AUTOIMMUNE/INFLAMMATORY OPTIC NEUROPATHIES

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LEARNING OBJECTIVES

1. To recognize features of neuromyelitis optica; similarities and differences from typical demyelinating optic neuritis.
2. To understand manifestations of optic neuropathy in systemic lupus erythematosus and other systemic autoimmune diseases.
3. To consider overlapping presentations of granulomatous inflammatory optic neuropathies that mimic optic neuritis.
4. To examine potential underlying mechanisms of inflammatory optic neuropathies.

CME QUESTIONS

1. How does vision loss present in neuromyelitis optica and how does it compare to typical demyelinating optic neuritis?
2. What are three types of optic neuropathy that have been associated with systemic lupus erythematosus?
3. What are three types of optic nerve involvement seen in sarcoidosis?

KEYWORDS

1. Autoimmune Optic Neuropathy
2. Neuromyelitis Optica
3. Inflammatory Optic Neuropathy

INTRODUCTION

Inflammatory, demyelinating optic neuritis is one of the most common optic neuropathies in young adults. It occurs idio pathically, or in association with multiple sclerosis, and follows a typical course of progressing visual dysfunction often with pain for one – two weeks, followed by significant resolution over the next few weeks. Due to the characteristic presentation and frequency of this presumably autoimmune process, optic neuritis is often high on the differential diagnosis for patients presenting with optic neuropathy. However, it is important to recognize that a number of other autoimmune disorders and systemic or localized inflammatory processes can also present with an optic neuropathy. While the presenting signs and symptoms often are distinct from typical inflammatory demyelinating optic neuritis, patients can present with very similar findings that may make diagnosis difficult. Here, the distinct features and etiologies of other autoimmune/inflammatory optic neuropathies (the zebras) are discussed, including neuromyelitis optica, systemic autoimmune diseases such as systemic lupus erythematosus, idiopathic orbital inflammatory syndrome with optic perineuritis, and sarcoid optic neuropathy. Potential overlapping features, as well as underlying etiologies, are examined.

NEUROMYE LITIS OPTICA

Neuromyelitis optica (NMO; also referred to as Devic disease), like multiple sclerosis and idiopathic optic neuritis, is characterized by inflammation and demyelination (Wingerchuk et al, 1999; Galetta and Bennett, 2007; Merle et al, 2007), along with loss of retinal ganglion cell axons (de Seze et al, 2008). Classically, NMO has been characterized as a severe demyelinating disease affecting the spinal cord and optic nerves, but sparing the brain. However, more recent descriptions and attempts to develop diagnostic guidelines for this disorder have suggested that some brain lesions can also be present in NMO (Wingerchuk et al, 2006).

NMO frequently presents with bilateral and severe optic nerve dysfunction (Merle et al, 2007), unlike the unilateral, variable severity commonly found in typical demyelinating optic neuritis (Arnold, 2005). The pain on eye movements that is almost always present in typical demyelinating optic neuritis is less common in NMO, although other features may overlap, including the presence or absence of disc swelling. Visual function does not always recover as well in NMO, but can occur, and recurrent episodes of optic nerve inflammation can be frequent. Many patients exhibit signs and symptoms of spinal cord dysfunction within several weeks of, before or after, the onset of visual loss (Merle et al, 2007). Like multiple sclerosis, NMO most commonly affects young adults, but also presents in childhood (Wingerchuk et al, 1999).

While NMO and multiple sclerosis share many common characteristics, some histopathologic differences have been noted, and it remains debated whether NMO represents a subtype of multiple sclerosis, or is a distinct disorder (Galetta and Bennett, 2007). The identification of an autoantibody that recognizes the aquaporin-4 channel that plays a role in fluid regulation across the blood-brain barrier (Lennon et
The identification of the NMO antibody as a potential disease marker (Weinshenker and Wingerchuk, 2008), although most reports continue to represent single case reports or small series, and it remains unclear if patients have one underlying autoimmune disorder with overlapping features of both, or two distinct processes in a patient susceptible to autoimmune diseases (Jarius et al, 2011).

Even for patients that present with what appears to be typical demyelinating optic neuritis, the visual prognosis is worse if they already carry a diagnosis of SLE or are later found to have SLE (Lin et al, 2009).

Optic neuropathies have also been observed in patients with other systemic autoimmune disorders such as Sjogren’s syndrome (Bejot et al, 2008), and similar to SLE, antibody testing has identified optic neuropathy patients with markers of both Sjogren’s and NMO (Jarius et al, 2011). Some patients present signs of optic neuropathy that mimic optic neuritis, but a follow a course more consistent with SLE associated optic neuropathy with less than expected spontaneous visual recovery, even though a specific underlying autoimmune diagnosis is not always found (Dutton et al, 1982; Kupersmith et al, 1988). These patients may respond to corticosteroids, and often have recurrences, suggestive of a potential autoimmune etiology. The underlying etiology of the optic neuropathy is likely variable, with autoimmune antibodies directly recognizing optic nerve antigens in only some case. Other cases may represent ischemia secondary to a hypercoaguable, as can be seen in the antiphospholipid antibody syndrome in SLE, or from vasculitis, as suggested by the presence of perivascular infiltrates and immune complex deposition in skin biopsies (Kupersmith et al, 1988; Riedel et al, 1998). Search for an underlying autoimmune disorder should be considered in optic neuropathies that fail to improve after steroid therapy, and in suspected cases, antibody testing for ANA and NMO antibodies should be considered, and skin biopsy for signs of vasculitis may be useful.

OPTIC NEUROPATHIES IN GRANULOMATOUS INFLAMMATORY DISEASE

SARCOIDOSIS

Sarcoidosis is a systemic disorder characterized by noncaseating epitheliod cell granulomas (Iannuzzi et al, 2007). Granulomatous lesions can occur in just about every organ, with pulmonary involvement, in about 90% of patients, being the most common manifestation. Inflammation affects the eyes in about 25% of sarcoid patients (Jabs and Johns, 1986), most commonly with anterior uveitis, but also conjunctival granulomas also occur, and posterior inflammation can be found in the form of vitritis, retinal vasculitis, or choroidal lesions.

Sarcoidosis only affects the central nervous system in about 5% of cases (Stern et al, 1985). Optic nerve involvement occurs infrequently, but can take several forms (Ing et

1. Mimicking typical demyelinating optic neuritis with or without mild disc swelling
2. Optic perineuritis
3. Granulomas of the optic nerve head
4. Disc swelling or atrophy from granulomatous thickening of the optic nerve sheath mimicking a compressive optic neuropathy from meningoia or glioma

Some presentations, such as visible granulomas of the optic nerve head, immediately raise suspicion for sarcoidosis, but frequently diagnosis may be delayed until a patient fails to follow an expected course for optic neuritis or when MR imaging shows an unexpected appearance such as marked thickening with mass features similar to meningoia or glioma. In rare cases, sarcoid optic neuropathy can remit spontaneously (Galetta et al, 1989), similar to idiopathic demyelinating optic neuritis, making this entity even harder to distinguish. Evaluation for granulomas elsewhere in the body, particularly the chest, can be useful for establishing the diagnosis, and serum levels of angiotensin converting enzyme are often elevated. Ideally, biopsy of tissue with an identifiable lesion is the best way to confirm the diagnosis. Bronchoscopy is frequently performed, but biopsy of conjunctival or lacrimal gland lesions can also be useful.

Sarcoid inflammation often responds rapidly to corticosteroid therapy, although continued treatment for several months may be needed for full treatment and to reduce the risk of recurrence. Some patients require chronic treatment, and steroid-sparing agents should be considered (Katz et al, 2003; Maust et al, 2003), while other patients may be refractory to steroid therapy.

IDIOPATHIC ORBITAL INFLAMMATORY SYNDROME

Idiopathic orbital inflammatory syndrome (IOIS) can present with either focal or diffuse orbital inflammation consisting of a mixed nonspecific chronic inflammation that is often granulomatous (Jacobs and Galetta, 2002; Gordon, 2006). Presenting signs and symptoms, including pain, proptosis, redness, periorbital edema, diplopia, or decreased vision, vary depending on which orbital structures are involved. Myositis, posterior scleritis, dacryocystitis, optic perineuritis, or diffuse orbital inflammation can all be seen.

Optic perineuritis typically presents bilaterally with pain, mild disc swelling, and decreased vision that may spare central fixation (Margo et al, 1989; Purvin et al, 2001). MRI shows specific enhancement of the optic nerve sheath with relatively little or no enhancement of the nerve itself. Optic perineuritis can occur in the setting of a systemic inflammatory disease, such as sarcoidosis, and can occur simultaneously with other areas of the orbit affected by IOIS such as myositis or posterior scleritis. Isolated optic perineuritis also occurs, and may represent a localized form IOIS. As perineuritis is often bilateral and can spare central vision, it can sometimes be difficult to distinguish from papilledema, and lumbar puncture may be necessary to rule out increased intracranial pressure. CSF may demonstrate a mild pleocytosis. Treatment for optic perineuritis, as for other forms of IOIS, is high dose corticosteroids. Patients typically respond rapidly, but a slow taper is recommended to reduce the risk of recurrence.

UNDERSTANDING MECHANISMS OF INFLAMMATORY OPTIC NEUROPATHIES

As described above, there are many shared, as well as distinct, features observed between typical inflammatory demyelinating optic neuritis and inflammatory optic neuropathies associated with other disorders. Identifying the underlying mechanisms mediating these optic neuropathies, including the type of inflammation present, the site of injury, and molecular signalling pathways that mediate pathologic changes, may help the clinician understand why different clinical phenotypes are observed, and will likely help lead to the development of disease-specific therapies as well as treatments that are effective in multiple conditions. Both human studies, and studies using animal models, help increase our understanding of optic nerve and CNS inflammatory diseases.

Multiple sclerosis, including demyelinating optic neuritis that occurs in multiple sclerosis patients, consists of a complex immune response involving most cell types of the immune system (Noseworthy et al, 2000). A particularly important role has been implicated for autoreactive T cells in mediating multiple sclerosis, with two subsets of T helper cells (Th1 and Th17) identified that can play a pathogenic role in the development of multiple sclerosis, or its most common animal model experimental autoimmune encephalomyelitis (EAE) (Axtell et al, 2011).

Examining the relative role of Th cell subsets in the context of treatment for various types of inflammatory diseases that present with optic neuropathy provides an important example of how therapies may be guided by our understanding of disease mechanisms. Interferon-beta is commonly used to treat relapsing-remitting multiple sclerosis; however, a significant number of patients fail to respond to interferon-beta (Rio et al, 2006). A recent study demonstrated that interferon-beta suppresses disease in a Th1 mediated EAE model, but actually exacerbates disease in a Th17 driven EAE model (Axtell et al, 2010). Correspondingly, the authors also show that high levels of IL-17F, a cytokine produced by Th17 cells, is present in multiple sclerosis patients that failed to respond to interferon-beta. Interestingly, Th17 cells play an important role in mediating other autoimmune disorders associated with optic neuropathy that do not respond to interferon-beta therapy, including NMO (Ishizu et al, 2005) and SLE (Shah et al, 2010). This may explain why interferon-beta has been known to exacerbate NMO (Shimizu et al, 2010; Palace et al, 2010), and highlights a need for understanding specific inflammatory...
mechanisms before choosing an immunomodulatory therapy. While exact protocols need to be examined, this type of evaluation raises the possibility of identifying which multiple sclerosis and high risk optic neuritis patients are most likely to respond to interferon-beta.

