes in the series of Dreyer et al (6), is a cecocentral or central scotoma, consistent with the presence of edema in the papillomacular bundle. A relative afferent pupil defect (RAPD) is often present, although not with the same frequency or magnitude as in demyelinating optic neuritis. This difference reflects the different mechanism of visual loss in these 2 conditions: visual loss is due largely to maculopathy in NR and entirely to optic nerve dysfunction in optic neuritis.

PROPOSED CLASSIFICATION OF NEURORETINITIS

NR can be classified on the basis of etiology (idiopathic vs specific infectious agent), although this classification is not always clear-cut. The large series reported by Dreyer et al (6)
Posterior vitreous cells are usually present; anterior chamber cell and flare are occasionally seen as well. The funduscopic appearance depends in large part on the timing of the examination (Fig. 1). The earliest finding is an isolated optic disc edema, which may be diffuse or segmental. Peripapillary nerve fiber layer hemorrhages are sometimes present. In most cases, optic disc edema is associated with an exudative peripapillary serous retinal detachment. It typically takes 9 to 12 days for the characteristic macular exudates to appear, and at this stage, disc edema is usually diminishing. The star figure is initially sharply defined and spoke-like; over time, the exudates become less well defined and eventually, after a number of months, disappear completely, often leaving residual subfoveal retinal pigment epithelial defects (Fig. 2). In most cases, optic disc edema resolves over 8 to 12 weeks. The disc may eventually regain a normal appearance or demonstrate pallor and/or gliotic changes.

Many patients with idiopathic NR have been managed conservatively, others treated with steroids. Most experience excellent recovery of vision with or without intervention, with a final acuity of 20/40 or better in 90% of reported cases. There appears to be a subset of patients, however, with a somewhat different clinical picture, in whom the visual prognosis is more guarded. Of the 12 patients with NR described by Maitland and Miller (7), 3 failed to experience excellent recovery. Two of the patients in the series of Dreyer et al (6) had disc-related field defects and a large RAPD, and in both of these cases, the visual outcome was poor. The authors suggested that these patients had a virus-induced occlusive vasculitis involving prelaminar arterioles, which led to disc infarction.

One recent report documented the results of treatment with intravitreal steroids plus bevacizumab in a patient with idiopathic NR (92). In this single case report, the diagnosis was made 10 days after onset of visual loss, treatment was given 3 days later, and at 1-week follow-up, visual acuity had returned to normal and macular edema resolved. One month later, optic disc edema had resolved as well. The significance of this report is difficult to evaluate, in part because the natural history of NR is usually favorable and also because 2 different forms of treatment were given. Furthermore, in cases of NR with poor visual outcome, the limiting factor for visual recovery appears to be residual optic nerve damage rather than maculopathy. Since the intravitreal treatment in this report did not hasten resolution of disc edema, it is not clear that it would improve the outcome in such cases.

**Cat Scratch Neuroretinitis**

The most common form of infectious NR is due to CSD. A number of single case reports and small case series have described the clinical features of NR secondary to CSD. We reviewed a total of 65 reported cases, 4 of which were

**FIG. 1.** Evolution of fundus findings in a patient with recurrent idiopathic NR. **A.** At presentation, the right disc is swollen and the macula has an opaque appearance. **B.** Three weeks later, there is a well-formed macular star. **C.** The left disc is pale due to a previous attack. **D.** Two months later, there is a well-formed macular star. **E.** The left disc is pale due to a previous attack. **F.** One year later, after a repeat episode of NR in the right eye, there is resolving disc edema, but now the exudates have a peripapillary distribution rather than forming a macular star.
bilateral (69 eyes) (see Table, Supplemental Digital Content 1, http://links.lww.com/WNO/A14). From the data available, the average age at onset was 24.5 years (median: 21 years) with a range of 4 to 64 years. There was a female to male predominance of 1.8:1, and both eyes were affected equally. Systemic symptoms were reported in 47 (73%) of 64 cases and eye pain in 4 (7.7%) of 52 cases. Initial Snellen acuity was 20/40 or better in 14.5% of eyes, between 20/50 and 20/200 in 33.3%, and worse than 20/200 in 52.2%. Final acuity was available for 58 eyes and was much improved in almost all cases: 93% had vision of 20/40 or better and none was worse than 20/200. The average number of lines gained was 7.7. The pattern of visual field loss was available for 27 eyes and usually consisted of a central defect (88%). A RAPD was present in 25 eyes (67.5%) and was variable in magnitude. There were 7 eyes with count fingers vision in which a RAPD was absent. This would suggest that much or all of the visual loss in these cases of NR secondary to CSD was due to serous detachment of the macula rather than optic nerve dysfunction. In these 7 eyes, visual acuity returned to 20/40 or better. In addition to optic disc edema and macular star formation, focal areas of chorioretinitis may be seen with CSD-NR (Fig. 3). In rare cases, visual recovery has been limited by macular hole formation (93,94).

Recurrent Idiopathic Neuroretinitis

The majority of reported cases of recurrent NR are idiopathic. With the exception of toxoplasmosis, most infectious agents do not cause recurrent attacks. Two of the patients in the series of idiopathic cases reported by Maitland and Miller (7) had evidence of a previous attack in the fellow eye, and an additional case was reported by Vaphiades et al (46). A patient with recurrent NR and inflammatory bowel disease has been described (80). The designation of recurrent idiopathic NR as an identifiable syndrome was based on a case series of 7 patients (96). An additional 6 cases were subsequently added in an article (97) focusing on the results of immunosuppressive therapy for this syndrome.

We further expanded this series in a recent review of 41 patients including clinical features and results of treatment (86). Median age at onset was 28 years with a range of 10 to 54 years. Average follow-up was 67 months. Overall, 147 episodes were documented in 75 eyes with an average of 3.6 attacks per patient and an average interval between attacks of 3 years (range, 1 month to 16 years). Most were not preceded by systemic symptoms, and eye pain was uncommon. Patterns of visual field loss consisted primarily of a central scotoma plus nerve fiber bundle defects, and loss was cumulative with repeated episodes. Some eyes sustained extensive field loss, despite preservation of visual acuity. In this series, only 36% of eyes were left with 20/40 or better acuity and retained more than two thirds of their visual field. The fundus features in recurrent NR were similar to other cases of NR but with repeated episodes, exudates may not form a macular star (Fig. 4).

We performed an additional analysis of a subgroup of these patients, looking only at features of the acute event in a previously unaffected eye. We analyzed data from 23 eyes of 21 patients and found several differences when compared to
our CSD and idiopathic cases. Visual acuity was similar at onset in all 3 groups, but the pattern and magnitude of visual field loss were different in recurrent cases. Whereas visual field loss was confined to the central field in the majority of CSD and idiopathic cases, this pattern was uncommon in recurrent NR. Rather, one half of the recurrent cases demonstrated a combination of central and nerve fiber bundle defects. This difference in visual field involvement may be due to the fact that in idiopathic and CSD cases, visual loss in large part reflects macular dysfunction, whereas in recurrent idiopathic cases, visual loss is due to optic disc vasculitis leading to optic neuropathy. In addition, the severity of field loss was significantly greater in recurrent cases, and recovery of both acuity and field was less substantial. This lesser degree of recovery also manifest as a smaller percentage of patients who showed improvement in the magnitude of the RAPD at follow-up (11% vs 59% and 50% of CSD and idiopathic cases, respectively). The fundus features at onset were similar in all 3 groups, except for the presence of chorioretinal white spots (Fig. 3), which were more common in CSD patients and rare in idiopathic NR. The presence of such white spots has been taken as evidence of a hematogenously spread organism in cases of CSD-NR, and likewise their absence in idiopathic cases favors a different mechanism. In cases of recurrent NR, hard exudates often become less prominent and more localized during subsequent attacks (Fig. 4).

Of 147 episodes of recurrent NR (86), most patients were treated acutely with corticosteroids, given orally or intravenously, but without significant improvement. In addition, 21 patients received long-term immunosuppressive treatment, and in 13 of these cases, adequate long-term information was available to judge efficacy. There were 40 episodes of NR during 67.4 patient-years prior to initiation of immunosuppression vs 11 episodes in 67.1 patient-years after starting treatment. This represents a reduction in the attack rate of 0.43 per year, amounting to a 72% decrease in the attack frequency. Treatment in our cases of recurrent idiopathic NR consisted of low-dose alternate day prednisone and/or azathioprine.

**ANCILLARY TESTING**

**Retinal Imaging Techniques**

OCT is a sensitive method for detecting serous retinal detachment, particularly in the early stages of NR before the appearance of a macular star. In occasional cases of optic disc edema secondary to CSD, peripapillary serous detachment occurs but a macular star never develops (98,99). In such cases, OCT may help establish the diagnosis. FA is not usually necessary for diagnosis but may furnish additional information. FA typically demonstrates diffuse disc edema and peripapillary dye staining during the midvenous and late phases of the angiogram. This staining may be segmental and is occasionally present in the fellow eye even when visual loss is unilateral. Fundus autofluorescence may also be helpful for demonstrating macular exudates (100).
Magnetic Resonance Imaging

Initial interest in the MRI findings in NR focused on the detection of periventricular white matter changes as seen in MS. The consistent absence of these changes and the failure to develop clinical MS on long-term follow-up (87) have put this issue to rest. Dedicated MRI of the orbit with fat suppression and intravenous contrast has emerged as the more sensitive sequence for the evaluation of optic neuropathies, but there are relatively few reports using this technique in patients with NR. Schmalfuss et al (101) evaluated the MRI findings in 82 patients with various optic neuropathies, including 9 with CSD. Of these 9 cases, 5 had macular exudates, and in 4 of these, MRI showed enhancement of the optic disc extending up to 4 mm posteriorly along the optic nerve. The authors suggested that this “short segment enhancement” is highly specific for CSD-NR. Two additional cases with similar findings have been reported (46,102). However, other authors have found other neuroimaging results in patients with NR. Wals et al (103) reported a patient with idiopathic NR in whom MRI showed enhancement confined to the optic nerve sheath. A combination of optic nerve and sheath enhancement was seen on CT in 1 case of idiopathic NR (104) and on MRI in 1 patient with recurrent idiopathic NR (46).

We reviewed the orbital MRI scans in 36 of our cases, looking particularly for features that might differentiate subtypes of NR. In the CSD-NR group, 2 of 4 scans were abnormal, both showing enhancement confined to the optic disc. In patients with idiopathic NR, 2 of 6 scans were abnormal, one showing disc enhancement and the other enhancement of the disc with slight posterior extension, similar to what has been described in CSD-NR (101). In patients with recurrent NR, 3 showed enhancement confined to the disc (Fig. 5) and 1 showed retrobulbar optic nerve enhancement; scans in the remaining 22 were normal. Based on these findings, it seems likely that the MRI findings described by Schmalfuss et al (101) are indeed characteristic of NR but not specific for NR due to CSD. Additional MRI studies in NR are needed to clarify this issue.

EMERGING CONCEPTS

Incidence of Recurrent Neuroretinitis

It is possible that recurrent NR is more common than would appear from the literature. Because the characteristic macular star is not present at the time of visual loss, the diagnosis may be missed if a careful repeat fundus examination is not performed at least 2 weeks after onset. In the absence of a macular star, such cases might be termed “recurrent optic neuritis” or “papillitis” rather than NR. Increased recognition of the syndrome of recurrent NR may lead to the diagnosis of more cases and greater accuracy of its frequency.

Geographic Distribution

From informal communication with colleagues, we have the impression that recurrent NR is more common in the Midwestern United States and rare in other parts of the country. One way to examine this issue would be a survey of the membership of the North American Neuro-Ophthalmology Society (NANOS). Collection of this information could be helpful in determining incidence as well as possible geographic clustering of cases. Another approach to the question of geographic distribution would be the examination of the database from a large tertiary referral base, such as Mayo Clinic, which draws from a large geographic area and tends to see a large number of such complex and rare disorders.

Advances in Serologic Testing

If recurrent NR cases have a particular geographic distribution, this might be a clue as to etiology. For example, the Midwest has a higher incidence of presumed ocular histoplasmosis syndrome (POHS), and we have considered this as a potential cause of recurrent NR. Our patients do not have a high frequency of fundus changes typical of POHS, but since serologic testing for this condition is not available, it remains a possibility. If recurrent NR is in fact an autoimmune disorder, progress in testing for other autoantibodies may reveal a marker for the disease, as we have seen for neuromyelitis optica.