Unlike multiple sclerosis which is dependent on T cell autoimmunity, recent studies have demonstrated that the NMO antibodies that recognize aquaporin-4 are not merely markers of NMO, but rather play a pathogenic role in development of the disease (Bennett et al, 2009; Bradl et al, 2009; Kinoshita et al, 2009; Saadoun et al 2010). Monoclonal recombinant aquaporin-4-specific antibodies generated from immunoglobulins isolated from the cerebral spinal fluid of an NMO patient administered to rats with EAE are capable of converting the EAE into a disease with histopathologic features more consistent with NMO (Bennett et al, 2009). Similar conversion of EAE to an NMO phenotype occurs with injection of aquaporin-4-specific antibodies isolated from the sera of NMO patients (Bradl et al, 2009; Kinoshita et al, 2009). Furthermore, injection of aquaporin-4 antibodies in conjunction with human complement induces an NMO-like disease in mice even without a prior underlying inflammatory disease (Saadoun et al, 2010). These animal studies confirm a pathogenic role of the NMO antibodies, and suggest that future therapies may be guided toward regulating aquaporin-4.

Specific studies examining animal models of optic neuritis provide further insight into the variability of inflammatory diseases that can present with similar histopathologic features. A high incidence of optic nerve inflammation occurs in both relapsing-remitting (Shindler et al, 2006) and chronic progressive (Shao et al, 2004; Quinn et al, 2011) mouse EAE. Optic nerve inflammation is followed sequentially by demyelination and axonal injury with loss of retinal ganglion cells (Shindler et al, 2008a), similar to demyelinating optic neuritis in multiple sclerosis patients. EAE is induced by immunization with myelin antigens, and thus is by definition an autoimmune disease, and is largely T cell mediated. Viral-induced models of multiple sclerosis also are used, including inoculation with neurovirulent strains of mouse hepatitis virus that leads to inflammation and demyelination in the central nervous system similar to multiple sclerosis lesions (Das Sarma et al, 2009). Optic nerve inflammation occurs in this model as well (Shindler et al, 2008b), and on a gross histological level is indistinguishable from EAE, but the type of inflammation is different consisting almost exclusively of activated macrophages (Shindler et al, 2011), and in fact the virus can induce demyelination even in the absence of lymphocytes (Matthews et al, 2002).

The findings from animal models of optic nerve inflammation demonstrate how a variety of inflammatory etiologies can share similar phenotypes, and yet the differences in specific immune cell responses and mechanisms of inflammation leading to optic nerve damage explain why others features may vary. It is likely that a similar range of overlapping and distinct immune mechanisms are involved in human inflammatory optic neuropathies, for both the common demyelinating optic neuritis patients, as well as the uncommon zebra. This may explain why some patients harbouring uncommon autoimmune or inflammatory optic neuropathies present with clinical features that are indistinguishable from demyelinating optic neuritis while others follow distinct courses. Ongoing studies hold the promise of leading to new diagnostic and prognostic testing that may help distinguish different inflammatory optic neuropathies and guide development of novel therapies.

**CME ANSWERS**

1. Classically, NMO patients can present with bilateral vision loss that is often severe, whereas typical demyelinating optic neuritis is usually unilateral and can range in severity.
2. Presentations include: unilateral inflammatory optic neuropathy similar to demyelinating optic neuritis, severe bilateral optic neuropathy as seen in NMO, an isolated papillitis, and ischemic optic neuropathy.
3. Presentations include: unilateral inflammatory optic neuropathy similar to demyelinating optic neuritis, optic perineuritis, granulomas of the optic nerve head, and disc swelling or atrophy from granulomatous thickening of the optic nerve sheath mimicking a compressive optic neuropathy from meningioma or glioma.

**REFERENCES**


LEARNING OBJECTIVES

1. The attendee will be able to recognize clinically and direct the molecular diagnosis of Leber’s hereditary optic neuropathy (LHON) and dominant optic neuropathy (DOA).

2. The attendee will have state of the art information on some of the unexplained features of LHON and DOA.

3. The attendee will have updated information on therapeutic options for LHON and DOA.

CME QUESTIONS

1. The major clinical difference between LHON and DOA is (choose one):
   a) Age of onset and timing of disease evolution
   b) Visual field defect
   c) Dyschromatopsia
   d) Retinal cell type affected

2. The incomplete penetrance in LHON is possibly related to:
   a) Environmental factors such as tobacco smoking and alcohol consumption
   b) Genetic polymorphisms related to the mtDNA background (haplogroups)
   c) Nuclear modifying genes
   d) All the above.

3. The therapeutic options currently available for LHON include:
   a) Gene therapy
   b) Use of antioxidants such as idebennone or EPI-743
   c) Antiapoptotic drugs
   d) Drugs activating mitochondrial biogenesis

INTRODUCTION

Leber’s hereditary optic neuropathy (LHON) and dominant optic atrophy (DOA) are the two most frequent mitochondrial hereditary optic neuropathies with monosymptomatic expression\(^1,2\). LHON and DOA are limited to a single cellular target, i.e. the RGCs that originate the optic nerve. Both LHON and DOA share the hallmark of early and preferential involvement of the small axons that form the papillomacular bundle, the anatomical substrate for central and colour vision.

LHON CLINICAL FEATURES

Theodor Leber first described LHON as a hereditary optic atrophy affecting mostly young males\(^3\). It is now well established that LHON is maternally inherited, being due to the three frequent pathogenic mtDNA point mutations at positions 11778/ND4, 3460/ND1, and 14484/ND6, affecting different complex I subunits\(^1,2\). Epidemiological studies demonstrated that LHON is among the most frequent mitochondrial disease\(^4\). LHON patients present with rapid and painless loss of central vision in one or both eyes accompanied by the fading of colours (dyschromatopsia). The second eye is usually involved within weeks. The loss of visual acuity is profound and levels off below 20/200 within a few months; the visual field defects show large centro-coecal absolute scotomata. At fundus examination, the characteristic signs include circumpapillary telangiectatic microangiopathy, swelling of the retinal nerve fiber layer (RNFL) around the disc (pseudoedema), and lack of leakage on fluorescein angiography (in contrast to true disc edema)\(^5,6\). The optic disc appears hyperemic initially, though the axonal loss in the papillomacular bundle leads to severe temporal pallor of the optic disc. In time, the optic disc turns completely atrophic. Microangiopathy and fundus changes such as RNFL swelling may be present in asymptomatic maternal family members\(^7\). The endpoint of LHON is usually optic atrophy associated with permanent loss of central vision and very poor general visual function although there is relative sparing of pupillary light responses\(^1,2\). Spontaneous recovery of visual acuity may infrequently occur even years after onset, and the most favourable prognostic factors are young age of onset and the 14484/ND6 mutation\(^1,2\). Recently, the use of optical coherence tomography (OCT) measurements re-described the essential features of LHON in acute and chronic cases\(^8,9\), defining a specific pattern of sequential involvement.
during the acute phase that goes from the temporal-inferior, to superior and only lastly to the nasal quadrants, the latter being the most spared sector in the chronic phase of the disease [10].

**LHON GENETICS AND PATHOPHYSIOLOGY**

Incomplete penetrance in homoplasmic LHON maternal lineages and male prevalence among the affected individuals are two features of LHON that remain a mystery and are currently matters of intense investigation. In this regard the genetic basis of LHON is very complex. There are three frequent pathogenic point mutations (11778/ND4, 3460/ND1, and 14484/ND6), and a handful of other rarer but truly pathogenic mtDNA point mutations, all affecting subunits of complex I [1,2]. Recently, the importance of mtDNA variation in LHON has been fully recognized. There is now solid evidence that two sublineages of haplogroup J (J1c and J2b) are relevant to increase penetrance of the 11778/ND4 and 14484/ND6 mutations [11,12].

The mtDNA pathogenic mutations and modifying background are a necessary but still not sufficient condition to determine the phenotypic expression. The role of nuclear modifying genes has been postulated and debated [13]. The X-chromosome has been under enquiry for a long time as a good candidate for modifying genes, which would also explain the male prevalence. This two-locus model was formally compatible with segregation studies in LHON pedigrees [14] and recent linkage analysis documented two loci on X chromosome [15,16]. However, to date no significant genetic variants associated with LHON were reported by the direct sequencing of candidate genes in the X-linked loci, as well as studies on the X-inactivation pattern in affected females failed to observe the predicted excess of skewed inactivation [17].

Recently, we provided a different view on the male prevalence in LHON, documenting the protective role played by estrogens in cultured cells carrying the LHON mutations [18].

Environmental factors such as tobacco smoking and alcohol consumption are now confirmed risk factors that may trigger LHON, in analogy with toxic and nutritional optic neuropathies [19]. Exposures to less common toxic agents such as solvent vapors [20], as well as head trauma, uncontrolled diabetes, or pharmaceutical agents that interfere with mitochondrial metabolism, such as ethambutol and antiretroviral drugs have also been reported [1,2].

The biochemical effects of LHON mutations and the possible pathogenic mechanisms remain areas of continuous investigation. Every model of LHON pathophysiology assumes a defective complex I function. Loss of energetic efficiency, increased oxidative stress, and propensity to apoptotic cell death have all been variably documented in patient’s tissues and cell models of the disease [1,2,21-23]. As a consequence, altered axonal transport of organelles and axoplasmic stasis with swelling of axons has been proposed as key features leading to the threshold for the acute phase of the disease [1,21-23]. The latter is characterized by a remarkably synchronous wave of RGCs degeneration, most likely involving apoptotic cell death. At this stage, the commitment to cell death might be already irreversible, as suggested by the recent failure of therapeutic trials designed to save the second eye by drug administration in the small window of time separating the optic neuropathy in the first from the second eye [14,23].

**DOA CLINICAL FEATURES**

DOA, also known as Kjer’s optic neuropathy [24], is characterized by slowly progressive, roughly bilaterally symmetrical visual loss in childhood, accompanied by temporal pallor of the optic discs [1,2]. Examination also demonstrates centrocaecal scotomas and impairments of color vision (tritanopia). The disease is frequently recognized during routine vision testing (school or driving license eye screenings). Disease progression may be quite variable within the same family, ranging from mild cases with visual acuity that stabilizes in adolescence, to slowly but relentlessly progressing cases, to cases with sudden, step-like decreases of visual acuity. This variability of clinical expression is reflected by the different extent of optic atrophy shown by different patients [27].

Despite the remarkably different clinical course, the endpoint of the pathological process in DOA is clinically indistinguishable from that in LHON [1,2]. A frequent feature of DOA’s end-stage fundus is optic disc excavation, which is also reported in LHON [1,2]. Recent studies using OCT documented a smaller optic nerve head in OPA1 patients, suggesting a reduced total number of RGCs and axons at birth [28].

Overall, despite a remarkably different natural history, LHON and DOA share a similar endpoint with predominant involvement of the papillomacular bundle. Both diseases also share a remarkable variability in penetrance.

**DOA GENETICS AND PATHOPHYSIOLOGY**

About 60% of DOA cases are now linked to mutations in the OPA1 gene identified in 2000 [29,30]. Three further loci have been reported (OPA4, OPA5, and OPA8), but the genes involved have not yet been identified [31-33]. The screening of numerous cohorts of DOA families of different ethnic origin led to the identification of a large number (over 100) of different mutations in the OPA1 gene, including missense, nonsense, deletion/insertion, and splicing mutations, mostly clustered in the GTPase domain and the 3’ end of the coding region [34, see http://hmba.univ-angers.fr/]. The large majority of OPA1 mutations are predicted to produce a premature truncated protein and haploinsufficiency is the mechanism assumed to underlay DOA in these cases, whereas missense mutations, mostly affecting the GTPase domain, are predicted to exert a dominant negative effect. In general, the genotype-phenotype correlation is weak, with great variability in both penetrance and clinical severity. As is the case for LHON, other as yet unknown genetic or epigenetic/environmental factors may play a role in the phenotypic expression of DOA.
neuropathy and spastic paraplegia involvement, white matter abnormalities, peripheral with progressive external ophthalmoplegia, cerebellar and deafness, followed later by mitochondrial myopathy encephalomyopathy including early onset optic atrophy subset of missense mutations, mostly affecting the GTPase a new role for OPA1 were prompted by the discovery that a involved in OXPHOS efficiency [37,38]. In particular OPA1 and to a drastic disorganization of the cristae. Recent fragmentation of the mitochondrial network concomitantly of OPA1 using specific small interference RNA leads to with cytochrome c storage and release. Down-regulation process and also in protection from apoptosis by dealing space and has an important role in the mitochondrial fusion brain, testis, heart, and muscle. OPA1 is anchored to the resulting from alternative splicing. These are expressed in mtDNA replication and mtDNA nucleoid organization suggesting the involvement of specific OPA1 isoforms in in mtDNA maintenance. A very recent study went further multiple deletions in the skeletal muscle, thus involving OPA1 achieved the target of mitigating vision loss.

TREATMENT OPTIONS

Until recently, only anecdotal data have been available about therapeutic attempts in mitochondrial optic neuropathies, in particular LHON, and in most cases these proved to be ineffective [1,2,43]. They include the following list.

VITAMINS

Anecdotal reports on the therapeutic use of vitamins (especially folic acid, B-2 and B-12) and nutritional supplements (including vitamins C and E) did not prove their efficacy in LHON. Although vitamin B-12 administration has not been a successful treatment for LHON, it may be helpful in the setting of a B-12 deficiency that precipitated the visual loss in LHON.

BRIMONIDINE

Topical brimonidine, an alpha-2 agonist, also failed in a small clinical trial as a prophylactic agent aimed to avoid the involvement of the fellow eye in LHON [44]. It had been hoped that brimonidine, by upregulating BCL-2, could inhibit the MPTP opening, thus forestalling mitochondrionally-induced apoptosis. The study was halted early, due to insufficient enrollment and because none of the patients achieved the target of mitigating vision loss.

ANTIOXIDANT AGENTS

Coenzyme Q-10 is a mitochondrial cofactor that shuttles electrons from complexes I and II to complex III. Coenzyme Q-10 (or ubiquinone) is available as a nutritional supplement. A few case reports of treatment with coenzyme Q-10 have been published, but the lack of any successful case series gives rise to skepticism for this treatment. One likely limitation of treatment with exogenous coenzyme Q-10 relates to its poor delivery crossing lipid membranes to mitochondria.

Idebenone, a coenzyme Q-10 derivative, is reported to have higher delivery to mitochondria as well as a higher efficiency for crossing the blood-brain barrier. Successful treatment with idebenone has been described in a few case reports and retrospective case series [25,43]. One such study evaluated the treatment of Japanese patients with LHON carrying all three mutations with a combination of idebenone, riboflavin (B-2) and ascorbic acid (vitamin C) [44]. The visual recovery was significantly earlier for treated patients carrying the 11778/N4 mutation and limited to small openings that appeared in the paracentral visual field (fenestrations).

Two recent studies, one prospective double-blind placebo-controlled trial [45] and one very large retrospective series investigating a large cohort of idebenone treated patients in Italy [25], validated some effectiveness of idebenone as treatment for LHON, suggesting greater recovery of visual acuity than that seen to spontaneously occur in LHON [1,2]. However, very early idebenone treatment in patients with asynchronous eye involvement (and the second eye still unaffected), failed to spare the second eye from undergoing the visual loss associated with the pathological process [25]. Thus, caution should be used in managing expectations for idebenone therapy in patients [46]. Studies are underway for a third generation quinone and further strategies of gene therapy are being studied for LHON, but these are not yet at the stage for clinical trials in humans [47,48].

CME ANSWERS

1. a
2. d
3. b

REFERENCES


MITOCHONDRIAL OPTIC NEUROPATHIES: TOXIC/METABOLIC

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LEARNING OBJECTIVES

1. To recognize the features of mitochondrial optic neuropathy.
2. To understand the particular susceptibility of the papillo-macular bundle to mitochondrial dysfunction.
3. To consider various nutritional deficiencies and toxic insults as they impact mitochondrial oxidative-phosphorylation.
4. To know the most common list of antibiotics and common medications that disturb mitochondrial function.

CME QUESTIONS

1. Toxic/metabolic optic neuropathies most likely cause RGC injury through events related to which of the following:
   a) NMDA receptors (excito-toxicity)
   b) Calcium channel effects
   c) Electron transfer chain
   d) Pro-inflammatory response
2. A good screening test for toxic/metabolic mitochondrial optic neuropathy would include all the below except:
   a) The fundus examination
   b) Testing of color vision
   c) Testing of visual acuity
   d) Testing of the central visual fields
3. Which of the following is true for mitochondrial optic neuropathies:
   a) Optic atrophy occurs early
   b) There is a central scotoma
   c) Color vision is spared
   d) RPE changes are likely

KEYWORDS

1. Mitochondrial Optic Neuropathy
2. Retinal Ganglion Cells (RGCs)
3. Papillo-Macular Bundle (PMB)
4. Toxic/Metabolic

INTRODUCTION

Ophthalmologists have known for centuries that certain toxins or nutritional deficiencies can cause permanent bilateral blindness. Beginning with the description of Tobacco or Tobacco-Alcohol Amblyopia by Mackenzie in 1830, this phrase and concept have probably done a great deal to obfuscate the issue. That is, under this term of tobacco-alcohol amblyopia, there are probably several toxic and metabolic forms of optic neuropathy, such as cyanide (from tobacco), B-12 and folate deficiencies. In the last few decades there has been a better understanding of the specific elements of mixed toxic and metabolic optic neuropathy (MON) and also the nature of the general class of injury as mitochondrial in nature.

In 1988, Wallace and coworkers first identified, in a subset of LHON families, a pathogenic mtDNA missense point mutation at position 11778 in the ND4 gene of complex I. This was followed by the identification of other point mutations, all affecting Complex I of the electron transport chain. This gave great insight into the pathophysiology of acquired as well as genetic causes of mitochondrial optic neuropathy. Subsequently, some investigators went back and reviewed their series of patients previously diagnosed with Tobacco-Alcohol Amblyopia and found that about 20% did in fact harbor LHON genetic mutations. This indicates that there can be either masquerading of LHON that presents as a toxic/metabolic optic neuropathy, or that toxic and nutritional status may be important environmental triggers that provoke mitochondrial optic neuropathy (MON) in genetically predisposed individuals.

The effect of toxins for in producing MON can therefore be considered in two general cases. There are agents to be identified and kept in mind as to be specifically avoided in individuals identified genetically to be at risk (LHON and TAA or Ethambutol). There are also agents so dangerous or so widespread in general usage as to require special consideration. For examples, it has been estimated that one hundred thousand people, worldwide, go blind every year from the use of Ethambutol.

In thinking about toxic optic neuropathies, it is also important to understand that they represent one class of injury under the broader rubric of MON. Most generally we can consider MON to be either congenital or acquired. Congenital MON can be simple hereditary (LHON and DOA),
or syndromic. Acquired can be nutritional deficiencies or toxic optic neuropathies. Finally, there are mixed syndromes such as the Cuban Epidemic of Optic Neuropathy (CEON).

![Diagram of mitochondrial optic neuropathies and their relationships]

**COMMON PRESENTATION**

As in most cases of MON, toxic/metabolic cases present with painless bilateral loss of visual acuity. Examination at this time is usually unrevealing for anterior or posterior biomicroscopy. However, careful testing will reveal dyschromatopsia and at least relative if not absolute central or cecocentral scotomas. These tend to be very symmetrical. All of these clinical features reflect the underlying common pathophysiology that affects initially affects the papillo-macular bundle (PMB). This may reflect the small caliber of the retinal ganglion cells in this area (52 that make them metabolically most vulnerable. Early involvement of the PMB also may make it difficult to demonstrate on Optical Coherence Tomography (OCT) and especially on GDx (scanning laser polarimetry) as these techniques are least sensitive in the area just temporal to the optic disc.

Toxic/Metabolic optic neuropathies clinically often follow the common theme of all mitochondrial optic neuropathies. However, there are two key features that can help in distinguishing inherited from acquired optic neuropathies: absence of family history and simultaneous involvement of both eyes. A history of exposure to toxins or antibiotics or lack of proper diet will of course be very helpful for the correct diagnosis. A thorough systemic examination in such a scenario must be emphasized. For instance, skin lesions may be observed with dietary or vitamin deficiencies.

The visual loss can vary from mild to severe. Visual loss is progressive and painless and may therefore lead to a late realization of the problem by the patient. One exception is that the visual loss in cases of methanol intoxication can be extremely rapid and severe. In such a case, the clinical picture may extend to signs and symptoms of methanol ingestion and formate acidosis - nausea, vomiting, and disturbances of consciousness leading to coma with severe acidosis requiring intensive care treatment.

In these acquired metabolic optic neuropathies, fundus examination often demonstrates a completely normal optic disc leading to the incorrect diagnosis of retrobulbar optic neuritis. The optic disc may be slightly hyperemic with small splinter hemorrhages on or just around the disc. Optic atrophy may early on be non-existent and only later become mild. In later stages the optic atrophy is severe and this indicates less opportunity for recovery. In ethambutol toxicity, for example, the fundus examination is normal initially, thereby rendering early diagnosis challenging. Optic disc atrophy only ensues later if the drug is not discontinued.

Some metabolic optic neuropathies may present in the early stages without the development of the full clinical picture. For example, the central scotomas may be small and not absolute in tobacco-alcohol amblyopia, whereas in most cases of LHON, the scotomas are large and dense.

**TOXIC OPTIC NEUROPATHIES**

**ANTIBIOTIC-RELATED OPTIC NEUROPATHIES**

Ethambutol is an anti-mycobacterial medication commonly used in the treatment of tuberculosis. The primary toxicity associated with ethambutol is a mitochondrial optic neuropathy. This complication is a dose and duration dependent phenomenon. The incidence of ethambutol-induced optic neuropathy has been reported to range from 1.0% to 22%, depending on the dosages employed. It is estimated that as many as 100,000 people, worldwide, lose vision from taking Ethambutol each year.

WHO recommends a daily ethambutol dose of 15-20mg/kg daily or in some cases three times a week. WHO also suggests discontinuing ethambutol once TB cultures have demonstrated sensitivity to another antibiotic. Since the toxicity of ethambutol is dose-dependent, age and renal function of the patient are important determinants.

Kidney function decreases with age and with diseases affecting the kidney. Overdose toxicity can also be avoided by taking into consideration the patient’s weight. Toxicity does not usually develop until after two months of treatment. The reported mean interval from onset of therapy to toxic effects usually occurs between 3 and 6 months, but optic neuropathy can begin as late as 12 months after treatment is initiated. Thus, it remains important to in optimize dosage for age, weight and renal function of the patient.