Retinal Imaging

Continued technical advances in retinal imaging, particularly the ability to correlate different imaging modalities, should further our understanding of these disorders. The work of Kitamei et al (5) is an example of the value of such correlation. These authors documented an isolated leakage from a single vessel in a case of idiopathic NR, in contrast to previous reports, which have described a more diffuse...
leakiness of disc capillaries. This focal leakage was more easily appreciated with indocyanine green than with FA, and it is not clear whether these findings are typical of NR or represent an unusual occurrence. Perhaps, the pathophysiology is different in the various subgroups of NR. Further application of these techniques should further our understanding of the pathophysiology in NR.

**Atypical Features**

As the typical clinical findings in NR are better characterized, atypical “outlier” cases will be easier to identify. For example, pain is an uncommon feature in all 3 forms, described by about one fourth of all our patients with a similar frequency in all 3 groups (unpublished data). When present, pain is mild. The presence of severe pain, especially with eye movement, should suggest an alternative diagnosis. In our series of patients initially diagnosed as NR, 3 cases were subsequently reclassified as having idiopathic posterior scleritis based on characteristic findings on ultrasonography. Each of these patients had recurrent attacks with severe pain that was steroid responsive. Extensive enhancement of the retrobulbar optic nerve (beyond 4 mm behind the globe) is suggestive of idiopathic NR, particularly the recurrent variety and, to our knowledge, has not been described in CSD-NR.

The optic disc edema in NR is self-limited. In cases with protracted disc edema, alternative diagnoses should be considered, such as disc tumor or chronic inflammatory disorders including sarcoidosis, diffuse subacute nematode syndrome (DUSN), or IRVAN.

Bilateral simultaneous NR is uncommon and should suggest the more likely possibility of malignant hypertension or increased ICP. When NR does present with bilateral involvement, it may also be due to a specific infectious etiology. For example, bilaterality occurred in only 2 of 27 patients in series of Dreyer et al (6) and in 2 of 12 in that of Maitland and Miller (7). In contrast, bilateral NR has been reported in patients with Bartonella infection (31,45), Lyme disease (63), mumps (65), secondary syphilis (59), toxoplasmosis (57), rabies vaccine (77), chikungunya fever (72,73), and dengue (74).

Management guidelines are given in Table 3. In obtaining a history in patients with NR, the clinician should focus on possible risk factors for specific infectious agents, such as animal exposure (especially cats), travel to endemic areas (Lyme disease or tuberculosis), exposure to waste material (leptospirosis), and sexual contact (syphilis). Patients should be questioned about systemic symptoms, such as fever, headache, lymphadenopathy, and skin rash. Laboratory testing should be tailored to the individual, based on information from the history and examination. In most cases, serologic testing should include cat scratch titers (Bartonella species), fluorescent treponemal antibody absorption test (FTA-ABS), and a tuberculosis skin test (PPD). In endemic areas and in patients with a history of tick exposure and/or characteristic symptoms, hematologic studies for Lyme disease should be obtained. Additional testing may include angiotensin-converting enzyme measurements and chest radiograph.

Cases that are strongly suspicious for CSD but with negative serologies should be retested 6 weeks later to look for rising IgG titers. A rise in convalescent IgG titers may be diagnostic, even in the absence of elevated IgM antibodies. In addition to a history of cat exposure, features that would be considered “suspicious” for CSD include young age (younger than 16 years), preceding systemic symptoms, and poor visual acuity but with small or no RAPD. In contrast, features that suggest a low likelihood of CSD and a high risk of recurrence are no systemic symptoms, visual field defect outside the central field, preserved acuity with a large RAPD, poor recovery, and evidence of a previous episode in either eye. In cases with the latter features, steroid treatment should be considered. Simultaneous bilateral involvement is suggestive of an underlying infectious etiology, although not specifically CSD. In most cases seen acutely, treatment with a broad-spectrum antibiotic is reasonable while serologic tests are pending, especially in cases with findings suggestive of an infectious cause. In patients with recurrence, long-term immunosuppressive treatment should be considered.

### REFERENCES


State-of-the-Art Review


Recent Progress in Understanding Congenital Cranial Dysinnervation Disorders

Darren T. Oystreck, OC(C) MMedSci, Elizabeth C. Engle, MD, Thomas M. Bosley, MD

Background: In 2002, the new term congenital cranial dysinnervation disorder (CCDD) was proposed as a substitute for the traditional concept of congenital fibrosis of the extraocular muscles (CFEOM) based on mounting genetic, neuropathologic, and imaging evidence, suggesting that many, if not all, of these disorders result from a primary neurologic maldevelopment rather than from a muscle abnormality. This report provides an update 8 years after that original report.

Evidence Acquisition: Review of pertinent articles published from January 2003 until June 2010 describing CCDD variants identified under PubMed MeSH terms congenital fibrosis of the extraocular muscles, congenital cranial dysinnervation disorders, individual phenotypes included under the term CCDD, and congenital ocular motility disorders.

Results: At present, a total of 7 disease genes and 10 phenotypes fall under the CCDD umbrella. A number of additional loci and phenotypes still await gene elucidation, with the anticipation that more syndromes and genes will be identified in the future. Identification of genes and their function, along with advances in neuroimaging, have expanded our understanding of the mechanisms underlying several anomalous eye movement patterns.

Conclusions: Current evidence still supports the concept that the CCDDs are primarily due to neurogenic disturbances of brainstem or cranial nerve development. Several CCDDs are now known to have nonophthalmologic associations involving neurologic, neuroanatomic, cerebrovascular, cardiovascular, and skeletal abnormalities.

CONGENITAL FIBROSIS OF THE EXTRAOCULAR MUSCLES TO CONGENITAL CRANIAL DYSINNERVATION DISORDERS

During the last half of the 20th century, pediatric ophthalmologists recognized that certain children were born with congenital ocular motility abnormalities associated with fibrotic extraocular muscles. This observation led to the concept of “congenital fibrosis of the extraocular muscles” (CFEOM) because of the assumption that the primary problem was a congenital abnormality of muscle development (1,2). The most common of these disorders is Duane retraction syndrome (DRS), although a number of other sporadic and familial congenital ocular motility syndromes were also recognized.

As time passed, evidence accumulated that a number of these syndromes had a neurogenic etiology. Therefore, in 2002, an alternative concept of “congenital cranial dysinnervation disorders” (CCDDs) was proposed (3), shifting the focus away from muscle development and toward a likely neurogenic etiology of congenital abnormalities of ocular muscle and facial innervation. Developments in the past 8 years have supported this concept, since all identified genes responsible for CCDDs affect brainstem and/or cranial nerve development. The purpose of this review is to update the original report proposing the CCDD concept (3) because much has happened over the past 8 years. Many of the syndromes described here are uncommon, and a number have autosomal recessive etiologies that make their occurrence more frequent in specific areas of the world. Yet with increased international travel, a patient with any one of these disorders might walk into the office of an ophthalmologist or neurologist anywhere in the world. Therefore, clinicians should be familiar with this heterogeneous group of syndromes. Not included here (or within

State-of-the-Art Review

Section Editors: Grant T. Liu, MD
Randy H. Kardon, MD, PhD

Recent Progress in Understanding Congenital Cranial Dysinnervation Disorders

Darren T. Oystreck, OC(C) MMedSci, Elizabeth C. Engle, MD, Thomas M. Bosley, MD

Background: In 2002, the new term congenital cranial dysinnervation disorder (CCDD) was proposed as a substitute for the traditional concept of congenital fibrosis of the extraocular muscles (CFEOM) based on mounting genetic, neuropathologic, and imaging evidence, suggesting that many, if not all, of these disorders result from a primary neurologic maldevelopment rather than from a muscle abnormality. This report provides an update 8 years after that original report.

Evidence Acquisition: Review of pertinent articles published from January 2003 until June 2010 describing CCDD variants identified under PubMed MeSH terms congenital fibrosis of the extraocular muscles, congenital cranial dysinnervation disorders, individual phenotypes included under the term CCDD, and congenital ocular motility disorders.

Results: At present, a total of 7 disease genes and 10 phenotypes fall under the CCDD umbrella. A number of additional loci and phenotypes still await gene elucidation, with the anticipation that more syndromes and genes will be identified in the future. Identification of genes and their function, along with advances in neuroimaging, have expanded our understanding of the mechanisms underlying several anomalous eye movement patterns.

Conclusions: Current evidence still supports the concept that the CCDDs are primarily due to neurogenic disturbances of brainstem or cranial nerve development. Several CCDDs are now known to have nonophthalmologic associations involving neurologic, neuroanatomic, cerebrovascular, cardiovascular, and skeletal abnormalities.

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During the last half of the 20th century, pediatric ophthalmologists recognized that certain children were born with congenital ocular motility abnormalities associated with fibrotic extraocular muscles. This observation led to the concept of “congenital fibrosis of the extraocular muscles” (CFEOM) because of the assumption that the primary problem was a congenital abnormality of muscle development (1,2). The most common of these disorders is Duane retraction syndrome (DRS), although a number of other sporadic and familial congenital ocular motility syndromes were also recognized.

As time passed, evidence accumulated that a number of these syndromes had a neurogenic etiology. Therefore, in 2002, an alternative concept of “congenital cranial dysinnervation disorders” (CCDDs) was proposed (3), shifting the focus away from muscle development and toward a likely neurogenic etiology of congenital abnormalities of ocular muscle and facial innervation. Developments in the past 8 years have supported this concept, since all identified genes responsible for CCDDs affect brainstem and/or cranial nerve development. The purpose of this review is to update the original report proposing the CCDD concept (3) because much has happened over the past 8 years. Many of the syndromes described here are uncommon, and a number have autosomal recessive etiologies that make their occurrence more frequent in specific areas of the world. Yet with increased international travel, a patient with any one of these disorders might walk into the office of an ophthalmologist or neurologist anywhere in the world. Therefore, clinicians should be familiar with this heterogeneous group of syndromes. Not included here (or within
the CCDD concept) are myopathies, genetic disorders involving the neuromuscular junction, or progressive and/or degenerative ocular motility, and neurologic problems such as chronic progressive external ophthalmoplegia or spino-cerebellar atrophy, even if recognized to have a genetic etiology.

**DISORDERS AFFECTING PREDOMINANTLY OCULAR MOTILITY**

**Duane Retraction Syndrome**

DRS is the most common CCDD ocular motility disorder and is characterized most commonly by limited abduction (DRS type 1) with variable limitation of adduction together with retraction of the globe and narrowing of the palpebral fissure on attempted abduction. DRS is generally sporadic, typically unilateral, and more common in females. The underlying mechanism is primary absence or hypoplasia of the sixth nerve with dysinnervation of the ipsilateral lateral rectus by a branch of the third nerve (4–6).

Up to 10% of DRS cases may be familial, including autosomal dominant inheritance in several distinct syndromes. The DURS1 locus (MIM %126800; Mendelian Inheritance in Man; http://www.ncbi.nlm.nih.gov/omim) was defined after finding overlapping cytogenetic abnormalities on chromosome 8q13 in multiple patients with syndromic DRS and may reflect a complexity of cytogenetic causes, including disruption of CPAH (7,8). The DURS2 locus was defined by linkage analysis of families segregating dominant DRS (MIM #604356), and affected individuals commonly have bilateral involvement and associated vertical movement anomalies. The responsible gene, CHN1, is involved in ocular motor axon path finding in the development of the sixth nerve and, to a lesser extent, the third nerve (9,10). CHN1 mutations were not found in a cohort of individuals with sporadic DRS (11).

Duane radial ray syndrome (Okihiro syndrome; MIM #607323) is characterized by DRS with hand and, in some cases, upper extremity anomalies and variable expression of cardiac, renal, hearing, and vertebral abnormalities. It is caused by mutations in the SALL4 gene, which is thought to be involved in the patterning of several embryonic structures, such as sixth nerve, limbs, and heart (12,13). DRS may also be associated with other developmental problems, such as the HOXAI spectrum, while limited abduction and globe retraction can also occur as part of more complicated congenital ocular motility syndromes, such as CFEOM1.