As in other toxic mitochondrial optic neuropathies, the symptoms of ethambutol-induced optic neuropathy can occur before there is fundus evidence of optic neuropathy on ophthalmologic examination. Visual acuity, color vision and central visual field testing is much more sensitive to early ethambutol-induced changes. The toxic optic
neuropathy is largely reversible if ethambutol treatment is withdrawn before severe optic atrophy develops.20,21 However, there are reports of some patients who develop severe, irreversible vision loss despite frequent monitoring and appropriate ethambutol doses.16,17,22 Some patients may have a susceptibility to optic neuropathy while on ethambutol and this includes LHON carriers.23

It has been hypothesized that ethambutol leads to optic neuropathy by chelating copper ions in cytochrome c oxidase (COX, complex IV) and sulphur-iron clusters in complex I, thus damaging the mitochondrial respiratory chain.2,24 Some studies have demonstrated that zinc may contribute to the pathogenesis of toxicity by formation of vacuoles, which are enlarged lysosomes and/or late endosomes.25

Not surprisingly, given the similarities between mitochondrial DNA, transcription/translation and that of the bacteria that are targeted, other antibiotics have also been noted to cause a mitochondrial optic neuropathy. Linezolid, a drug used for methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin resistant enterococcus (VRE), can cause a mitochondrial optic neuropathy. Previous reports have shown linezolid-induced optic and peripheral neuropathies to occur beyond the 28 day safety window26-32 suggested but there have been a few recent case reports of linezolid-induced optic neuropathy after very short term (16day) use.33,34 Retinal nerve fiber layer swelling in linezolid-induced optic neuropathy has been demonstrated by OCT, and this is consistent with the proposed mitochondrial mechanism for this disorder.35

Linezolid inhibits protein synthesis by binding to the 23S rRNA of the 50S ribosomal subunit and thus inhibiting the formation of an initiation complex for protein synthesis36. Mammalian ribosomes lack the 50S component, however, mitochondria in mammalian cells are susceptible to this blockage. This mitochondrial specific impairment can lead to similar respiratory chain dysfunction producing a mitochondrial optic neuropathy. There is marked decrease in the activity of complexes I and IV found in muscle, kidney and liver samples from a patient with linezolid induced optic neuropathy.37

Chloramphenicol is another antibiotic associated with mitochondrial optic neuropathy as it too can inhibit mitochondrial protein synthesis.38 For similar reasons, streptomycin has also been reported to cause mitochondrial optic neuropathy.

As previously noted, ethambutol and other antibiotic-associated toxicity may act in combination with inherited genetic factors (figure 1) predisposing to this type of blindness. In particular, mtDNA haplogroups or specific mtDNA polymorphisms may be associated with antibiotic-induced optic neuropathy. Soon, it may be possible to identify these haplotypes to help predict which patients are susceptible to such toxicities.

OTHER TOXINS
Toxins such as arsacetin, carbon monoxide, clioquinol, cyanide, hexachlorophene, lead, methanol, plasmocid and triethyl tin also interfere with oxidative phosphorylation and thus cause mitochondrial optic neuropathy.3 Other less common toxins known to cause optic neuropathy are carbon disulfide, pheniprazine, quinine, thallium, carbon tetra chloride, cassava, dapson and Suramin.3

NUTRITIONAL OPTIC NEUROPATHIES
Isolated nutritional optic neuropathies are rare. They are usually encountered mixed with each other or in combination with a toxic component2,4,38 Vitamin B12 (cobalamin),40,41 Vitamin B1 (thiamine)2,4,38,42,43 and folic acid39,44,45 are the best described deficiency related mitochondrial optic neuropathies. Malabsorption, such as from gastric bypass surgeries, as well as poor nutrition may result in deficits of sulfur amino acids and these vitamins which in combination can cause mitochondrial optic neuropathy.46 There are a few case reports documenting optic neuropathy in patients carrying a primary LHON mtDNA mutation precipitated by vitamin B12 deficiency, thus suggesting a synergism between genetic and acquired mitochondrial optic neuropathies.37,46

MIXED TOXIC/METABOLIC AND NUTRITIONAL MITOCHONDRIAL OPTIC NEUROPATHY

TOBACCO-ALCOHOL AMBLYOPIA (TAA)
As mentioned in the introduction, tobacco-alcohol amblyopia (TAA) is an old and poor term for several combined elements that can lead to a mitochondrial optic neuropathy. TAA characteristically affects men with a history of heavy alcohol and tobacco consumption. There is evidence that tobacco-derived compounds including reactive oxygen species, and cyanide add to a nutritional mitochondrial impairment. It has been hypothesized that TAA is due to the cumulative cyanide toxicity from tobacco smoke and/or isolated deficiency of thiamine, riboflavin, pyridoxine, and vitamin B12. As noted, there is overlap between LHON and TAA and such patients should be checked for their mtDNA. It has been reported that patients previously diagnosed with TAA were actually misdiagnosed cases of LHON.6 Treatment of TAA with adequate diet, supplemental vitamins and intramuscular injections of hydroxycobalamin is often successful.

CEON (CUBAN EPIDEMIC OF OPTIC NEUROPATHY)
An epidemic of optic neuropathy involving nearly 50,000 people occurred in Cuba in 1992-1993.49 Patients were affected with optic neuropathy, sensory and autonomic peripheral neuropathy, neural deafness, and in a few cases, myelopathy.50,51 The most common pattern of symptoms consisted of severe weight loss, fatigue and a subacute loss of vision. An objective sign, a wedge defect of the temporal optic disc and the loss of the corresponding PMB.49 Most of the patients reported high consumption of alcohol particularly homemade rum and smoking cigarettes.52 This was associated with severe deficiencies of protein and vitamin intake, in particular of vitamin B12.
and folate. This picture of vitamin deficiencies was further complicated by small amounts of methanol present in homemade rum. It was thought that the Cuban epidemic may have been caused by the chronic accumulation of formate from methanol metabolism in a population with severe folic acid depletion and the accumulation of cyanide from cigarette smoke. This conclusion was supported by evidence of improvement in visual acuity on prompt and daily administration of cyanocobalamin (3mg) and folate (250 mg) along with dietary supplementation.

Clinical similarities of CEON with LHON, TAA and methanol poisoning have been established. However, CEON was not associated with mtDNA mutations found in LHON. Thiamine deficiency was not demonstrated in CEON patients when compared with local controls though this deficiency was more prevalent in the geographical regions where the disease had a higher incidence, suggesting it was a surrogate for poor nutrition or part of the underlying mechanism.

COMMON PATHOPHYSIOLOGY:
Mitochondrial optic neuropathies, whether inherited or acquired, share impairments in the mitochondrial respiratory chain (OXPHOS) leading to both ATP depletion and increased reactive oxygen species and eventual retinal ganglion cell (RGC) loss (figure 2). Why should this mitochondrial insufficiency be so selective for RGCs and their axons that form the optic nerve? Immunohistochemical staining for cytochrome c oxidase and ultrastructural studies have shown a preferential localization of mitochondria to various areas of the optic nerve. This is especially the case in the pre-laminar unmyelinated portion of the optic disc as well as under the nodes of Ranvier in the post-laminar portion of the myelinated optic nerve. The non-homogeneous distribution of mitochondria along the RGC axons parallels the specific energy requirement of these segments; the myelinated posterior portion of these axons have few mitochondria as they are energy efficient from saltatory conduction. Conversely, the intraocular stretches of the optic nerve terminal is itself a very energy dependent process, energy depletion will also lead to defective mitochondrial transport compounding the metabolic crisis.

The mitochondrial respiratory chain is also a major source of reactive oxygen species that chronically increase as a consequence of genetic or acquired impairments of oxidative phosphorylation. Oxidative stress is also harmful to the mtDNA causing the accumulation of multiple deletions. Furthermore, lipid peroxidation due to ROS may lead to mitochondrial membrane damage.

Ultimately, RGCs may undergo apoptosis. Cytochrome c, the electron shuttle between complex III and IV, when released from mitochondria is at the center of the apoptotic cascade. Respiratory dysfunction, oxidative stress, loss of mitochondrial inner membrane potential, and calcium fluxes all converge causing an opening of the mitochondrial permeability transition pore (MPTP). Through the MPTP, the pro-apoptotic cytochrome c is released into the cytoplasm to initiate the apoptotic cycle. See figure 2.

Acquired, as well as genetic, alterations of mitochondrial function result in vision loss due to optic neuropathy. The optic nerve is thus the canary in the coal mine for this type of injury.

It is unfortunate that patients with toxic or nutritional mitochondrial optic neuropathy are at risk for profound bilateral and irreversible visual loss. It is incumbent for the clinician to be astute to these diseases and especially in regards to acquired causes, to promptly diagnose and manage and mitigate the problem.

Figure 2. Adapted from JNO: Sadun & Wang, J Neuroophthalmol, 28(4), 265-268 (2008).

CME ANSWERS
1. c
2. a
3. b

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SYNDROMIC MITOCHONDRIAL OPTIC NEUROPATHIES

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LEARNING OBJECTIVES

1. Know which syndromic neurodegenerative disorders manifest optic neuropathy.
2. Appreciate the role of mitochondrial dysfunction in many of the syndromic disorders which manifest optic neuropathy.
3. Know some of the gene defects, both in the nuclear and mitochondrial DNA, which are associated with syndromic mitochondrial optic neuropathies.

CME QUESTIONS

1. True or False? Syndromic mitochondrial optic neuropathies are all caused by defects in mitochondrial DNA.
2. True or False? All cases of Wolfram syndrome are related to a single gene defect in the WFS1 gene on chromosome 4.
3. True or False? Optic atrophy is uncommon in Friedreich’s ataxia.

KEYWORDS

1. Optic Neuropathy
2. Mitochondrial Disease
3. Wolfram Syndrome
4. Friedreich Ataxia
5. Charcot-Marie-Tooth

INTRODUCTION

In some of the hereditary optic neuropathies, optic nerve dysfunction is typically isolated. In others, various neurologic and systemic abnormalities are regularly observed. Additionally, inherited diseases with primarily neurologic or systemic manifestations, such as the multisystem degenerations, can include optic atrophy. Whether inherited in Mendelian fashion or as a result of mitochondrial DNA point mutations with maternal transmission, many of these disorders have been linked to a final common pathway of mitochondrial dysfunction, suggesting that optic nerve function is particularly susceptible to perturbations of mitochondrial physiology (1-4).

SYNDROMIC OPTIC NEUROPATHIES WITH OPTIC NEUROPATHY AS A DEFINING CHARACTERISTIC

AUTOSOMAL DOMINANT OPTIC ATROPHY AND SENSORINEURAL HEARING LOSS

Several pedigrees with autosomal dominant optic atrophy and hearing loss have been described. In many of these pedigrees, there are no other systemic or neurologic abnormalities. Some, but not all of these pedigrees have now been shown to harbor OPA1 mutations that in other pedigrees cause only optic neuropathy (1-4). In one Italian family, a new locus on chromosome 16 (16q21-q22) was designated OPA8, and preliminary studies suggest its pathogenesis may also be via mitochondrial dysfunction (5).

In a Dutch pedigree with DOA and deafness, OPA1 mutations were excluded, but a novel missense mutation was found in the WFS1 gene on chromosome 4 (4p16.1), a common locus for mutations typically causing the autosomal recessive DIDMOAD or Wolfram syndrome, a syndromic optic neuropathy with diabetes mellitus, diabetes insipidus and hearing loss (see below) (6). Similarly, in another DOA pedigree with hearing impairment and impaired glucose regulation, mutation analysis excluded mutations within the OPA1, OPA3, OPA4 and OPA5 genes, but identified a novel missense mutation in the WFS1 (Wolfram) gene (7).

In other pedigrees with DOA and deafness, there may be associated ataxia, limb weakness or polyneuropathy. The hearing loss in these pedigrees may be severe at birth with poor speech development, or may be only moderate and slowly progressive. The acronym CAPOS (cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural deafness) has been suggested, but is as yet genetically undefined (1,4). “DOA Plus” with OPA1 mutations (8) may ultimately account for many of these more complicated syndromic pedigrees, but clearly the syndromic combination of DOA and hearing loss is genetically heterogeneous.

AUTOSOMAL DOMINANT OPTIC ATROPHY WITH PREMATURE CATARACTS

Two independent French families manifest optic atrophy and premature cataract in an autosomal-dominant mode of inheritance. Mutations in the OPA1 gene were excluded and pathogenic mutations were found in the OPA3 gene on chromosome 19 (19q13.2-q13.3), a locus for mutations which typically cause Costeff syndrome, an autosomal recessively-inherited syndromic optic neuropathy (see below). Screening
for OPA3 mutations as a cause of monosymptomatic DOA cases in multiple other pedigrees has failed to identify any pathogenic OPA3 variants, suggesting that OPA3 mutations as a cause of DOA are likely very rare (9).

**AUTOSONAL RECESSIVE OPTIC ATROPHY WITH PROGRESSIVE NEURODEGENERATION AND TYPE III 3-METHYLGLUTACONIC ACIDURIA (COSTEFF SYNDROME)**

In this autosomal recessive syndrome most commonly seen in Iraqi Jewish pedigrees, severe optic atrophy is associated with extrapyramidal signs, cognitive impairment, increased urinary levels of 3-methylglutaconic acid, and elevated plasma levels of 3-methylglutaric acid. The causative gene is located on chromosome 19 (19q13.2-13.3), and has been designated OPA3 (3,9). The OPA3 gene product localizes to the mitochondrial membrane and has an important role in mitochondrial fission (9).

**AUTOSONAL RECESSIVE OPTIC ATROPHY WITH JUVENILE DIABETES MELLITUS, DIABETES INSIPIDUS, AND HEARING LOSS (WOLFRAM SYNDROME, DIDMOAD)**

The hallmark of this syndrome is the association of juvenile diabetes mellitus and progressive visual loss with optic atrophy, almost always associated with diabetes insipidus, sensorineural hearing loss, or both (hence, the eponym DIDMOAD for diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) (3,4,10). Diabetes mellitus usually develops within the first or second decade of life and usually precedes the development of optic atrophy. In several cases, however, visual loss with optic atrophy is the first sign of the syndrome. In the early stages, visual acuity may be normal despite mild dyschromatopsia and optic atrophy. In later stages, visual loss becomes severe. Visual fields have shown both generalized constriction and central scotomas. Optic atrophy is uniformly severe, and there may be mild to moderate cupping of the disc. Both hearing loss and diabetes insipidus begin in the first or second decade of life and may be quite severe. Atonia of the effenter urinary tract is present in half of patients and is associated with recurrent urinary tract infections, neurogenic incontinence, and even fatal complications. Other systemic and neurologic abnormalities include ataxia, axial rigidity, seizures, startle myoclonus, tremor, gastrointestinal dysmotility, vestibular malfunction, central apraxia, neurogenic upper airway collapse, ptosis, catacata, pigmentary retinopathy, iritis, lacrimal hyposcretion, Adie’s pupil, ophthalmoplegia, convergence insufficiency, vertical gaze palsy, nystagmus, mental retardation, psychiatric abnormalities, short stature, primary gonadal atrophy, other endocrine abnormalities, anosmia, megaloblastic and sideroblastic anemia, abnormal electroretinography, and elevated CSF protein. Neuroimaging and pathology in some patients reveal widespread atrophic changes and malformations of cortical development, and suggest a diffuse neurodegenerative disorder, with particular involvement of the midbrain and pons. When the syndrome is accompanied by anemia, treatment with thiamine may ameliorate the anemia and decrease the insulin requirement.

Linkage analysis in several families has shown localization of a Wolfram gene to chromosome 4 (4p16.1). The gene responsible at this locus has been designated WFS1, in which multiple point mutations and deletions have been identified. The gene product, wolframin, is an endoplasmic reticulum protein which plays a role in the regulation of intracellular calcium (11). A second causative Wolfram gene on the other arm of chromosome 4 (4q22-24) has been identified and designated CISD2 in consanguineous Jordanian families (12). These patients show additional symptoms of bleeding tendency and peptic ulcer disease. Interestingly, knockout of the CISD2 gene in mice results in a Wolfram type syndrome associated with mitochondrial-mediated premature aging. Indeed, many of the associated abnormalities reported in Wolfram syndrome are commonly encountered in patients with presumed mitochondrial diseases, especially those patients with the chronic progressive external ophthalmoplegia syndromes. This has led to speculation that the Wolfram phenotype may be nonspecific and reflect a wide variety of underlying genetic defects in either the nuclear or mitochondrial genomes, with a final common pathway of mitochondrial dysfunction (2-4). Indeed, most cases of Wolfram have been classified as sporadic or recessively inherited, the latter usually concluded from sibling expression (which is now known to also be consistent with maternal transmission).

**SPASTIC PARAPLEGIA, OPTIC ATROPHY, AND NEUROPATHY (SPOAN SYNDROME)**

In a large inbred Brazilian family, an autosomal recessive neurodegenerative disorder was clinically defined by nonprogressive congenital optic atrophy; infantile-onset spastic paraplegia; childhood-onset of progressive motor and sensory axonal neuropathy; dysarthria starting in the third decade of life; exaggerated acoustic startle response; and progressive joint contractures and spine deformities (13). Linkage is to chromosome 11q13, but the responsible gene has not yet been detected.

**CONGENITAL CEREBELLAR ATAXIA, MENTAL RETARDATION, OPTIC ATROPHY, AND SKIN ABNORMALITIES (CAMOS)**

In a large inbred Lebanese Druze family, non-progressive autosomal recessive congenital ataxia associated with optic atrophy, severe mental retardation, and structural skin abnormalities was linked to a locus on chromosome 15 (15q24-q26), but the responsible gene has not yet been detected (14).

**DEAFNESS, DYSTONIA, AND OPTIC NEUROPATHY (DDON, MOHR-TRANEBJAERG SYNDROME)**

In this X-linked disorder, sensorineural deafness, dystonia and ataxia present in late childhood, followed by optic atrophy by age 20, and cognitive decline and psychiatric manifestations before age 50 (15). The visual prognosis is poor with most patients legally blind by age 40. The disorder is caused by mutations in the TIMM8A gene on the X chromosome (Xq22) whose gene product localizes to the mitochondrial intermembrane space. Mitochondrial biochemical dysfunction has been demonstrated.
COMPLICATED HEREDITARY INFANTILE OPTIC ATROPHY (BEHR SYNDROME)
The designation of Behr syndrome reflects optic atrophy beginning in early childhood, associated with variable pyramidal tract signs, ataxia, mental retardation, urinary incontinence, and pes cavus. Both sexes are affected and the syndrome is usually inherited as an autosomal recessive trait. Visual loss usually manifests before age 10 years, is moderate to severe, and is frequently accompanied by nystagmus. In most cases, the abnormalities do not progress after childhood. Neuroimaging may demonstrate diffuse symmetric white matter abnormalities. Clinical findings in some patients with Behr syndrome may be similar to those in cases of hereditary ataxia. Behr syndrome is likely heterogeneous, reflecting different etiologic and genetic factors [1].

HEREDITARY ATAXIAS
The hereditary ataxias comprise a group of chronic progressive neurodegenerative conditions involving the cerebellum and its connections, and are sometimes associated with optic atrophy. A genomic classification by chromosomal location is available for many of these disorders and the abnormal gene products involved are under investigation, many of them localized to the mitochondria [1-3,15,16].

FRIEDREICH ATAXIA
Friedreich ataxia is inherited in an autosomal recessive manner, and the gene defect has been localized to the proximal long arm of chromosome 9 (9q13–q21). The majority of cases are homozygous for a GAA trinucleotide expansion in a gene designated FRDA/X25 that codes for a protein called frataxin, which regulates iron levels in the mitochondria [2,3,16]. The disease usually begins during the second decade of life and includes progressive ataxia, dysarthria, loss of joint position and vibratory sensation, absent lower extremity tendon reflexes, and extensor plantar responses. Scoliosis, foot deformity, diabetes mellitus, and cardiac disease are common. Other manifestations include pes cavus, distal wasting, deafness, nystagmus, eye movement abnormalities consistent with abnormal cerebellar function, and optic atrophy. The course is progressive, with most patients unable to walk within 15 years of onset, and death from infectious or cardiac causes usually in the fourth or fifth decade. Although optic atrophy is a common feature of Friedreich ataxia, most patients are visually asymptomatic, and severe visual loss occurs only rarely. In a study of 26 patients with genetically-confirmed Friedreich ataxia, all patients were found to have an underlying optic neuropathy, although 21 were completely visually asymptomatic [17]. Three symptomatic patients had slowly progressive central visual dysfunction, but two patients presented with the sudden onset of bilateral central scotomas, resembling LHON. A condition resembling Friedreich ataxia associated with decreased vitamin E levels has been localized to chromosome 8. Vitamin E supplementation of these patients may be efficacious early in the course of the disease.

SPINOCERESELLAR ATAXIAS
The spinocerebellar ataxias, previously called olivopontocerebellar atrophy (OPCA) and autosomal dominant cerebellar ataxia, include a group of dominantly-inherited ataxic disorders in which the ataxia is related more to degeneration of the cerebellum rather than the spinal cord [1,15,16]. As of 2010, there were at least 29 different genetic loci for the SCAs (SCA1 through SCA31). The combination of SCA1 (chromosome 6p), SCA2 (chromosome 12q), SCA3 (chromosome 14q), SCA6 (chromosome 19p), and SCA7 (chromosome 3p) comprises approximately 80% of the autosomal dominant ataxias. Most of the SCAs are caused by mutations involving the expansion of a CAG trinucleotide repeat in the protein-coding sequences of specific genes. As with other diseases that involve abnormal repeats, the expanded regions can become larger with each successive generation, resulting in a younger age of onset in each generation, so-called anticipation. Clinically, the SCAs are characterized by signs and symptoms attributable to cerebellar degeneration and sometimes other neurologic dysfunction secondary to neuronal loss. Loss of vision is usually mild but may be a prominent symptom, occurring in association with constricted visual fields and diffuse optic atrophy. However, it is not clear in some cases whether the primary process is retinal with secondary optic atrophy or primarily involving the optic nerve. SCA7 is specifically associated with retinal degeneration, whereas optic neuropathy is usually associated with SCA1 or SCA3, [15]

HEREDITARY POLYNEUROPATHIES

CHARCOT-MARIE-TOOTH DISEASE
Charcot-Marie-Tooth disease (CMT) encompasses a group of heredofamilial disorders characterized by progressive muscular weakness and atrophy that begins during the first two decades of life [1-4]. This group of hereditary polyneuropathies accounts for 90% of all hereditary neuropathies, with a prevalence of at least one in 2500 individuals. Most forms of CMT begin between the ages of 2 and 15 years, and the first signs may be pes cavus, foot deformities, or scoliosis. There is slowly progressive weakness and wasting, first of the feet and legs, and then of the hands. Motor symptoms predominate over sensory abnormalities. As of 2011, causative mutations for the hereditary peripheral neuropathies have been identified in more than 30 different genes [2,3]. Numerous patients with CMT and optic atrophy have been reported. Taking into account both electrophysiologic and clinical data, up to 75% of patients with CMT have some afferent visual pathway dysfunction, demonstrating that subclinical optic neuropathy may occur in a high proportion of patients with CMT. A subtype of CMT, hereditary motor and sensory neuropathy type VI (HMSN VI), is defined by the combination of axonal peripheral neuropathy and optic atrophy, and has both autosomal dominant and autosomal recessive forms of inheritance [4-6]. The optic
atrophy typically develops in late adolescence, a decade or more after the peripheral neuropathy, with a subacute visual decline, usually to below 20/400. As in LHON, a subset of these patients may recover vision years after the onset of optic neuropathy. The autosomal dominant form of HMSN VI is caused by a mutation in the nuclear mitofusin-2 gene, and constitutes a subclass of CMT2A, the most common autosomal dominant form of axonal CMT (18). The mitofusin-2 protein is GTPase localized to the mitochondrial outer membrane, and shares many structural and functional similarities with the OPA1 protein in DOA (2,3).