**Congenital Fibrosis of the Extraocular Muscles Type 1 (CFEOM1; MIM #135700)**

This is the most common CFEOM phenotype. It is autosomal dominant and has been reported worldwide (14) with primary clinical features including bilateral ptosis and severe restriction of up gaze so that neither eye is able to reach midline (Fig. 1) (15,16). Down gaze and horizontal movements are variably restricted. Misdirected eye movements are common, including bilateral convergence on attempted up gaze (synergistic convergence) and globe retraction with attempted globe movement. Autopsy study and careful orbital imaging show profound atrophy of levator and superior rectus, variable reduction in the size of other extraocular muscles, absence of ocular motor nerves, and optic nerves that are reduced 30% to 40% in cross section (16). CFEOM1 is caused by heterozygous missense mutations in KIF21A, a gene that encodes a kinesin microtubule-associated protein associated with anterograde organelle transport in neuronal cells (15).

**Congenital Fibrosis of the Extraocular Muscles Type 2 (CFEOM2; MIM #602078)**

The main clinical features of this autosomal recessive syndrome are bilateral ptosis and absence of adduction, up gaze, and down gaze, creating the appearance of bilateral third nerve palsies (Fig. 2) (17). Abduction is present, although generally limited, and pupils often are variable in size and shape and nonreactive to light even though they do respond to pupillary pharmacologic agents (18). Neuroimaging shows that the third nerves are absent bilaterally (18). The syndrome is caused by homozygous loss-of-function mutations in the PHOX2A gene (17), a homeodomain transcription factor that is prominently expressed in developing third and fourth motor neurons and is essential to their survival. In the mouse, Phox2a also regulates the expression of 2 catecholaminergic biosynthetic enzymes essential for the differentiation and maintenance of the noradrenergic neurotransmitter phenotype (19–21).

**Congenital Fibrosis of the Extraocular Muscles Type 3 (CFEOM3)**

This disorder is autosomal dominant, and the ocular motility findings are similar to CFEOM1 except that it is more variable and sometimes associated with the ability to elevate the eyes above the midline (Figs. 3, 4) (22). It is now known to be caused by heterozygous mutations in at least 2 genes, TUBB3 (CFEOM3A; MIM #600638) (23) and rarely KIF21A (CFEOM3B) (24).

**TUBB3** is a component of microtubules, and the phenotype of an individual harboring a **TUBB3** mutation depends in part on the specific heterozygous missense mutation. Some mutations can be nonpenetrant, while others result in isolated CFEOM3, and in these individuals, the ocular phenotype is quite variable, including individuals with only absent up gaze. Other mutations can cause CFEOM3 in association with facial palsy, peripheral neuropathy, wrist and finger contractures, and intellectual, social, and behavioral impairments. Orbital imaging of
individuals with TUBB3 mutations (25) is similar to that found in CFEOM1 resulting from KIF21A mutations (26). With brain MRI, dysgenesis of the corpus callosum and anterior commissure has been reported (23).

Patients have been described with a syndrome that looks similar to CFEOM1, although generally without complete restriction of up gaze, who do not harbor mutations in TUBB3. Several of these individuals do harbor one of the common mutations in KIF21A, and this syndrome is referred to as CFEOM3B. Both TUBB3 and KIF21A have a role in directing growing cranial nerves to a correct termination in extraocular muscles. A CFEOM3C variant (MIM %609384) has been recognized in 3 generations of a single family, where all affected members carry a reciprocal translocation involving chromosomes 2q and 13q (27).

**HOXA1 Spectrum (MIM #601536)**

This autosomal recessive syndrome consists most notably of bilateral DRS type 3 (limited adduction and absence of abduction), deafness, and internal carotid and cerebrovascular malformations, and sometimes autism (Fig. 5) (28–30). Some individuals may have associated intellectual disabilities, facial weakness, and/or central hypoventilation (31). Neuroimaging has demonstrated absence of the sixth nerve bilaterally and almost completely absent development of the hearing and vestibular apparatus in the petrous bone (28–30). The syndrome is due to homozygous mutations in HOXA1 that probably cause loss of rhombomere 5 and an early and profound brainstem patterning defect (28). HOXA1 mutations were not found in cohorts of individuals with sporadic DRS (32) or Möbius syndrome (MBS) (33).
Horizontal Gaze Palsy and Progressive Scoliosis (HGPPS; MIM #607313)

This syndrome is characterized by complete or almost complete bilateral horizontal gaze limitation with full vertical gaze, variable convergence, variable congenital nystagmus, and asynchronous blinking (34). Scoliosis begins in early childhood and is commonly rapidly progressive and severe (Fig. 6) (35). Neuroimaging shows intact sixth nerves bilaterally and deep anterior and posterior clefts in the medulla and lower pons, a large fourth ventricle, and no decussation of the axons within the corticospinal tract, medial lemniscus, or superior cerebellar peduncle (36,37). HGPPS is an autosomal recessive syndrome caused by mutations in ROBO3 (38), a gene that promotes decussation of developing neural tracts in the pons, medulla, and spinal cord (in the mouse model) (39).

Möbius Syndrome (MBS; MIM %157900)

MBS is the eponym reserved for congenital facial weakness associated with restricted horizontal eye movements. Facial weakness is usually bilateral and asymmetric; limited horizontal eye movements always affect abduction and common adduction, while vertical gaze is only rarely affected. Esotropia is common, convergence is variable, Bell’s phenomenon is intact, nystagmus is rare, and ptosis is unusual. MBS is frequently accompanied by nonocular and facial features, such as lingual and/or pharyngeal dysfunction, craniofacial dysmorphism, and limb malformations. In most patients, the syndrome is sporadic, although HOXA1 and TUBB3 mutations can result in atypical Möbius phenotypes (23,28). MBS is likely quite heterogeneous in origin and may have more than 1 genetic and/or developmental etiology.

DISORDERS WITH NORMAL OCULAR MOTILITY

Hereditary Congenital Facial Palsy

This syndrome causes an autosomal dominant, isolated facial weakness that is often asymmetric and bilateral and is distinct from MBS in that ocular motility is normal. Postmortem pathological studies have shown reduced

FIG. 3. CFEOM3A phenotype. A. Primary position. B. Right gaze with absence of adduction and slight down shoot of the left eye. C. Left gaze with absence of adduction, slight down shoot of the right eye, and limited abduction on the left. D. Attempted up gaze is limited bilaterally with the left eye unable to reach midline and becoming esotropic. E. Down gaze fixating with the right eye shows slight downward movement of the right eye and only outward movement of the nonfixating left eye. F. Similarly, down gaze fixating with the left eye shows slight downward movement of the left eye and only outward movement of the nonfixating right eye.

FIG. 4. CFEOM3B phenotype. All images are in primary position. A. Patient has unilateral ptosis and esotropia. B. Patient has severe bilateral ptosis in primary position despite marked frontalis effort. C. Same patient as B in primary position with lids held showing resting globe position with exotropia and bilateral infraduction.
FIG. 5. HOXA1 spectrum phenotype. A–C. Right gaze, primary gaze, and left gaze of a girl with bilateral Duane retraction syndrome type 3. Note up shoot of the left eye on attempted left gaze. D. Axial CT scan of the same patient shows almost no development of the petrous bones except for mastoid air cells. E. MRA demonstrates absence of the left internal carotid artery, relatively large caliber of the basilar and both posterior cerebral arteries, and asymmetric filling of the transverse sinuses.

FIG. 6. Horizontal gaze palsy and progressive scoliosis phenotype. A. Primary position. B. Attempted right gaze showing complete gaze palsy. C. Attempted left gaze showing complete gaze palsy. D. Moderately severe scoliosis concave right. E. Hypoplasia of the pons. F. Deep anterior and posterior clefts in the medulla causing the classic “butterfly medulla” appearance (arrows).


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number of neurons within the facial nerve motor nuclei and poorly developed facial nerve roots. Two genetic loci, termed HCFP1 (MIM %601471) and HCFP2 (MIM %604185), have been defined, but neither gene has been identified yet; there does not appear to be any major phenotypic differences between the loci (40–42).

### Hereditary Congenital Ptosis

Hereditary congenital ptosis is defined as an isolated drooping of the upper eyelid with no accompanying ocular features. Bilateral involvement is common, but unilateral cases have been reported. Severity of ptosis ranges from mild to severe and can be asymmetric in bilateral cases. There are

<table>
<thead>
<tr>
<th>Genes</th>
<th>Phenotype</th>
<th>Main Neuro-ophthalmologic Features</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHN1</td>
<td>DURS2</td>
<td>DRS, often bilateral and associated with vertical motility abnormalities</td>
<td>—</td>
</tr>
<tr>
<td>SALL4</td>
<td>DRRS</td>
<td>DRS</td>
<td>Variable hand and upper extremity anomalies; variable cardiac, renal, auditory, and vertebral abnormalities</td>
</tr>
<tr>
<td>KIF21A</td>
<td>CFEOM1</td>
<td>Bilateral ptosis; bilateral severe limitation of up gaze in both eyes with less severe limitations in other directions</td>
<td>—</td>
</tr>
<tr>
<td>CFEOM3B</td>
<td>As above</td>
<td>but up gaze limitation typically not as severe</td>
<td>—</td>
</tr>
<tr>
<td>TUBB3</td>
<td>CFEOM3A</td>
<td>Variable unilateral or bilateral ptosis and limitation of up gaze that may not be as severe as CFEOM1; bilateral, asymmetric restrictions in other directions in both the eyes</td>
<td>—</td>
</tr>
<tr>
<td>CFEOM3A plus</td>
<td>Similar to or more severe than CFEOM3A, when more severe the findings are bilateral and eyes are exotropic</td>
<td>Peripheral neuropathy; facial palsy; wrist and finger contractures; and/or intellectual, social, and behavioral impairments</td>
<td></td>
</tr>
<tr>
<td>PHOX2A</td>
<td>CFEOM2</td>
<td>Bilateral severe ptosis and bilateral palsies of adduction, elevation, and depression with significant exotropia, occurs rarely without exotropia</td>
<td>—</td>
</tr>
<tr>
<td>HOXA1</td>
<td>BSAS</td>
<td>Bilateral DRS type 3 or horizontal gaze palsy</td>
<td>Bilateral deafness; variable cerebrovascular and cardiovascular anomalies</td>
</tr>
<tr>
<td>ABDS</td>
<td>AS above</td>
<td>Often more severe phenotype, including facial weakness and central hypoventilation</td>
<td>—</td>
</tr>
<tr>
<td>ROBO3</td>
<td>HGPPS</td>
<td>Complete or almost complete horizontal gaze palsy</td>
<td>Scoliosis, usually severe</td>
</tr>
</tbody>
</table>
**TABLE 2. Loci associated with congenital cranial dysinnervation disorders (CCDDs)**

<table>
<thead>
<tr>
<th>Genetic Loci</th>
<th>Phenotype</th>
<th>Main Neuro-ophthalmologic Feature</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>13q12.1 (cytogenetic; 1 family)</td>
<td>CFEOM3C</td>
<td>Bilateral ptosis and bilateral limitation of up gaze typically not as severe as CFEOM1; bilateral, asymmetric restrictions in other directions in both the eyes; bilateral excyclotorsion</td>
<td>Facial dysmorphism; mental retardation</td>
</tr>
<tr>
<td>22pter (cytogenetic in 3 patients)</td>
<td>DRS</td>
<td>Duane retraction syndrome</td>
<td>—</td>
</tr>
<tr>
<td>DURS1 (cytogenetic)</td>
<td>DRS</td>
<td>Duane retraction syndrome</td>
<td>Contiguous gene deletion syndrome, usually with additional findings</td>
</tr>
<tr>
<td>1p22 (cytogenetic in 2 patients)</td>
<td>MBS</td>
<td>Lower motor neuron facial weakness, often bilateral and asymmetrical; variable restriction of horizontal eye movements</td>
<td>Presumed contiguous gene deletion syndrome with variable ptosis, dysmorphism, developmental delay, Poland syndrome, etc</td>
</tr>
<tr>
<td>1q12.2-q13 (cytogenetic in 1 family)</td>
<td>As above</td>
<td>Variable flexion finger contractures</td>
<td>—</td>
</tr>
<tr>
<td>3q21-q22</td>
<td>HCFP1</td>
<td>None</td>
<td>Isolated dysfunction of the facial nerve</td>
</tr>
<tr>
<td>10q</td>
<td>HCFP2</td>
<td>None</td>
<td>Isolated dysfunction of the facial nerve</td>
</tr>
<tr>
<td>1p34.1-p32</td>
<td>PTOS1</td>
<td>Isolated unilateral or bilateral ptosis</td>
<td>—</td>
</tr>
<tr>
<td>Xq24-q27.1</td>
<td>PTOS2</td>
<td>Isolated unilateral or bilateral ptosis</td>
<td>—</td>
</tr>
</tbody>
</table>

Currently 2 loci mapped by linkage analysis: an AD locus on chromosome 1 (43) (PTOS1; MIM %178300) and an X-linked locus (44).