FAMILIAL DYSAUTONOMIA (RILEY-DAY SYNDROME)
Familial dysautonomia (Riley-Day syndrome) is an autosomal recessive disease that almost exclusively affects Ashkenazi Jews. Abnormalities of the peripheral nervous system cause the clinical manifestations of sensory and autonomic dysfunction. Optic atrophy is very common in patients with familial dysautonomia, usually noted after the first decade of life (1,19). In one recent study, optic nerve damage, especially in the papillomacular bundle, was noted in all eyes of the 16 patients examined, aged 12 to 61 years (19). However, in many cases, early mortality from the disease probably precludes the later development of optic atrophy (2,19).

HEREDITARY SPASTIC PARAPLEGIAS
The hereditary spastic paraplegias (Strumpell-Lorrain disease) are inherited disorders characterized by progressive spasticity of the lower limbs with degeneration of the corticospinal system. The prevalence of these disorders is about 3-10 per 100,000. As of 2011, there were at least 41 mapped loci for the hereditary spastic paraplegias, and 17 identified genes (2,3). Hereditary spastic paraplegia is classified as pure, if spasticity is the only manifestation, or as complicated if other features, such as optic atrophy, are present. Complicated hereditary spastic paraplegia with optic atrophy may result from several different nuclear DNA mutations. The SPG7 gene, found on chromosome 16 (16q24.3), encodes for a mitochondrial metalloproteinase, paraplegin (20). Mutations in the SPG7 gene have been identified in an autosomal recessive form of hereditary spastic paraplegia in which some patients have bilateral optic atrophy as a prominent manifestation of their disorder (2,3).

PRIMARY MITCHONDRIAL DISORDERS
The subacute necrotizing encephalomyelopathy of Leigh results from multiple different biochemical defects that all impair cerebral oxidative metabolism. (1-4). This disorder may be inherited in an autosomal recessive, X-linked, or maternal pattern, depending on the genetic defect. The onset of symptoms is typically between the ages of 2 months and 6 years, and consists of progressive deterioration of brainstem functions, ataxia, seizures, peripheral neuropathy, intellectual deterioration, impaired hearing, and poor vision. Visual loss may be secondary to optic atrophy or retinal degeneration. The syndrome of Leigh is likely a nonspecific phenotypic response to certain abnormalities of mitochondrial energy production. Other presumed mitochondrial disorders of both nuclear and mitochondrial genomic origins may manifest optic atrophy as a secondary clinical feature, often a variable manifestation of the disease (1-4). Examples include cases of MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes, DCMA (dilated cardiomyopathy with ataxia), MERRF (myoclonic epilepsy and ragged red fibers), MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), and chronic progressive external ophthalmoplegia, both with and without the full Kearns-Sayre phenotype. The other, more constant, phenotypic characteristics of all of these mitochondrial disorders usually distinguish them from diseases such as LHON in which visual loss from optic nerve dysfunction is the primary manifestation of the disorder (1-4).

OTHER FAMILIAL-STORAGE DISEASES AND CEREBRAL DEGENERATIONS OF CHILDHOOD ASSOCIATED WITH OPTIC NEUROPATHIES

| Mucopolysaccharidoses (MPS IH, IS, IHS, IIA, IIB, IIA, IIB, IV, VI) |
| Lipidoses (infantile and juvenile GM1-1 and GM1-2, GM2, infantile Niemann-Pick disease) |
| Metachromatic leukodystrophy |
| Krabbe’s disease |
| Adrenoleukodystrophy |
| Zellweger syndrome |
| Pelizaeus-Merzbacher disease |
| Infantile neuroaxonal dystrophy |
| Hallervorden-Spatz disease |
| Menkes syndrome |
| Canavan’s disease |
| Cockayne syndrome |
| COFS |
| Allgrove syndrome (“4A”) |
| Smith-Lemli-Opitz syndrome |
| GAPO syndrome |
| PEHO syndrome |
| Blepharophimosis-mental retardation syndromes (BMR) |
| Cerebral palsy |


CME ANSWERS

1. False
2. False
3. False

REFERENCES

PLATFORM PRESENTATION

LEBER HEREDITARY OPTIC NEUROPATHY G11778A GENE THERAPY CLINICAL TRIAL: SERIAL PRETREATMENT EVALUATION FROM BASELINE TO TWO YEARS

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Introduction:
The preparatory phase of the LHON gene therapy trial aims to characterize affected patients and carriers for the planned gene therapy study that will utilize “allotopic expression,” delivering copies of normal nuclear-encoded ND4 gene into the nuclei of retinal ganglion cells via an adeno-associated virus vector. The normal ND4 protein expressed in the cytoplasm is then imported into the mitochondria.

Methods:
LHON patients with acute or chronic visual loss and their asymptomatic maternally-related relatives undergo ocular examination, visual fields, pattern electroretinogram (PERG), Cirrus OCT and fundus photography every 6 months. Blood samples for phosphorylated neurofilament heavy chain (NfH) quantitation of axonal loss are obtained.

Results:
95 persons with G11778A have been recruited and more are needed. The two-year serial evaluations of 22 patients and 15 asymptomatic carriers are available. Mean two year LHON ETDRS acuity, 13.6, was within one letter of baseline). HVF mean defect (MD), –24.3, was within one dB of baseline. PNF-H was unchanged at year one with year two results pending (0.44 ng/ml one year, 0.41 baseline). Average RNFL was 55.2 µm year two, 55.1 µm year one, 64.2 µm baseline. PERG amplitudes, 0.51 µV, were within 0.05 µV of baseline. In carriers, acuity, 86.3, was within one letter of baseline. HVF MD, -1.8, was within one dB of baseline. PNF-H levels were pending year two, 0.67 ng/ml year one, 0.59 baseline (p=0.13). PERG was 0.72 µV year two, 0.77 µV year one, 0.99 µV baseline (p=0.034).

Conclusion:
For affected LHON patients, clinical measures were stable through two years, and spontaneous improvement was rare (<5%), thus making gene therapy improvements with injection of AAV containing a normal ND4 easy to detect. For carriers, the PERG amplitudes continue to decrease in year two suggesting subclinical retinal ganglion cell dysfunction. Contact information for patient recruitment is available by googling “BPEI LHON”.


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HIV-ASSOCIATED OPTIC NEUROPATHY
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LEARNING OBJECTIVES
1. HIV itself may be a cause of optic neuropathy
2. There is evidence to suggest direct degeneration of ganglion cell axons in the optic nerve primarily due to HIV infection
3. Human immunodeficiency virus infection should be considered in the differential diagnosis of acute optic neuritis.

CME QUESTIONS
1. Does direct degeneration of ganglion cell axons in the optic nerve of HIV infected patients suggest that there may be an AIDS associated primary optic neuropathy?
2. Which antiretroviral agents used to treat HIV patients have been associated with mitochondrial toxicity?
3. Are most cases of optic neuropathy in patients with HIV infection considered to be a primary or secondary optic neuritis?

KEYWORDS
1. HIV Optic Neuropathy
2. HIV Infection
3. Primary HIV Infection
4. Secondary HIV Infection
5. Axonal Degeneration

INTRODUCTION
The differential diagnosis of visual loss in patients infected with the human immunodeficiency virus (HIV) is rather extensive. There is a spectrum of ophthalmologic findings in HIV infection that affects the anterior segment of the eye to the visual pathways. Most cases of optic neuropathy in patients with HIV infection are associated with opportunistic infections such as syphilis, cryptococcus, herpes zoster, toxoplasmosis, cytomegalovirus, histoplasmosis, and tuberculosis. 1,2. Ocular, orbital, and neuro-ophthalmologic complications can also occur as a direct effect of HIV infection or from drug-related side effects. The primary complications of HIV, encountered in our neuro-ophthalmic practices, are retinopathy, optic neuropathy, and retrochiasmal visual field defects. 3

HIV INFECTION ASSOCIATED WITH OPTIC NEUROPATHY CAUSED BY SECONDARY INFECTIONS:
Most neuro-ophthalmologic manifestations of HIV infections are secondary in nature. Patients with HIV infection who present with unilateral or bilateral optic neuropathy will usually undergo an extensive work-up to rule out the presence of opportunistic infections.

Several of the herpesviruses, HSV, VZV, and CMV, may produce a severe retinitis or chorioretinitis as well as have optic nerve involvement in HIV infected persons. In many, the process may be unilateral or bilateral. VZV may produce a non-specific retinal vasculitis or acute retinal necrosis (ARN) as the initial manifestation. There may be an associated anterior chamber reaction, vitritis, and papillitis. Patients with cytomegalovirus (CMV) may have severe retinitis associated with optic disc swelling and peripapillary hemorrhages. Optic neuritis may result from contiguous spread of peripapillary retinitis to the optic nerve or it may occur as a primary process without associated retinitis. 3,4

Some HIV patients may have papilledema as a result of elevated intracranial pressure from a CNS infection or tumor. Often there is meningeal inflammation with or without direct optic nerve invasion. AIDS patients may have involvement of the optic nerve with visual loss due to cryptococcal meningitis. Most of these patients have chronic papilledema at the time vision becomes affected, although some initially have normal-appearing optic discs.

Syphilis can cause a neuroretinitis, optic neuritis and perineuritis in AIDS patients. Konjevic-Pernat et al report a case of bilateral optic neuritis as the initial manifestation of neurosyphilis in an HIV-positive patient. In this report, the patient presents with bilateral decreased visual acuity. His Treponema pallidum hemagglutination reactivity test was highly reactive and he was HIV positive; therefore, he was given a working diagnosis of optic neuritis and started on pulse corticosteroid therapy. This case was the first report of optic neuritis as the first and only manifestation of HIV and syphilis co-infection. 5

Some HIV infected patients may develop an optic neuritis secondary to the immune reaction of tuberculosis or to tuberculosis itself. The optic neuritis in HIV infection has
been associated with histoplasmosis. There is a biopsy-proven case report of optic neuritis from sub-acute disseminated histoplasmosis infection in a single patient with AIDS. Open biopsy of the optic nerve sheath and orbital fat demonstrated H. capsulatum. Neuroretinitis, optic disc edema with the development of a macular star composed of lipid, may occur in patients with HIV infection. The underlying cause may be due to syphilis, Toxoplasmosis or Bartonella henselae. Toxoplasmic papillitis has occurred as the initial manifestation of AIDS or there may be a toxoplasma retinochoroiditis and optic neuritis in AIDS patients.

**PRIMARY HIV-ASSOCIATED OPTIC NEUROPATHY**

Although HIV may be a cause of optic neuropathy, there is no well-recognized clinical syndrome of optic neuropathy or optic neuritis that is specifically attributed to the infection. Nevertheless, evidence suggests that direct degeneration of ganglion cell axons in the optic nerve can be primarily due to the HIV virus itself. The extent and pattern of the axonal loss in the optic nerves suggests that there may be an AIDS-associated primary optic neuropathy. Ninety percent of AIDS patients are estimated to have neurologic findings at autopsy; however, only half of these findings are recognized clinically. The purpose of the collaborative study of Drs. Tenhula, Shizao, Madigan, Heller, Freeman and Sadun was to demonstrate the degree of optic nerve axonal damage in patients with AIDS. The optic nerves of AIDS patients were morphometrically analyzed with a computer-assisted image and measurement system. Compared to normal age-matched control optic nerve fibers, there was approximately 40% loss of optic nerve fibers in the AIDS patients. This study provides important evidence that there is primary damage to the optic nerves of AIDS patients in the absence of opportunistic secondary infections. Furthermore, this study demonstrates that while many patients with AIDS have an associated optic neuropathy, most are asymptomatic. As with other optic neuropathies, it may be merely a matter of time before the extent of the axonal loss results in visual loss.

In later studies by Dr. Sadun et al, optic nerves in AIDS-related optic neuropathy were studied for their histological, virological and ultrastructural composition. Varying states of optic nerve axonal degeneration were found in patients lacking retinal abnormalities or optic nerve infections. Their study concluded that degeneration in the optic nerve may be mediated by HIV-infected macrophages rather than by direct viral infection of the neurons. They documented that the axonal degeneration was patchy and scattered throughout the optic nerve. There was astroglial proliferation and hypertrophy, degeneration of oligodendrocytes, activation of mononuclear phagocytes series cells and thickening of interfascicular septa. These findings are consistent with progressive diffuse leukoencephalopathy, a non-inflammatory degeneration observed in AIDS-infected brain tissue. Thus, mononuclear phagocytes may be involved in producing the axonal degeneration and glial changes observed in optic nerves, and the central nervous system, of AIDS patients. These observations suggest that AIDS-associated optic neuropathy is a distinct primary optic nerve degeneration that is unrelated to secondary retinal or optic nerve infections; however, the optic nerve degeneration may not be caused by direct HIV viral infection of axons, but by HIV-infected mononuclear phagocyte series cells and glial cells.

Other case reports suggest HIV virus is a direct cause of the optic neuropathy. In 1992, Newman and Lessell reported two HIV-positive men with bilateral retrobulbar optic neuropathies. In both patients, compressive, infectious, and infiltrative processes were extensively ruled out. HIV virus was postulated as the causative etiology. In 1993, Sweeney et al reported another case of a patient with HIV-1 infection who developed a spontaneously remitting optic neuritis associated with probable CNS lymphoma. The cause of the optic neuritis remained obscure, but closely linked to HIV infection itself. Larsen et al, 1998, reported a case of bilateral optic neuritis in which acute HIV infection is strongly suggested as the cause. The proposed mechanisms for the clinical findings of the HIV-mediated optic neuropathy include direct viral infection, HIV-mediated vasculitis, postviral-mediated immune attack, or autoimmune destruction on neural and/or vascular structures as a result of the primary HIV infection. It may be that there are direct or indirect neurotoxic effects of the HIV-1 infection on the optic nerve similar to that seen in the CNS. This, too, could be the culprit in the development of primary HIV-associated optic neuropathy. Hence, human immunodeficiency virus infection should be considered in the differential diagnosis of acute or chronic optic neuritis.

**MULTIPLE SCLEROSIS-LIKE ILLNESS WITH HIV INFECTION**

Multiple sclerosis (MS)-like illnesses have been reported in HIV-positive patients. Berger et al report seven patients with relapsing and remitting neurologic disease characteristic of multiple sclerosis occurring in the setting of HIV infection. All seven of these patients had no evidence of the immunodeficiency virus or any other type of viral prodrome preceding their neurologic symptoms. In three of the patients, HIV-1 was detected within 3 months of the neurologic disorder. In the other four patients, MS had been suspected 41 months to 18 years prior to HIV-1 infection detection. The close temporal relationship between the onset of the MS-like illness and the HIV infection in the three reported patients suggested an association. It has been speculated that MS has a viral etiology. Although, the exact cause of the relapsing and remitting neurologic disorders in Berger, et al case reports cannot be known, it is speculated that there may have been simultaneous occurrence of both MS and HIV infection. Chronic experimental allergic encephalomyelitis (EAE) acting through cell-mediated immunity has been proposed as a model for MS; however, these patients had progression of their demyelination despite lymphopenia and depressed T4 cell populations. Although the clinical syndromes may be similar, the depletion of cell-mediated immunity in
HIV infected patients suggests that there is a different pathogenesis. This alternatively raises the possibility that the HIV infection was directly responsible for the remitting-relapsing MS-like illness 14,15.

**AION IN AIDS SYNDROME**

Primary HIV infection has been postulated as the underlying mechanism in a case of anterior ischemic optic neuropathy (AION). The case of AION reported by Brack et al was diagnosed clinically and confirmed by intravenous fluorescein angiography. Serological titers for infectious agents were negative except for an elevated serum titer of antibodies to HIV. This patient had ischemia of the optic nerve head caused by injury to the posterior ciliary arteries and changes in the retinal circulation 16. This correlates with the increased prevalence of retinal nerve fiber layer infarcts, hemorrhages, and foci non-perfusion of small retinal vessels found clinically in at least 50% of AIDS patients, and in a higher percentage of AIDS patients at autopsy 10. The case reported by Laurent-Coriant et al in the French literature is an HIV patient with bilateral painless optic neuropathy who was unresponsive to antiretroviral and steroid treatments. His clinical course suggested a microvascular ischemia of the optic nerve head related to HIV infection 17.

**ANTITRETROVIRAL THERAPY FOR HIV AS TRIGGER FOR LHON**

Antiviral drugs such as nucleoside and nucleotide analogues used in the management of HIV infection are known to be associated with mitochondrial toxicity. Experimental evidence has demonstrated that nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) affect DNA gamma polymerase, the enzyme is involved in mitochondrial DNA (mtDNA) replication. Leber’s hereditary optic neuropathy (LHON), attributed to mtDNA mutations, causes acute, painless central visual loss. Visual loss does not occur in all patients with mtDNA mutations therefore, it has been postulated that there are other genetic or environmental factors that may trigger the LHON-mutation. There are several case reports of Leber’s Hereditary Optic Neuropathy associated with the use of antiretroviral therapy in HIV infected patients. The cases cited in the literature have been reported by Luke et al and Shaik et al who each reported a case of an HIV patient with the 11778- mutation. Warner and Ries reported a patient with the 14484-mutation, and Mackey et al reported 2 other cases with the same mtDNA mutation. These clinical cases suggest that the effects of antiretroviral treatments on the mitochondrial biogenesis incite LHON in susceptible individuals. Long-term treatment with antiretroviral nucleoside analogues may result in acquired mitochondrial dysfunction. The reported cases imply that visual loss in these patients may be due to a combination of the LHON mutation and the antiretroviral therapy. Warner and Ries speculated that the onset of visual loss is oxidative stress induced by mitochondrial toxicity in patients who already have mutated mtDNA. Due to the possible mechanism of action of antiretroviral drugs of the nucleoside/nucleotide analogue class triggering LHON and the severity of visual loss in this type of optic neuropathy, HIV infected patients should be warned of the potential risk especially if there is a family history suggestive of LHON. NRTIs may need to be discontinued in an HIV infected patient who develops a monocular or binocular optic neuropathy of unknown etiology until LHON is excluded.

**CONCLUSION**

The evaluation of visual loss in AIDS patients is complex, often requiring a detailed work-up to exclude infectious causes. Often, the etiology of the optic neuropathy in HIV patients is not determined. Although in some instances, the cause may be HIV infection itself. Therefore, human immunodeficiency virus infection should be considered in the differential diagnosis of acute or chronic optic neuropathy.

**CME ANSWERS**

1. Yes, the extent and pattern of the axonal loss in the optic nerves suggests that there may be an AIDS-associated primary optic neuropathy. There is some evidence to suggest that direct degeneration of ganglion cell axons in the optic nerve can be primarily due to the HIV virus itself. Recent studies show that the optic nerve degeneration may not be caused by direct HIV viral infection of axons, but by HIV-infected mononuclear phagocyte series cells and glial cells.

2. Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) used in the management of HIV infection are known to be associated with mitochondrial toxicity.

3. Most cases of optic neuropathy in patients with HIV infection are associated with secondary (opportunistic) infections.

**REFERENCES**


DEBATES IN NEURO-OPHTHALMOLOGY

RESOLVED: THAT OPTICAL COHERENCE TOMOGRAPHY (OCT) HAS “REVOLUTIONIZED OUR ASSESSMENT, MANAGEMENT, AND UNDERSTANDING OF NEURO-OPHTHALMIC DISEASE (SUBEI AND EGGENBERGER 2009).”

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LEARNING OBJECTIVES
1. Determine the usefulness of OCT in various clinical situations
2. Evaluate the limitations of OCT in the diagnosis of optic neuropathy

CME QUESTIONS
1. RNFL thinning is a hallmark of compressive optic neuropathy
   a. True
   b. False

2. Which of the following RNFL abnormalities may be seen in patients with myopia and tilted optic nerves?
   a. RNFL thinning
   b. Increased RNFL thickness
   c. Normal RNFL thickness
   d. All of the above
   e. A and B

KEYWORDS
1. Optical coherence tomography
2. Retinal nerve fiber layer analysis
3. Macular disease
4. Optic neuropathy

To make this issue more concrete, here are three cases in which OCT might be used. Each of these three cases presents a common diagnostic challenge in neuro-ophthalmology. Would OCT be helpful in the work-up?

Case 1: A 40-year-old man reports slowly progressive visual loss in both eyes for 6 months. He has a non-contributory history except for heavy alcohol consumption in the past. There is no family history of visual loss or of neurologic disease. He does not particularly like his job as a Ford assembly line worker. Best-corrected acuities are 20/50. Ishihara color plate scores are 5/11. Pupils are normal. Automated visual fields show non-clustered high threshold points with mean deviations of -5 dB OU. The optic discs are tilted with questionable temporal optic disc pallor, but he is a 5-diopter myope.

FRIEDMAN:
Slowly, progressive, bilateral, symmetric visual loss raises several diagnostic possibilities. This man may have retinopathy, optic neuropathy, chiasmal disease or non-organic visual loss. The visual field description essentially excludes a chiasmal problem. A great mnemonic for diagnosing unexplained visual loss, courtesy of Dr. Michael Slavin, is SOFA: Spectacles to Occiput (the visual system from anterior to posterior), Functional & Amblyopia.

Nutritional (“tobacco-alcohol”) amblyopia seems unlikely given that his alcohol consumption was remote, although one never really knows for sure. Heavy drinkers are often smokers, so a cancer associated retinopathy is a consideration. He is in the age range for demyelinating disease, which occasionally presents with slowly progressive visual loss. We are also given a clue about job dissatisfaction (although he is lucky to have a job these days if he works in the auto industry). Patients with “mid-level (20/40-20/80)” bilateral visual loss are the toughest to sort out with respect to functional visual loss, and the disc appearance doesn’t help us. His color vision loss may
be real or feigned. As with many functional neurologic disorders, there may be a combination of real disease and non-organic embellishment.

OCT would definitely be helpful in the armamentarium of tools at our disposal. Pre-OCT, our options were: review the old records, “brute force” refraction, various manipulations at the phoropter to try and prove 20/20 vision (more difficult when the visual loss is binocular than uniolocular), visual evoked potentials (helpful if there is a delay in P100 but not if normal or unrecordable), ERG and mfERG, neuroimaging (a structural lesion is highly unlikely in this case; perhaps helpful if demonstrates small optic nerves or buried disc drusen), orbital ultrasound (buried drusen), fluorescein angiography, quantitative color vision testing and genetic testing (e.g., atypical Leber, CAR). While helpful, some of these tests are quite costly.

Subtle manifestations of macular edema, intraretinal cysts, subtle detachments and macular degenerative changes are discernible on OCT. An abnormal macular OCT with a preserved RNFL scan in our patient would at least deflect him to the Retina service and likely avoid an expensive and time-consuming neuro-ophthalmic evaluation.