**DISCUSSION**

In 2002, the CCDD concept included 10 syndromes, 2 confirmed genes, and 14 genetic loci. Eight years and more than 80 published articles later, 7 genes are recognized to cause 10 phenotypes (Table 1) and another 6 syndromes are associated with at least 11 genetic loci (Table 2). Every CCDD gene characterized since 2002 has been associated with neuronal development at the nuclear, brainstem, or peripheral nerve level, supporting the hypothesis that CCDDs are neurogenic in origin (3).

With genotypic definitions have come better phenotypic characterizations, including the realization that syndromes caused by different genetic mutations may present confounding clinical similarities. For example, DRS most commonly occurs sporadically but can be caused by heterozygous (10,15) or homozygous (28–30) mutations of several genes. The CFEOM1 (15) and CFEOM3 (23) phenotypes can be quite similar, and severe horizontal gaze restriction is a hallmark of both HGPPS (34) and the HOXA1 spectrum (30).

Some CCDDs include nonocular abnormalities. For example, CFEOM3 due to TUBB3 mutations can be associated with a peripheral neuropathy, joint contractures, and intellectual and behavioral disabilities (23). We now realize that ocular motility and other clinical aspects of these syndromes are variable, and even within families, there is presumably genetic homogeneity. Thus, some patients with HOXA1 mutations may lack ocular motility abnormalities or deafness, 2 of the cardinal clinical features (30). Perhaps, most importantly, certain CCDD diagnoses may call attention to important features of a syndrome such as cerebrovascular maldevelopment and congenital heart disease in the HOXA1 spectrum (28–30).

The North American Neuro-Ophthalmology Society (NANOS) has recently created the NOVEL Rare Disease Registry under which there is now a category for Unusual Congenital Ocular Motility Disorders and Strabismus. The Web site now contains a link (http://library.med.utah.edu/NOVEL/diseases/rare-registry/view/Unusual_Congenital_Oscular_Motility_Disorders) by which a clinician can contact the stewards, Drs. Thomas M. Bosley and Elizabeth C. Engle, and submit clinical descriptions and genetic material for analysis. We encourage broad participation.

since such an effort will likely be necessary to clinically and genetically characterize new CCDDs.

REFERENCES


Bilateral Simultaneous Central Retinal Vein Occlusions in an Otherwise Healthy Adult

Ana G. Alzaga Fernandez, MD, Romina Shirka, DO, Barry Skarf, PhD, MD, Brian Silver, MD, Selma J. Matloob, MD, Michael D. Ober, MD, Patrick Luetmer, MD, Caterina Giannini, MD, PhD

Dr. Skarf:

A 53-year-old man presented with a 5-day history of progressive painless loss of vision in his right eye and a 1-day history of a similar deterioration in the left eye. He denied headaches, diplopia, transient visual obscurations, or other neurological symptoms. He stated that he was in good health and denied any systemic diseases. He was a vegetarian who exercised regularly.

Ophthalmological examination revealed that the patient’s best-corrected visual acuity was 20/200 in the right eye and 20/40 in the left eye. His pupils were equal and reactive to light; there was a questionable right relative afferent pupillary defect. Confrontation visual field testing showed that he could count fingers in all quadrants of both eyes. Kinetic perimetry of the right eye performed using the I-4e and I-2e test targets showed a moderately dense central scotoma, an enlarged blind spot, and slightly constricted peripheral isopters. The central scotoma in the right eye was confirmed using an Amsler grid. In the left eye, kinetic perimetry showed minimal constriction of the isopters superotemporally. With an Amsler grid, the patient noted distortion and waviness of lines superotemporally. The patient was able to identify 12 of 15 Ishihara plates with the right eye by fixating eccentrically with his nasal field. He identified all 15 color plates with his left eye. Extraocular movements were full, and the slit-lamp examination revealed no abnormalities. Intraocular pressures were within normal limits. Both optic discs were swollen and surrounded by multiple flame-shaped hemorrhages that radiated from the optic discs and obliterated the disc margins (Fig. 1). Small exudates and scattered dot and blot hemorrhages surrounded both optic discs; there was no substantial hemorrhage noted along the retinal vascular arcades outside the immediate peripapillary area. In both eyes, the retinal veins appeared distended and engorged, with boxcarring of the blood column. There were serous macular detachments in both eyes. There were no abnormalities in the retinal periphery of either eye.

Patient evaluation showed mild pancytopenia (white blood cell count, 3.1 K/µL; hemoglobin B, 9.7 g/dL; platelets, 135 K/µL), high serum protein, low serum albumin, and high lactate dehydrogenase. Serum vitamin B12, folate, and iron levels were normal. CT and MRI of the brain, MRA, and venography were performed.

Dr. Luetmer:

CT of the head without contrast shows no abnormalities; however, magnetic resonance studies reveal a poorly defined heterogeneous infiltrate involving the clivus consistent with a marrow replacement process (Fig. 2).

Dr. Skarf:

Given the magnetic resonance findings, a whole-body bone scan and a metastatic bone survey were performed.

Dr. Luetmer:

The bone scan shows multiple areas of uptake involving the ribs on both sides, the right scapula, and the left femur (Fig. 3). The metastatic bone survey reveals vague lucenties throughout the skull.

Dr. Skarf:

Serum electrophoresis with immunofixation revealed a large IgA lambda monoclonal protein in the beta region. The urine electrophoresis with immunofixation revealed similar results. The patient’s serum viscosity was elevated at 7.24 centipoise. A bone marrow biopsy was performed.

Dr. Giannini:

The biopsy reveals diffuse infiltration by a monomorphous plasmacytic cell population, morphologically consistent...
with a plasma cell neoplasm (Fig. 4). According to the report (not shown), these cells are CD38- and CD56-positive and show exclusive cytoplasmic lambda light chain expression supportive of a clonal population and, therefore, of the proposed diagnosis of myeloma (Fig. 4).

**Pathological Diagnosis:**
Multiple myeloma IgA, lambda monoclonal type.

**Dr. Alzaga Fernandez:**
The patient underwent 2 courses of plasmapheresis in addition to treatment with lenalidomide, allopurinol, zoledronic acid, and dexamethasone. After the second plasmapheresis, the patient’s visual acuity in the right eye improved to 20/80, but there was minimal improvement in the left eye. The retinal veins were less engorged, and there appeared to be fewer retinal hemorrhages. One month later, there was significant resorption of the retinal hemorrhages, improvement in the appearance of the retinal vessels, and improvement in visual acuity to 20/25 in both eyes. Shallow serous detachments were still present in both maculae. Six months after treatment, the patient’s visual acuity was 20/20 in both eyes. The fundi demonstrated marked improvement (Fig. 5). The patient subsequently underwent an autologous bone marrow transplant and is asymptomatic 18 months after his initial presentation.

**DISCUSSION**

**Dr. Alzaga Fernandez:**
Multiple myeloma is the most common of the plasma cell dyscrasias; it accounts for 10% of hematologic malignancies and 80% of plasma cell neoplasms (1). The median age of presentation is 72 years, with the most common features being bone pain, anemia, renal insufficiency, infection, and plasmacytomas (1,2). Although almost every part of the eye and visual pathways can be affected by multiple myeloma, ocular involvement rarely occurs early in the course of the disease.
The ocular manifestations can be separated into 2 categories: 1) those attributed to plasmacytoma growth in and about the eye, including deposition of light-chain immunoglobulin and 2) those due to hematologic abnormalities such as hyperviscosity syndrome (4). Ocular findings in the first category include ciliary body cysts, ciliochoroidal effusions, uveal plasmacytomas, conjunctival and corneal deposits (both crystalline and noncrystalline), orbital involvement, detachment of the sensory retina, retinal pigment epithelium detachment, and optic nerve infiltration (1,3–5). Manifestations of the hematologic abnormalities in the second category mainly include the effects of hyperviscosity on the retinal, choroidal, and optic nerve blood supply (3,4). A third category of involvement has been proposed in which ocular signs are related to infection secondary to immunosuppression (4).

Our patient’s manifestations resulted from the effects of hyperviscosity, which results in impaired blood flow due to alterations in the rheologic properties of blood (6). This syndrome produces a variety of manifestations such as headache, vertigo, hearing loss, nystagmus, visual disturbances, retinal vein congestion, retinal hemorrhages, mucosal hemorrhages, congestive heart failure, and renal failure (2). Other symptoms include fatigue, anorexia, and weakness (7).

Blood viscosity is measured in centipoise (cP) and varies according to the hematocrit, red cell aggregability, and plasma viscosity (6,7). Symptoms related to hyperviscosity syndrome occur more frequently when the viscosity is above 6 cps, as was the case in our patient; however, the level of viscosity at which the symptoms become apparent varies among patients (6). Symptoms usually occur when an excess of immunoglobulin interacts with other blood elements leading to impairment in blood flow and increased viscosity (7,8). Other laboratory findings such as hypercalcemia, pseudohyponatremia, and pseudohypoglycemia may suggest hyperviscosity indirectly (2,7).

Hyperviscosity syndrome was first described with monoclonal gammopathies (6). It occurs in 10%–30% of patients with Waldenstrom macroglobulinemia, 3%–4% of IgG myeloma, and 5%–20% of IgA myeloma (6,9). Multiple myeloma is 10 times more common than Waldenstrom macroglobulinemia and therefore a more frequent cause of hyperviscosity syndrome (2,6). The most common type of immunoglobulin associated with the syndrome is IgM; the association of IgA and IgG monoclonal...
gammopathies with hyperviscosity syndrome is much less common (7,10). IgM is a larger molecular compound secreted as a pentamer and is found mainly in the intravascular compartment due to its size (11). IgM has the ability to bind with water and form aggregates that may contribute to increase blood viscosity (11). IgA normally is present as a monomer; however, in IgA multiple myeloma, a large amount of the IgA is present as a dimer in the serum, and this contributes to its hyperviscosity (12).

Early funduscopic findings in hyperviscosity retinopathy include dilation and tortuosity of retinal veins secondary to stasis of blood flow (7,13). The pathognomonic finding is *fundus paraproteinaemius*, a term used to describe engorged tortuous retinal veins that have a boxcar or “sausage-link” appearance (7,8). This entity may progress to complete central retinal vein occlusion (CRVO), with flame-shaped hemorrhages, microaneurysms, or exudates, as found in our patient (7). Other diseases with similar funduscopic findings include leukemia and aplastic anemia (14–16).

The first report of a patient with bilateral CRVO as the initial manifestation of multiple myeloma was that of a 65-year-old woman who was diagnosed with IgG-associated (kappa type) multiple myeloma (17). The second case was a 16-year-old boy who initially presented with bilateral blurry vision and epistaxis (8). He was treated for presumed papilledema with oral steroids and experienced a transient improvement of his symptoms. Three months later, the diagnosis of CRVO was established, and the patient was found to have IgA multiple myeloma. To our knowledge, our patient represents the third reported case with bilateral CRVO as the initial manifestation of multiple myeloma due to an IgA monoclonal gammopathy.

Other entities to consider in patients with bilateral CRVO include systemic lupus erythematosus, antiphospholipid antibody syndrome, and hyperhomocysteinemia (18). Positive laboratory tests may include lupus anticoagulant antibodies, congenital deficiency of protein S, and acquired protein C resistance (19,20). Defects in platelet function, acquired von Willebrand disease, inhibition of fibrin formation, and acquired factor X, IX, V, or II deficiency with amyloidosis have been associated with gammapathies and hyperviscosity syndrome (6). Bilateral CRVO also has been induced iatrogenically in young patients, without preexisting comorbidities, who are treated with intravenous immunoglobulins and other medications for various disorders (21,22). There have also been reports of patients with congenital cardiac defects, such as Eisenmenger syndrome, who have developed bilateral CRVO (23).

Therapeutic measures for hyperviscosity syndrome include plasmapheresis to ameliorate the signs and symptoms associated with blood flow stasis (2). This is an effective but temporizing measure, as the immunoglobulin reaccumulates within a few days. Melphalan and prednisone have been the standard treatment for multiple myeloma for more than 40 years and are associated with a median survival of 28–37 months (24). Renal failure is associated with a poor outcome (2). The addition of bortezomib to melphalan and prednisone delays the onset of progression (24). For patients aged 65 or less with adequate performance status, American and European guidelines recommend high-dose melphalan therapy and autologous hematopoietic stem cell transplantation (25).

In summary, patients who present with bilateral CRVO warrant a systemic investigation for underlying hyperviscosity syndromes including blood dyscrasias such as multiple myeloma. An initial complete blood count may offer the first clue. With treatment, patients may experience excellent visual recovery.

**ACKNOWLEDGMENT**

The authors thank Ms. Elaine Lok, Ophthalmic Imaging, Henry Ford Hospital, who provided assistance and support in the preparation of the photographs for this article.

**REFERENCES**


Should Patients With Radiation-Induced Optic Neuropathy Receive Any Treatment?

Michael S. Lee, MD, Francois Xavier Borruat, MD

**Clinical Presentation: Michael S. Lee**

Rarely, a patient treated with radiation therapy develops optic nerve or chiasmal injury. This typically occurs several months to years after completion of radiation (mean onset: 18 months) most frequently for paranasal sinus tumors or other skull-based lesions. While the most common site of injury involves the chiasm and/or retrobulbar optic nerve, anterior radiation optic neuropathy (RON) may also occur (1–5).

The risk of RON increases with total radiation doses of more than 50 gray (Gy) or a single fraction of greater than 2 Gy using fractionated radiotherapy (1–5). Radiosurgery (eg, Gamma Knife and Cyberknife) doses of greater than 8 Gy also raise the risk of RON (6). Patients with diabetes mellitus or those receiving concomitant chemotherapy may have an increased risk for RON. The threshold for RON may be lower following radiation for pituitary tumors (42–50 Gy) possibly from the additive effect of chiasmal compression (7).

Patients typically suffer painless vision loss in one or both eyes, with bilateral disease developing in 75% of cases either simultaneously or sequentially (8). Symptoms may progress over weeks to months from mild visual loss to complete blindness. Overall, the prognosis is very poor with a final visual acuity of 20/200 or worse in 85% of the affected eyes (9). At the time of examination, the optic disc may appear normal (posterior RON), swollen (anterior RON), or pale (previous optic atrophy). Brain and orbit CT demonstrate normal results, but MRI with gadolinium during the acute phase of RON reveals enhancement of the optic nerves and/or chiasm. Interestingly, an MRI performed for other reasons may show visual pathway enhancement prior to visual loss (2). Spontaneous recovery has been reported but is uncommon (2,10).

**Pathophysiology**

The pathophysiology of RON is unknown. It is presumably ischemic because of the demyelination, reactive astrocytes, and obliteratorative endarteritis seen on histopathologic specimens (1). One study showed that the optic nerves exposed to radiation plaques for ocular melanoma treatment had significant loss of vascular endothelial cells, supporting a vascular injury (11). This observation also helps explain the obvious gadolinium enhancement seen on MRI with RON. However, vascular injury alone, does not adequately explain the long-time delay between radiation therapy and visual loss. One hypothesis includes a critical role for replicating glial cells in axonal conduction. Because of the slow turnover rate of these cells, several months may pass prior to the onset of visual loss (2,5).

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**PRO—Patients with radiation-induced optic neuropathy should be treated with hyperbaric oxygen: François Xavier Borruat, MD**

As Dr. Lee notes, RON is an unpredictable and dramatic complication of radiotherapy (1,8,26). Supporting an ischemic mechanism from vascular endothelial cell damage, magnetic resonance spectroscopy (MRS) in cerebral radio necrosis shows elevated lactate levels associated with severe morphologic changes. There was no MRS support for a primary demyelinating process as no elevation of choline was found within the injured tissues (30). In addition, pathology studies of human irradiated optic nerves showed a depletion of vascular endothelial cells (11). Other changes found in irradiated tissues are consistent with a state of chronic hypoxia without any signs of spontaneous microvascular revascularization (previously irradiated bones) (31). Given this evidence, a vascular/ischemic process appears to be the most important component in the development of RON.

**Can RON be prevented?**

Ideally, irradiated patients at risk should be medically protected to prevent the development of RON. Ramipril,
an angiotensin-converting enzyme inhibitor, has led to modest improvement in optic nerve function and anatomy in an animal model of RON when given soon after irradiation (32,33). With controlled irradiation and ramipril doses, 4 of 7 rats were protected, while 3 of 7 lost optic nerve function (33).

Large-scale application of such a potentially protective agent to all irradiated patients at risk of developing RON raises several questions. The safety and the costs of such a treatment have to be considered. Also, the timing of such treatment is uncertain given the variable time interval between radiotherapy and onset of RON. Finally, if the results of the animal model are extrapolated to humans, nearly 50% of treated patients would still develop RON.

Can RON be treated and which therapy is adequate?

In humans, therapeutic options include corticosteroids, anticoagulants, antiaggregants, and hyperbaric oxygen (HBO). There has been no randomized double-blind study for any treatment of RON. A retrospective literature review found no favorable effect of either corticosteroids or anticoagulation (4), and cases of radiation damage and visual loss have been reported to develop despite anticoagulation (19,20).

Hyperbaric oxygen therapy

The evidence of a vascular/ischemic etiology for RON suggests a possible role for increasing oxygenation of the irradiated tissues using hyperbaric oxygen therapy. HBO therapy consists of breathing O2 at 100% concentration at a pressure higher than 1 atmosphere (ATA). HBO induces a steep oxygen gradient between the healthy and the irradiated hypoxic tissues. This enhances both the proliferation of fibroblasts and the synthesis of collagen, creating supportive tissue for the proliferation of new blood vessels. Revascularization of hypoxic hypocellular irradiated tissues has been demonstrated not only in experimental animal models but also in humans (34,35). Oxygenation of previously hypoxic irradiated tissues has been demonstrated to persist in vivo in humans (34).

The favorable effect of HBO requires both a minimal threshold of oxygen pressure and a minimum number of sessions (35). Using HBO at 2.0 ATA instead of 2.4 ATA led to a lower rate of success for treatment of osteoradionecrosis (34). That might explain why some authors using HBO at 2.0 ATA failed to report success in treating RON patients (3).

Based on experimental and clinical studies, the following HBO protocol is recommended: 30 sessions of HBO therapy, breathing 100% oxygen at 2.4 ATA for 90 minutes per session. HBO therapy is a widely used, safe, and proven technique for a variety of conditions (Table 1). With these settings, systemic complications are rare (Table 2). The incidence of convulsions varies between 2.4 and 7 per 100,000 (Table 2) (28,35,36). Ocular side effects are also rare including transient myopia and cataract. One case of transient blindness was reported in a patient with a previous history of optic neuritis who underwent an unusually long course of HBO (6-hour session at 2.0 ATA) (37).

Spontaneous improvement of retrobulbar RON is exceedingly rare, and only 1 such case has been reported (2). The poor natural history and the lack of efficacy for corticosteroids, antiaggregants, or anticoagulants make HBO a reasonable treatment option (5,35–37).

**TABLE 1. Approved indications for hyperbaric oxygen therapy**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Reason or Risk Factor</th>
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<tbody>
<tr>
<td>Air or gas embolism</td>
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<tr>
<td>Carbon monoxide poisoning and carbon monoxide poisoning complicated by cyanide poisoning</td>
<td></td>
</tr>
<tr>
<td>Clostridial myositis and myonecrosis (gas gangrene)</td>
<td></td>
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<tr>
<td>Crush injury, compartment syndrome, and other acute traumatic ischémies</td>
<td></td>
</tr>
<tr>
<td>Decompression sickness</td>
<td></td>
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<tr>
<td>Enhanced healing of selected wounds (diabetic)</td>
<td></td>
</tr>
<tr>
<td>Exceptional blood loss (anemia)</td>
<td></td>
</tr>
<tr>
<td>Necrotizing soft tissue infections</td>
<td></td>
</tr>
<tr>
<td>Osteomyelitis (refractory)</td>
<td></td>
</tr>
<tr>
<td>Delayed radiation injury (soft tissue and bony necrosis)</td>
<td></td>
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<tr>
<td>Skin grafts and flaps (compromised)</td>
<td></td>
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<tr>
<td>Thermal burns</td>
<td></td>
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<tr>
<td>Intracranial abscess</td>
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</table>

**TABLE 2. Complications of hyperbaric oxygen therapy**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Reason or Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>Current fever or history of seizure disorder</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Air trapping in asthma, COPD, pulmonary bleb</td>
</tr>
<tr>
<td>Tympanic membrane rupture</td>
<td>Eustachian tube dysfunction</td>
</tr>
<tr>
<td>Hemolysis of red blood cells</td>
<td>Congenital spherocytosis</td>
</tr>
<tr>
<td>Impaired wound healing</td>
<td>Recent use of cisplatin, disulfuram, or sulfamylon</td>
</tr>
<tr>
<td>Interstitial pneumonitis</td>
<td>Recent use of bleomycin</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>Recent use of doxorubicin</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Claustrophobia</td>
</tr>
<tr>
<td>Pacemaker dysfunction</td>
<td>Raised pressure may damage device</td>
</tr>
<tr>
<td>Epidural pain pump</td>
<td>Raised pressure may damage device</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease.
HBO is the only therapy that has favorably influenced the visual outcome of patients with RON. Guy and Schatz (4) were the first to report visual improvement in 2 patients with RON treated with HBO within 72 hours of visual loss. Their 2 other patients did not improve but were treated later at 15 days and 6 weeks after the onset of visual loss. Several additional cases of visual improvement following HBO have been reported in the literature (38). Among 5 personal cases of RON, 3 were treated with HBO and 1 markedly improved from 20/200 to 20/30 following HBO (unpublished data). Others have reported their experience with HBO in treating RON patients with no cases of visual improvement (2,3,9).

Possible reasons for the unpredictability of visual improvement after HBO in RON patients include: 1) HBO is applied too late after the onset of RON, 2) HBO parameters (oxygen pressure and number of sessions) are inadequate, and 3) visual loss in some patients might be mainly from axonal loss rather than vasculopathy. None of the 13 patients with RON treated with HBO showed any visual improvement, but they were all treated with oxygen at 2.0 ATA instead of 2.4 ATA (3). Further, none were treated within 15 days of onset of visual loss, and 75% were given fewer than 30 sessions of HBO. There is no scientific study providing the appropriate timing for initiating HBO in RON, but common sense implies the sooner the better.

To give patients with RON a chance to recover or stabilize vision, they should be treated with HBO as early as possible after the onset of visual loss. HBO therapy is a safe procedure, and current guidelines suggest a treatment protocol of 30 sessions at a pressure of 2.4 ATA.

**CON—Patients with radiation-induced optic neuropathy should not be treated with hyperbaric oxygen:** Michael S. Lee, MD

**Proposed therapies**

No randomized, masked, controlled clinical trials (class 1 evidence) to treat RON exist for any proposed therapy of RON. Previous studies have reported the use of intravenous corticosteroids (12,13), anticoagulation (14), intravitreal vascular endothelial growth factor inhibitors (15), optic nerve sheath fenestration (ONSF) (16), and hyperbaric oxygen therapy with scattered success (8). Unfortunately, these reports used retrospective data collection from routine clinical charts. These case reports and small case series suffer from potential bias. The examiner and patient were not masked to therapy, and both may develop expectations of outcome based on treatment vs no treatment. Patients are rarely refracted in a standardized fashion using a uniform chart at each routine visit, which makes it difficult to assess true improvement in acuity. Finally, patients with central visual field loss may demonstrate improved performance as acuity, and visual fields are serially tested. Scanning techniques or increased familiarity with perimetry might result in improved visual fields. For example, in the Ischemic Optic Neuropathy Decompression Trial (IONDT), there were 245 eyes with visual field and acuity follow-up at 12 months (17). Regardless of treatment, there were 75 eyes with improvement of ≥3 lines of acuity. Of those that improved, only 38% demonstrated visual field improvement, suggesting that eyes with stable or even worsening visual fields learned to read the eye chart better (17).

Spontaneous improvement in RON has been reported albeit infrequently. Three of the 4 patients experienced anterior RON, while the other suffered posterior RON (2,10). While the paucity of reports may reflect the true natural history of the disease, it may also represent lack of reporting. We learned a lesson from the IONDT; 43% of the observation group improved by 3 or more lines of acuity at 6-months follow-up, which came as a surprise to the neuro-ophthalmic community.

Corticosteroids

High-dose corticosteroids have been used in RON but with limited success. Girkin et al (12) reported 4 patients with RON, all of whom received systemic corticosteroids and 1 received adjuvant hyperbaric oxygen therapy. One of the patients who received corticosteroids alone had acuity improved from 20/70 to 20/30. Lee et al (13) reported 3 cases of RON, and 1 stabilized on corticosteroids alone. Meanwhile, Borruat et al (8) reviewed the existing literature and did not find that corticosteroids affected the outcome of RON. Although uncommon, corticosteroid use carries a risk of avascular necrosis, gastrointestinal bleeding, and psychosis. I personally have not observed any success with corticosteroids for RON.

Anticoagulation

Neurologic deficits due to radionecrosis in other parts of the central nervous system have responded to anticoagulation (14). However, this has not translated into therapy for RON. There are several cases of patients developing RON while taking warfarin, suggesting anticoagulation may not be helpful (19,20). However, in the absence of a control group, it is unknown whether anticoagulation affects the outcome of RON.

Other therapies

There is 1 report of a patient with anterior RON who received intravitreal bevacizumab. The visual acuity improved from 20/32 to 20/20, and optic disc edema resolved (15). Another report described 3 patients with anterior RON who underwent ONSF. Each enjoyed substantial improvement.
improvement suggesting that Lee and Borruat: ultrar RON, there is only 1

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functional recovery. His argument is based on the results of the IONDT, where 75 of 245 patients with NAION had improvement in visual acuity but only 38% of the 75 patients had improved visual fields (17). However, improved vision in NAION can result from other mechanisms, such as resorption of subretinal fluid, detected by optical coherence tomography (39). Further, some of the RON patients treated with HBO had improvement in both acuity and visual fields (4,8). The assumption that visual improvement from HBO therapy results from a learning process is not necessarily correct.

Dr. Lee raises the possibility of dangerous effects of HBO including seizures and death. Cerebral oxygen toxicity results mainly from the formation of reactive oxygen species resulting in oxidative cell membrane damage, whereas in the lungs, capillary endothelial damage and pulmonary edema can be present (37). In a large series of HBO-treated patients, there were only 2 cases of seizures among 80,679 patient-treatments (rate: 2.4 per 100,000 patient-treatments) (28). One of the 2 patients died in status epilepticus. This 22-year-old man had benefited of 30 HBO sessions when he developed seizures during the last session. After a 45-minute postictal stage, he recovered consciousness and received anticonvulsant therapy. On the fifth day, he again went into status epilepticus and eventually died. Autopsy was not carried out (28). In another series of more than 50,000 HBO patient-treatments, 1 sudden death was reported in a 72-year-old man who presented respiratory arrest during his tenth HBO session (40). Autopsy was not performed. Hence, the incidence of sudden death during HBO therapy can be estimated at 1 per 50,000 to 1 per 100,000 patient-treatments. Two other cases of death during HBO have been reported: myocardial infarction in a 80-year-old woman and pulmonary edema in a patient with aortic stenosis (40). In these cases as well, a causal role of HBO is uncertain. With careful evaluation and screening of patients prior to HBO therapy, this treatment modality can be safely given to individuals with RON.

Dr. Lee is correct that questions remain regarding the natural history of RON, and no class 1 evidence exists regarding treatment. An international registry of RON cases should be created to expand and share our knowledge of the clinical profile of this visually devastating disorder.

**Rebuttal: Dr. Michael S. Lee**

The strongest argument for a benefit of HBO in RON depends upon a hypoxic environment in the absence of irreversible axonal loss. Yet, this pathophysiologic mechanism remains unproven. Dr. Borruat extrapolates from studies of HBO for radiation injury to nonneurologic tissues to RON. I agree that revascularization of hypoxic hypocellular irradiated tissues occurs in the mandible and its surrounding soft tissue, but I would caution against making this assumption in the anterior visual pathways. There is no definitive evidence that this happens in RON.

The data do not exist to support routine HBO in RON. While it is impressive that Dr. Borruat has successfully treated 3 of 5 patients with RON, these numbers are not sufficient to generate broad generalizations about the treatment. I would advocate for a controlled trial, but given the rarity of this disorder, this seems unlikely to happen.

**Acknowledgment**

Dr. Michael Lee thanks Dr. Tariq Bhatti for his assistance with the literature review.

**REFERENCES**


We report 12 aquaporin 4 antibody–positive patients (12% of seropositive Mayo Clinic patients identified since 2005) whose initial presenting symptom of neuromyelitis optica was intractable vomiting. The initial evaluation in 75% was gastroenterologic. Vomiting lasted a median of 4 weeks (range, 2 days to 80 weeks). Optic neuritis or transverse myelitis developed after vomiting onset in 11 patients (median interval, 11 weeks; range, 1–156 weeks). At last evaluation (median, 48 months after vomiting onset), 7 patients fulfilled neuromyelitis optica diagnostic criteria. Our clinical, pathologic and neuroimaging observations suggest the aquaporin 4–rich area postrema may be a first point of attack in neuromyelitis optica.

This is a very interesting description of 12 NMO-IgG–positive patients who presented with severe intractable vomiting at a median of 3 months prior to a first episode of optic neuritis or transverse myelitis. Extensive GI workups were negative. The authors postulate that this is caused by the involvement of the chemosensitive vomiting center in the area postrema since capillaries in this region lack tight endothelial junctions. It might serve as the portal for circulating NMO-IgG entry into the CNS.

Although this is a retrospective case series, it provides an important clinical observation that has not been described in typical demyelinating optic neuritis. In future, neuroophthalmologists who see patients presenting with severe vomiting prior to optic neuritis may have an insight into those who have NMO—prior to the lack of recovery or the frequent recurrence. This should allow earlier decision making for the appropriate treatment for an NMO spectrum disorder, which requires more aggressive immunosuppression than demyelinating disease.

—Mark L. Moster, MD

The authors make a compelling point with an autopsy showing loss of aquaporin 4 channels in the area postrema and another 4 MRIs showing abnormal signal there too. Interestingly, 8 of the 12 enjoyed spontaneous recovery of their intractable vomiting, which is very different than the recovery of optic neuritis and transverse myelitis with or without treatment. I have not observed intractable vomiting in patients with optic neuritis from NMO, but it is also something that I would not typically ask about especially since the median delay from vomiting to visual loss in this study was 3 months and in 1 case, more than 6 months. I will have a lower threshold to consider serologic testing if I get a hit on this historical clue.

—Michael S. Lee, MD


There has been growing interest in the use of retinal imaging for tracking disease progression in multiple sclerosis. However, systematic and detailed pathological descriptions of retinal tissue in multiple sclerosis are lacking. Graded histological evaluations on eyes of 82 patients with multiple sclerosis and 10 subjects with other neurological diseases, with immunohistochemistry on a subset, were performed and correlated with clinical and pathological findings. Multiple sclerosis cases demonstrated evidence of retinal atrophy and inflammation even in late-stage disease. Retinal ganglion cell loss was significant, and the remaining neurons appeared shrunken and were partially engulfed by human leukocyte antigen-DR–positive cells with the phenotype of microglia in samples subjected to immunohistochemistry. Neurofilament staining revealed variable but prominent degrees of axonal loss and injury. Neuronal loss was noted in the inner nuclear layer with focal reduction in cell density. Foamy-appearing human leukocyte antigen-DR–positive cells were evident near vessels, and perifoveitis was found in a small but significant number of multiple sclerosis cases. Glial fibrillary acidic protein staining showed extensive astrocytic hypertrophy and proliferation with prominent gliosis in multiple sclerosis cases. Frequent but previously unreported abnormalities in the iris were documented in the majority of chronic multiple sclerosis cases. The injury to both iris and retina could be seen at all stages of disease. Severity of retinal atrophy correlated with the overall brain weight at time of autopsy (P = 0.04), and a trend for increased atrophy was seen with longer disease duration (P = 0.13). This study provides the first large-scale pathological description of retinas in multiple sclerosis, including patients with different subtypes of disease at all stages and with variable clinical
To describe 2 unrelated patients with novel Detailed clinical and laboratory Both patients subsequently developed bilateral Clinicians should be aware of the existence of Case report. Ragged red fibers and multiple deletions of mi-

of retinal pathology may aid us in understanding the Deciphering the relationships between the different types alogrithms to judge axon loss in the nerve fiber layer. standard techniques exploit presumed differences in tis-

nence to utilize automated edge detection al-

Deciphering the relationships between the different types of retinal pathology may aid us in understanding the factors that drive both inflammation and tissue atrophy in multiple sclerosis.

This is the largest description of ocular pathology in MS to date. As expected, retinal nerve fiber layer (RNFL) and retinal ganglion cell layer (RGC) atrophy and decreased RGC density were common and prominent. However, inner nuclear layer (INL, horizontal and bipolar cells) atro-

rophy was seen in 40% of cases, most common in long-

standing and progressive disease. The authors offer 3 possible explanations including that the INL may be a target of the immune process and may share a susceptibility to the neurodegenerative process, or that it represents retrograde transneuronal degeneration. The latter makes the most sense, since RGC loss was more pronounced than INL, no acute MS cases had INL loss, and no inflammatory cells were found in the INL.

Inflammatory retinal periphlebitis was seen in 29%, independent of disease duration, including secondary pro-

gressive MS. Scattered mononuclear inflammatory cells were also seen in the RNFL and RGCL in 12%.

A surprise was prominent iris involvement in 72% of MS patients—findings included rubecosis iridis, evasion of pigmented layer, and stromal inflammation, sometimes with anterior uveitis. The authors postulate either a direct inflammatory response or a response to a “distressed retina.”

Limitations of the study include a control group consist-

ing of only 10 cases, mainly with peripheral neuropathy. Perhaps, evaluation of other CNS diseases as controls would show that some of these retinal changes are nonspecific correlates of CNS disease. The lack of exhaustive clinical information (eg, coexisting glaucoma or other diseases) also may create bias in this study.

The strength of the study is that almost all cases were obtained prior to availability of immunomodulatory ther-

apies and therefore reflect the natural course of the disease. Additionally, 2 pathologists reviewed the slides in a masked fashion, not knowing the small size of the control group.

The findings of inflammatory and degenerative features in RRMS and SPMS at all stages of disease suggest that both of these processes may play a role during the entire course of MS.

—I wish the authors had divided up the iris findings instead of lumping rubecosis, pigment evasion, and stromal inflammation together. To me, these are very different. I agree with Dr. Moster that it is very surprising how uncommon it is to see these anterior segment findings clinically given the high proportion seen histopathologically. I think it would be fascinating to repeat this study on a group of MS patients treated in the immunomodulatory era and determine if the frequency or severity of pathologic findings improves.

—Michael S. Lee, MD


Objective: To describe 2 unrelated patients with novel variations in the POLG1 gene and features undistinguishable from multiple sclerosis, that is, optic neuritis, brain white matter hyperintense areas, and unmatched cerebrospinal fluid oligoclonal bands.

Design: Case report.

Setting: University hospital.

Patients: Both patients subsequently developed bilateral ophthalmoplegia, ptosis, myopathy, cardiomyopathy, ataxia, dysphagia, and hearing and cognitive impairment.

Main Outcome Measures: Detailed clinical and laboratory examinations including brain MRI, morphological analysis of a muscle biopsy, characterization of mitochondrial DNA integrity, sequencing of the POLG1 gene, and screening of control subjects for POLG1 sequence variants.

Results: Ragged red fibers and multiple deletions of mitochondrial DNA were detected in the skeletal muscle. Four compound heterozygous variations, including 3 previously unreported, were identified in POLG1.

Conclusion: Clinicians should be aware of the existence of POLG1-related multiple sclerosis–like illness, as it has important implications on management, treatment, and genetic counseling.

In an era of earlier and more aggressive treatment of MS and clinically isolated syndromes, this article raises a “red flag.” It describes 2 patients with POLG1 mutations who presented with a clinical picture of optic neuritis, MRI with white matter lesions, and oligoclonal bands in the CSF, quite typical for MS. It was only after many years and a more typical clinical progression for a POLG1 mutation (ophthalmoplegia, ptosis, ataxia, myopathy, depression, hearing loss, dysphagia, cognitive impairment, and cardiomyopathy) that the correct diagnosis was pursued. Both were treated with steroids initially for MS. Had they presented today, they may have been given immunomodulating agents for MS, likely not the correct treatment.

This report adds to a growing list of MS mimickers, including other mitochondrial disorders, such as LHON.
Prior to prescribing immunomodulating agents, one must at least consider these other possibilities.

—Mark L. Moster, MD

The clinical description in the article notes only “blurred vision” in 1 eye and “bilateral increased P100 latency” on VEP testing for both patients. As we all know that story alone does not equal optic neuritis. There is also no comment on the MRI of the optic nerve. Likely, if we put the screws to them, these patients did not have a story or clinical findings consistent with optic neuritis. That being said, I can see how the white matter lesions on MRI could have led to a lumbar puncture, which led to oligoclonal banding and a misdiagnosis of MS.

—Michael S. Lee, MD

I agree there is not a lot of detail provided on the blurred vision in these patients—onset, course, duration, pain, and the like. However, one was a 30-year-old man and the second a 37-year-old woman and both had white matter abnormalities on MRI, oligoclonal bands in the CSF, and were diagnosed by university neurologists as optic neuritis.

—Mark L. Moster, MD

...Which may tell us something about university neurologists! =)

—Michael S. Lee, MD


Background: Benign essential blepharospasm (BEB) is a common form of focal dystonia. Besides pathology in the basal ganglia, accumulating evidence suggests pathologic changes in the anterior cingulate cortex (ACC).

Methods: This is a randomized, sham-controlled, observer-blinded, prospective study. In 12 patients with BEB, we evaluated the effects of a 15-minute session of low-frequency (0.2 Hz) repetitive transcranial magnetic stimulation (rTMS) over the ACC with stimulation intensities at 100% active motor threshold with 3 stimulation coils: a conventional circular coil (C-coil), a sham coil (S-coil), and a Hesed coil (H-coil), which stimulates deeper brain structures, and 3) S-coil or sham therapy. Patients evaluated subjective improvement and a masked evaluator objectively graded videos before, immediately after, and 1 hour following rTMS. The S-coil showed no benefit, but both the H- and the C-coil showed a similar benefit subjectively and objectively. The authors anticipated a large difference between rTMS and sham TMS and calculated a small study sample. Botulinum toxin injections can be painful, but they can last for 2–4 months. RTMS is not painful but it lasts approximately 1 hour. The authors comment that perhaps modifying the duration or frequency could improve treatment duration, but I don’t see that happening with only an hour of improvement. It seems to me that a constant portable stimulator would need to be developed. Deep brain stimulator implants placed in the globus pallidus internus in patients with Meige syndrome have shown improvement (1). So, I also talked to a neurosurgeon who does deep brain stimulator implants who said that these could be placed in the ACC. Obviously, it would have to be a pretty debilitated patient who has failed botulinum toxin and orbicularis myectomy to even consider going there.

—Michael S. Lee, MD

Alternative treatments to botulinum toxin injections for blepharospasm are very important, particularly for patients refractory to treatment. This preliminary study shows promising results and must be further investigated. I wouldn’t take the 1-hour response as a negative as Dr. Lee does—patients with rTMS for other conditions (eg, dystonia, depression) have had a course of multiple treatments over days to weeks followed by up months to years of benefit on occasion (2,3). Presumably, there is some plasticity in the system that can be modified by this technique. I think these preliminary results are promising.

—Mark L. Moster, MD

Thanks for pointing out the rTMS article in movement disorders (2). I was not aware of this. I just read it and the active motor threshold was significantly lower for the H-coil compared to the other 2 coils.

Conclusions: rTMS could be used as a therapeutic tool in BEB. Further studies will be necessary to show whether repeated stimulation applications result in lasting clinical effects.

Classification of evidence: This study provides Class II evidence that for patients with BEB, H- and C-coil rTMS is safe and improves clinical symptoms of BEB immediately and 1 hour after stimulation.

Functional imaging studies show increased excitability in the anterior cingulate cortex (ACC) among patients with benign essential blepharospasm (BEB). Each patient in this study underwent 3 sessions of repetitive transcranial magnetic stimulation (rTMS) for 15 minutes using different coils: 1) Standard C-coil, 2) H-coil, which stimulates deeper brain structures, and 3) S-coil or sham therapy. Patients evaluated subjective improvement and a masked evaluator objectively graded videos before, immediately after, and 1 hour following rTMS. The S-coil showed no benefit, but both the H- and the C-coil showed a similar benefit subjectively and objectively.

The authors anticipated a large difference between rTMS and sham TMS and calculated a small study sample. Botulinum toxin injections can be painful, but they can last for 2–4 months. RTMS is not painful but it lasts approximately 1 hour. The authors comment that perhaps modifying the duration or frequency could improve treatment duration, but I don’t see that happening with only an hour of improvement. It seems to me that a constant portable stimulator would need to be developed. Deep brain stimulator implants placed in the globus pallidus internus in patients with Meige syndrome have shown improvement (1). So, I also talked to a neurosurgeon who does deep brain stimulator implants who said that these could be placed in the ACC. Obviously, it would have to be a pretty debilitated patient who has failed botulinum toxin and orbicularis myectomy to even consider going there.

—Michael S. Lee, MD

—Mark L. Moster, MD
authors found that the rTMS effect can last up to a few months, but that the effect was subtherapeutic. Also, daily stimulation for weeks is a large burden on patients who can enjoy months of benefit using botulinum toxin A. Finally, the biggest benefit in the rTMS in movement disorders was observed with the highest stimulation intensities. These intensities come with scalp tingling and most likely the patients were not masked to the sham therapy. So, I am still a bit pessimistic for rTMS as an alternative to botulinum toxin A in the treatment of blepharospasm.

——Michael S. Lee, MD


No abstract.

The authors recorded opening pressures on pediatric patients over a 2-year period. None of the patients had papilledema, hydrocephalus, meningitis, or used diuretics. Opening pressures were obtained in the lateral decubitus position. A total of 197 patients were enrolled. The normal distribution of opening pressures based on the 10th to the 90th percentile was 11.5–28.0 cm H₂O. Sedatives and BMI increased the opening pressure slightly. A post hoc analysis of 52 nonobese patients who received minimal or no sedation resulted in a 90th percentile of 25 cm H₂O. The authors conclude that a normal opening pressure in children is 28 cm H₂O or less. This is a surprising outcome given the typical opening pressure in adults is thought to be less than 20 cm and a previous article had suggested 18 cm as the upper limit of normal in children younger than 8 years (1).

Recently, I had a 13-year-old patient with optic disc drusen mistaken as papilledema. Her opening pressures were 27 cm and 29 cm. She had some mild arcuate defects bilaterally. This article supported the idea that this pressure may be normal for her. On the other hand, if I saw another child with obvious bilateral optic disc edema and an opening pressure of 25 cm, I would not have any trouble with the fact that the pressure is too high for her.

——Michael S. Lee, MD

I agree with Dr. Lee. This study is helpful in clinical practice and reassures us that an ICP in the 20s may be normal in children and allows a slightly higher reading for an increased BMI and sedation. Next, we need a study of normal ICP in the prone position, since increasingly our patients are having LPs under fluoroscopy by radiologists.

——Mark L. Moster, MD


Background: Fingolimod (FTY720), a sphingosine-1-phosphate receptor modulator that prevents lymphocyte egress from lymph nodes, showed clinical efficacy and improvement on imaging in a phase 2 study involving patients with multiple sclerosis.

Methods: In this 12-month, double-blind, double-dummy study, we randomly assigned 1,292 patients with relapsing-remitting multiple sclerosis who had a recent history of at least 1 relapse to receive either oral fingolimod at a daily dose of either 1.25 or 0.5 mg or intramuscular interferon beta-1a (an established therapy for multiple sclerosis) at a weekly dose of 30 μg. The primary endpoint was the annualized relapse rate. Key secondary endpoints were the number of new or enlarged lesions on T(2)-weighted MRI scans at 12 months and progression of disability that was sustained for at least 3 months.

Results: A total of 1,153 patients (89%) completed the study. The annualized relapse rate was significantly lower in both groups receiving fingolimod—0.20 (95% confidence interval [CI], 0.16–0.26) in the 1.25-mg group and 0.16 (95% CI, 0.12–0.21) in the 0.5-mg group—than in the interferon group (0.33; 95% CI, 0.26–0.42; P < 0.001 for both comparisons). MRI findings supported the primary results. No significant differences were seen among the study groups with respect to progression of disability. Two fatal infections occurred in the group that received the 1.25-mg dose of fingolimod: disseminated primary varicella zoster and herpes simplex encephalitis. Other adverse events among patients receiving fingolimod were nonfatal herpes virus infections, bradycardia and atrioventricular block, hypertension, macular edema, skin cancer, and elevated liver-enzyme levels.

Conclusions: This trial showed the superior efficacy of oral fingolimod with respect to relapse rates and MRI outcomes in patients with multiple sclerosis, as compared with intramuscular interferon beta-1a. Longer studies are needed to assess the safety and efficacy of treatment beyond 1 year. (ClinicalTrials.gov number, NCT00340834.)
The FDA granted approval for oral fingolimod in the treatment of relapsing remitting MS in September 2010. In this study, known as TRANSFORMS (the Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing–Remitting Multiple Sclerosis), 1,153 RRMS patients were randomized to receive either oral fingolimod at 1.25 or 0.5 mg or intramuscular interferon beta-1a at a weekly dose of 30 μg for 12 months. There was a significantly lower relapse rate and significantly fewer new or enlarged white matter lesions in both fingolimod groups compared to the interferon group.

The cost of fingolimod is almost twice that of interferon beta-1a, which isn’t that cheap to begin with. However, fingolimod appears to be a better treatment and it is much easier to administer. I could envision a trial of optic neuritis patients (CIS) receiving oral fingolimod vs. oral placebo or injectable immunomodulating agents for the prevention of MS. I am hoping that the long-term safety data show good results.

―― Michael S. Lee, MD

With the approval of the first oral immunomodulating agent, a new era in MS treatment begins: one that is more exciting and more complicated. Although this study showed better efficacy with fingolimod than with weekly interferon beta-1a, it was only 1 year in length, and therefore, longer studies will be necessary to demonstrate safety, particularly for the immune-related toxicities of infection and tumors. A special role neuro-ophthalmologists will play is in the assessment of patients for macular edema, which occurred in 1% of the high-dose group and 0.5% with the lower dose (FDA approved dose).

― Mark L. Moster, MD
Orbital Involvement in Bing-Neel Syndrome

We read the article “Orbital Involvement in Bing-Neel Syndrome” by Stacy et al (1) with great interest and commend the authors for their excellent discussion of the manifestations of Waldenström macroglobulinemia (WM) in the orbit and brain. We had the opportunity recently to see a similar patient with WM and diffuse orbital involvement whose clinical course demonstrates that the visual outcome in these patients may be poor despite aggressive therapy.

A 57-year-old man was referred to a retina specialist with a 3-week history of progressive, painless, bilateral visual loss. His medical history was significant for WM diagnosed 9 years previously, for which he was treated with 5 cycles of cyclophosphamide, rituximab, and prednisone, most recently 1 year prior to presentation. On examination, visual acuity was 20/160, right eye, and 20/32, left eye. Anterior segments were quiet, eye movements were full, and there was no proptosis. Dilated fundus examination revealed bilateral optic disc edema greater in the right eye than in the left eye, with a normal appearance of the retinal vessels, macula, and periphery. Fluorescein angiography showed leakage and staining of the optic discs.

Infiltrative optic neuropathy was suspected, and he was started on oral prednisone 80 mg daily and referred immediately to his oncologist. MRI of the orbits revealed enhancement of the orbital fat and optic nerves (Fig. 1). Serum IgM was elevated at 1,350 mg/dL (range, 40–230 mg/dL). Chemotherapy with cyclophosphamide, vincristine, prednisone, and rituximab was initiated. However, vision declined to hand motions, right eye and 20/50, left eye, within 3 weeks of initial presentation. A right orbital biopsy was performed, and histopathologic examination revealed fibroadipose tissue with patchy aggregates of small lymphocytes, scattered plasma cells, and histiocytes. Immunoperoxidase staining of the lymphocytes was positive for CD20, CD79a, and CD138 and negative for CD23, CD5, CD10, and BCL-1. These matched markers from the patient’s previous bone marrow biopsies, confirming orbital infiltration of WM.

The patient was hospitalized for intravenous infusion of high-dose methotrexate and intrathecal cytarabine. A lumbar puncture yielded lymphocytes in insufficient number for flow cytometry. The patient received external beam orbital radiation therapy in 18 fractions for a total dose of 30.6 Gy. Despite treatment, the patient’s vision declined to no light perception in each eye.

Stacy et al (1) noted that other than slight resistance to retropulsion, their patient’s external examination gave no hint of the diffuse infiltration of the orbital fat and optic nerves by malignant cells found on neuroimaging and confirmed with orbital biopsy. They suggested the absence of proptosis could be explained by an almost equal replacement of fat by tumor. Similarly, except for bilateral optic disc edema and progressive visual loss, our patient’s clinical examination offered no clues to the extent of the orbital and optic nerve involvement found on MRI.

Our case differed somewhat in that severe visual loss occurred early and progressed rapidly to complete bilateral blindness despite aggressive therapy. In addition, our patient’s MRI demonstrated involvement of the extraocular muscles. That such diffuse infiltration of orbital tissue can

FIG. 1. Contrast-enhanced axial (A) and coronal (B) fat-suppressed T1 orbital MRI scans show patchy enhancement of orbital fat, enlargement of the extraocular muscles, and thickening and enhancement of the orbital segments of the optic nerves.
occur without proptosis or orbital congestion, and with preservation of eye movements, is striking.

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REFERENCE

Idiopathic Intracranial Hypertension With Dan and Beyond: The 2010 Jacobson Lecture

A historical note apropos of Quincke:

In her masterly review of idiopathic intracranial hypertension (1), Friedman stated that Quincke described the lumbar puncture more than 100 years ago yet refers to his report on meningitis serosa (2), the terminological forerunner of idiopathic intracranial hypertension (3). In his 1891 articles that Quincke introduced the lumbar puncture (4,5).

Felix Tyndel, MD, FRCPC
Division of Neurology, University of Toronto
Toronto, Ontario, Canada
f.tyndel@utoronto.ca

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Cup-to-Disc Ratio in Patients With Idiopathic Intracranial Hypertension Is Smaller Than in Normal Subjects?

We read with interest the article by Geddie et al (1) that might better have been titled “Cup-to-Disc Ratio in Patients With IIH and Frisén Grade 0-2 Is Smaller Than in Normal Subjects.”

The authors should be commended for tackling a difficult and complicated study. There are a variety of obstacles with a study like this, but a main one is the inclusion of cases with optic disc edema. The authors state that grade 0–2 is minimal or resolved optic disc edema. Frisén Grade 2 can be mild or moderate but is usually not minimal edema.

To test the hypothesis that there is no difference in the vertical cup-to-disc ratio between idiopathic intracranial hypertension (IIH) patients and normal controls, we analyzed data from our prospective study of 50 IIH patients (2). It is well known that as optic disc edema progresses, the optic cup fills in (3). So, in our analysis, we included only Frisén grade 0 papilledema. Twenty-one of our IIH patients had grade 0 optic disc edema at their final visit. The average cup size was 0.191 ± 0.14 in the right eye and 0.187 ± 0.13 in the left eye. This compares to the results of Geddie et al of 0.143 in the right eye and 0.127 in the left eye.

Another issue is that differences in cup size relate to the grading process itself. This is more subjective than it appears. The grader (B.E.G.) only graded papilledema eyes. No controls were intermixed. Was the grader aware of the hypothesis being tested? If so, could this have influenced the results? It would appear necessary in a study like this for masked graders to evaluate intermixed controls and these values be used rather than controls graded by others.

Another confounding factor is that it has been our experience that some swollen optic discs never completely defervesce following treatment for IIH, even when they are...
technically grade 0. The mechanism may be either similar to skin not returning to normal after prolonged stretching or the effect of the presence of intermittent, prolonged, mild, increased intracranial pressure. This mechanism, we believe, can also result in a smaller optic cup appearance in IIH.

In our opinion, the study of Geddie et al does not adequately demonstrate that cup-to-disc ratio is smaller in IIH patients. As stated above, this is a complicated and difficult study to undertake. Ideally, one would want to grade optic disc photographs taken before the onset of IIH. Given that this is not realistic, we urge the authors to reanalyze their data set as follows:

1. Grade a large number of intermixed normal controls with proportions intermixed to reflect racial differences in cup size.
2. Use 3 graders masked to the diagnosis and take the mean of the measures.
3. Limit the analysis to grade 0 optic disc edema, where the disc does not appear elevated on stereoscopic fundus photographs.

If this is performed and their results are the same, we would have more confidence in their title and conclusions.

Michael Wall, MD
James J. Corbett, MD
Department of Neurology
College of Medicine, University of Iowa
Iowa City, Iowa
michael-wall@uiowa.edu

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This large multiauthored newly introduced companion volume to Adler's Physiology of the Eye correlates basic science and clinical management of ophthalmic disorders and covers all areas of disease in ophthalmology, including retina, cornea, cataract, glaucoma, and uveitis. The Neuro-Ophthalmology section includes optic neuritis, abnormal ocular motor control, idiopathic intracranial hypertension, giant cell arteritis, ischemic optic neuropathy, optic nerve axonal injury, Leber's hereditary optic neuropathy, optic atrophy, nystagmus, and toxic optic neuropathies.

The book is beautifully illustrated with the liberal use of color with 330 full-color line artwork, tables, clinical photographs, and schematics.

This book includes access to the fully searchable text online at expertconsult.com, along with images and references.

**Optic Nerve Disorders: Diagnosis and Management**

Jane W. Chan.

Referenced

**Intended audience:** Ophthalmologists, neuro-ophthalmologists, neurologists, residents, and fellows.

This multiauthored book (all but 2 chapters written by Dr. Chan) focuses on optic nerve disorders commonly encountered in a neuro-ophthalmologic clinic. Updated information on diagnostic techniques, including OCT, PET, SPECT, diffusion-weighted imaging, electrophysiology testing, and genetic testing for hereditary optic neuropathies, are discussed. Chapters include optic neuritis, ischemic optic neuropathies, papilledema, compressive and infiltrative optic neuropathies, traumatic optic neuropathies, nutritional and toxic neuropathies, hereditary optic neuropathies, congenital disc anomalies, optic disc tumors, optical coherence tomography in optic nerve disorders, and the use of multifocal electroretinograms and visual evoked potentials in diagnosing optic nerve disorders. Multiple color illustrations and tables complement this user-friendly practical reference.
Research in Neuro-Ophthalmology: Update on NORDIC and the IIHTT

On February 6, 2009, the Neuro-Ophthalmology Research Disease Investigator Consortium (NORDIC) was officially established. Its mission, organizational structure, requirements, and announcement of the first clinical trial were detailed in the Journal of Neuro-Ophthalmology (1). Significantly, NORDIC is funded for 5 years through a National Eye Institute (NEI) U10 mechanism. Although NORDIC was originally developed through the efforts of the members of the North American Neuro-Ophthalmology Society (NANOS), NORDIC is independent of NANOS and NORDIC investigators are not required to be members of NANOS. For further information about NORDIC and the requirements of investigators, please consult the NORDIC Web site: www.nordicclinicaltrials.com. The purpose of this report is to detail the progress of the first prospective, placebo-controlled, randomized clinical trial under the NORDIC umbrella: the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT).

What is the IIHTT?

The IIHTT was developed by the study director, Michael Wall, MD, and the IIHTT steering committee, along with the chair of the NORDIC executive committee, Mark Kupersmith, MD. The purpose of the IIHTT is 1) to determine if acetazolamide provides additional benefit to a low-sodium weight-reduction diet in reducing visual loss in patients with IIH associated with a mildly decreased mean deviation on automated perimetry. Secondary endpoints for the study include papilledema grade, multiple visual field parameters, and quality-of-life measures, and 2) to identify proteomic and genetic risk factors for IIH patients and controls. In particular, an attempt will be made to determine the pathogenesis of IIH, particularly as it relates to obesity or at least being overweight. A data coordination and biostatistics center (DCBC) functions as a resource for study investigators and as a central repository for database control and management. Centralized reading centers have been set up to evaluate tests of visual function as well as OCT and fundus photographic images. Patients will be followed for 4 years.

What is the current status of the IIHTT?

At the present time, 43 centers are participants in the IIHTT and currently are prepared to enroll patients (Fig. 1).

FIG. 1. IIHTT trial sites.
The study plans to enroll a total of 152 subjects and controls. Participating sites can be found on the following Web site: http://www.nordicclinicaltrials.com/Pages/CurrentResearchIIHTT.aspx. These sites received approval to conduct the study under their local institutional review board and have received certification for individuals participating in data collection (ophthalmic technicians, visual field technicians, and photographers). As of November 1, 2010, 16 subjects and 1 control had been enrolled in this study.

What are the enrollment criteria for potential subjects?

To be included in the IIHTT, potential subjects must be referred to a participating center in a timely way in order to determine eligibility. The following summarizes the inclusion criteria:

1. Meets the modified Dandy criteria for IIH
2. Perimetric mean deviation of −2 to −5 dB
3. Diagnosis of IIH was made within 6 weeks of study entry
4. Subject has received treatment for IIH for less than 1 week
5. Subject has bilateral optic disc edema
6. Patient must be willing to comply with the study protocol and be randomized to either acetazolamide or placebo in addition to the dietary changes.

It is preferable to refer a potential subject for evaluation prior to the lumbar puncture in order to be able to obtain CSF for additional testing.

Why might patients be willing to enter the study?

In addition to the typical reasons that patients may enter clinical trials, all enrolled subjects will receive access to individual counseling and a formalized weight loss regimen through the New York Obesity Research Organization. This organization has a waiting list for patients and is highly regarded. The majority of individuals who have IIH are obese or at least overweight and may obtain benefit from participating in this program, which includes dietary changes and monitoring, physical activity as measured with a pedometer, and behavioral changes. Counseling is provided through a weekly telephone appointment.

If I am not a NORDIC site, how can I refer patients for the IIHTT trial?

Information can be found at the IIHTT Web site http://www.nordicclinicaltrials.com/Pages/CurrentResearchIIHTT.aspx or you can contact either the individual site or NORDIC headquarters by telephone: 212-636-3516 or by e-mail: info@nordicclinicaltrials.com.

Are there NORDIC studies or trials other than the IIHTT?

NORDIC seeks to initiate other prospective clinical trials and is in the process of reviewing potential new studies; however, at the present time, the IIHTT is the only study or trial being performed by NORDIC members.

How are new studies developed?

NORDIC is always interested in new proposals for the consideration of future clinical studies and trials. Each study ideally should be hypothesis driven, have clinical and scientific underpinnings, tackle an important health issue, and have measurable outcome measures.

Anyone who has an idea for new research should access the project proposal template on the Web site at: http://www.nordicclinicaltrials.com/Pages/default.aspx. The proposal should include the objectives and rationale for the project as well as a brief synopsis. Once a project proposal is submitted, the NORDIC New Project Proposal Review Committee (NPPRC) will evaluate the proposal and make a recommendation for approval or disapproval to the NORDIC Executive Committee. If the study is approved by the NORDIC Executive Committee, the project will be developed in conjunction with NORDIC. Further details and requirements were previously published (1).

Lynn K. Gordon, MD, PhD
Neil R. Miller, MD

on behalf of NORDIC (Neuro-Ophthalmology Research Disease Investigator Consortium)

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