Moving on to the optic nerve, an abnormal OCT would help us but there are a few possible confounders in our patient. He is a moderate myope with tilted optic nerves. OCT may reveal increased temporal RNFL thickness compared to eyes with non-tilted nerves (Hwang et al 2011). If that were the case, RNFL thinning in our patient would likely be significant. However, myopia and tilted optic nerves may be associated with peripapillary atrophy (PPA). Abnormal retinal nerve fiber layer (RNFL) structure is frequently present in eyes with PPA with areas of both increased and decreased retinal thinning (Majnunath et al 2011). Additionally, increased axial length may affect RNFL thickness, with decreasing average 360 degree thickness with increasing axial length (Yoo et al, 2011). This structural artifact associated with myopia may potentially classify a normal eye as abnormal.

Jeoung et al studied Stratus OCT and perimetry for the detection of diffuse RNFL atrophy in glaucoma suspects (which was originally described by neuro-opthalmologists Hoyt, Frisen and NM Newman using good old ophthalmoscopy!). They studied 102 eyes of 102 patients with diffuse RNFL atrophy and an equal number of age-matched controls (Jeoung et al 2011). Specificity using average RNFL thickness ranged from 61.5% (range 53.1-69.4) with abnormal values at the 5% level to 54.1% (range 45.7-62.3) with abnormal values at the 1% level and overall specificity approaching 100%. Having a corresponding visual field defect increased the sensitivity considerably. They concluded that using OCT with an internal normative database should be evaluated with caution, especially in the early stages of glaucoma with diffuse NFL thinning.

Amblyopia does not affect the OCT (Walker et al 2011).

My approach to this patient would be:

1. Obtain old records to be sure that this isn’t longstanding amblyopia with recent delusions of Workers Compensation

2. Brute force refraction and other maneuvers to determine whether or not he can be coaxed into seeing 20/20

3. OCT

   a. If OCT shows buried drusen, follow the patient
   b. If OCT shows macular abnormality, send for retinal evaluation
   c. If OCT shows RNFL thinning, proceed with other testing to look for underlying cause of optic neuropathy
   d. If OCT is normal, consider CAR if he is a smoker and get an ERG

TROBE:
The differential diagnosis is between a bilateral retinopathy, a bilateral optic neuropathy from heavy alcohol consumption or from another cause, and malingering.

I must concede that OCT has made a genuine contribution in the diagnosis of maculopathy, which often causes a visible structural alteration. But in this setting, how often is OCT positive when ophthalmoscopy is not? Is OCT the preferred test over electroretinography (ERG)? Are they complimentary, one diagnosing structural alteration, the other dysfunction? I have sometimes ordered visual evoked potentials in this setting, but admit that they are often unreliable. Should OCT and ERG be performed before one would consider ordering brain/orbit MRI to rule out a bilateral optic nerve compressive lesion?

In this case, I would probably order OCT, although it will almost certainly not show a macular lesion. It might or might not show a thinned retinal nerve fiber layer (RNFL), and then I would be left to decide whether to perform further work-up, including brain MRI, testing of blood for a thiamine level, and of urine for heavy metals (!). In truth, I have found that checking for gradient sensory loss in the lower extremities (part of nutritional peripheral neuropathy) is much the most helpful maneuver here!

Case 2: A 60-year-old woman with previous traumatic optic neuropathy taking vision to no light perception in the OS, now complains of slowly progressive visual loss in the OD. Best-corrected visual acuities are OD 20/40, OS NLP. There is an afferent pupil defect in the OS. Automated perimetry shows some scattered high threshold points with a mean deviation of -8 dB OD, but repeated testing shows that the location of the high threshold points shifts and mean deviations vary between -5 and -10 dB. The right fundus appears normal but is slightly obscured by cataract. The left fundus shows a pale disc.
FRIEDMAN:
This patient has progressive visual loss in her only seeing eye and we don’t have the usual optic neuropathy calling cards (APD, optic atrophy) to make a diagnosis in the right eye. She is a bit inconsistent with perimetry but there is no specific pattern to her visual field loss. Let’s go back to the SOFA:

Is her visual loss from cataract, retinal disease or optic neuropathy? (Any of these processes could be bilateral but we won’t know if it has affected her left eye. Likewise, it’s possible that posterior pathway disease could be the culprit in a monocular patient but I am excluding a chiasmal or post-chiasmal origin based on her visual field.) Functional visual loss is always a possibility. She has likely been the beneficiary of many years of ophthalmic follow-up after her initial eye injury, so undiagnosed amblyopia is unlikely.

This woman wouldn’t be the first to present to a neuro-ophthalmologist for visual loss caused by a cataract. If the view of her right fundus was slightly obscured by a cataract (especially if viewed with the indirect ophthalmoscope or using slit lamp bimicroscopy), the lens opacity may be the cause of her problem.

There are a few things on the examination which might help sort this out regarding retina vs. optic nerve. Color vision would likely be abnormal with an optic neuropathy. Amsler grid testing may reveal metamorphopia, which would point me toward the retina. Aside from the exam, my first step would be a slit lamp exam, view with a direct ophthalmoscope, and potential acuity meter testing to determine the extent of visual impairment caused by the cataract. If the cataract is excluded as the source of her visual loss, an OCT would be helpful to determine whether there may be a macular process (if the optic nerve can’t be seen well on her exam, her macula probably can’t either). However, progressive monocular visual loss may be caused by a mass lesion, and RNFL and macular thinning may occur from optic nerve or chiasmal compression. If the compression has either (1) not been present long enough or (2) is relatively posterior along the course of the optic nerve such that the retinal axons have not been damaged, the OCT may be misleadingly normal. In this case, OCT could help define a retinal process in a patient with a limited view of the fundus but would probably not hold up in court if she was later diagnosed with a treatable tumor causing optic nerve compression...

TROBE:
The patient is reporting progressive visual loss in her only sighted eye. An optical cause is not it. The loss of optic function in the contralateral eye eliminates the use of the most valuable test for unilateral optic neuropathy: the swinging light test for an afferent pupil defect. Serial visual field testing yields fluctuating results, so that test is probably not reliable. You are left to judge whether there is optic nerve damage on the basis of the appearance of the optic disc—hardly fail safe.

This case seems like a natural for OCT—a way to assess whether the RNFL is of normal thickness. If OCT shows that the RNFL is thin, you would certainly have to order MRI imaging to rule out a compressive lesion. But here is the problem: if OCT shows that the RNFL is of normal thickness, you would still have to order the imaging study, because compressive lesions can damage optic nerve function without killing axons.

Suppose you found a compressive lesion, would OCT serve as a predictor of how much visual recovery would occur with decompression? There is evidence that it might, but the studies (Jacob et al 2009, Danesh-Meyer et al 2008), although intriguing, have limited clinical value. Jacob et al showed that visual recovery eventually occurred months later even in those with RNFL thinning. Thus, RNFL thinning cannot be an argument against surgery. Danesh-Meyer et al showed that those with severe visual field defects pre-operatively yet a normal RNFL had substantial visual improvement post-operatively, indicating that visual dysfunction and RNFL thickness are not necessarily connected, even in chronic compressive lesions! This finding exposes a major drawback of OCT. That is, a normal OCT does not exclude an optic neuropathy! Would OCT serve as a useful baseline to follow such a patient post-operatively in lieu of conventional measures like visual acuity and visual field? Probably not, as we would be depending on axon death to thin the RNFL. (The same argument could presumably be used in following patients with other chronic optic neuropathies like glaucoma and idiopathic intracranial hypertension, where waiting for RNFL thinning might be a little too late.)

In this case, I would not order OCT. Instead, I would go straight to brain/orbit MRI.

Case 3: A 4-year-old boy complains of recent headaches. There is no pertinent history except that his mother has headaches. A pediatrician finds elevated discs. For your examination, he is too squirrely to get a reliable acuity or confrontation fields. Pupils are normal. Optic discs are both elevated without visible drusen. The neurologic examination is grossly normal.

FRIEDMAN:
The combination of elevated optic nerves and headaches raises the alarming possibility of increased intracranial pressure. Making the distinction of true papilledema from pseudopapilledema can be challenging, even in the most cooperative adult. However, one would not want to miss a brain tumor or hydrocephalus in a young child!

The fact that the pediatrician found elevated optic nerves in a child who is difficult to examine leads me to believe that the optic nerve changes are not subtle.

Spectral-domain OCT is helpful in identifying optic nerve head drusen (ONHD) and distinguishing them from papilledema. One study of 45 patients with ONHD, 15
patients with optic disc edema and 32 normal controls found that OCT showed characteristic changes in patients with ONHD: focal, hyperreflective, subretinal masses with discrete margins, a deformed retinal nerve fiber layer with pseudoedema and high reflectance, and a hyporeflective boot-shaped area adjacent to the drusen (Lee et al 2011). The peripapillary RNFL was thicker in all sections in optic nerves with edema than in optic nerves with drusen.

But what if the drusen are buried? An OCT study of 21 eyes with buried drusen (confirmed with ultrasound) and normal visual fields found focal RNFL defects in some eyes and normal average RNFL thickness in all eyes (Katz and Pomeranz 2005). Thus, patients with buried drusen may not affect the average RNFL and cannot be relied upon as a screening technique.

With respect to our four-year-old, the presence of spontaneous venous pulsations would be reassuring for pseudopapilledema, although not 100% reliable. Venous pulsations may be absent with either papilledema or optic disc drusen. The utility of an OCT is to quickly identify relatively superficial disc drusen that may be hard to distinguish by ophthalmoscopy (or blurred fundus photographs if he was a “wiggle worm”). In that respect, OCT would save unnecessary testing, much of which would likely require that the child be sedated. (Even an examination under anesthesia may not add much to the diagnostic yield and cause further delays and expense.) Orbital ultrasound with a 30 degree test is useful but not universally available; the child's ability to cooperate may be a limiting factor. In the face of an inconclusive OCT, I would proceed with additional evaluation with an MRI of the brain at least, and possibly a lumbar puncture.

TROBE:
The challenge is to distinguish congenital from acquired optic disc elevation, a VERY common problem in clinical practice. I concede that I frequently cannot make this distinction ophthalmoscopically. That history and neurological examination are overwhelmingly normal in these patients hardly excludes increased intracranial pressure. Cerebral hemispheric tumors, especially those originating in frontal and temporal lobes, may be clinically silent for long periods. In children, supratentorial tumors are rare, with papilledema occurring much more commonly from infratentorial masses that obstruct the fourth ventricle or from aqueductal stenosis. Although such tumors usually produce an alteration in balance and consciousness, these manifestations are often delayed. Headache is also a late symptom. Surprisingly, low-grade meningitis can also be clinically silent. And of course, idiopathic intracranial hypertension may have no other clinical manifestations.

But is OCT a reliable differentiator of congenital from acquired optic disc elevation? Is it the best test?

One study using time-domain OCT (TD-OCT) (Johnson et al 2009) and one study using spectral-domain OCT (SD-OCT) (Lee et al 2011) have examined patients with congenital optic disc elevation from drusen and from acquired optic neuropathies to see if OCT could distinguish them. Using TD-OCT, Johnson et al studied, among other patients, 11 with buried drusen and 10 with papilledema. They could differentiate these conditions with approximately 65% sensitivity and specificity. The drusen cases were affirmed by separate diagnostic criteria, including ultrasound and autofluorescence. Using SD-OCT, Lee et al found that all 45 patients with drusen had a focal hyperreflective subretinal mass with discrete margins that was not present in those with other causes of optic disc elevation. However, they did not disclose in what proportion of cases the drusen were buried. Moreover, the diagnosis of drusen was not independently verified with other modalities. Among those with other causes of optic disc elevation, only 4 had papilledema.

B-scan ultrasonography can detect buried drusen (McNicholas et al 2004) but its sensitivity has never been measured against a standard such as CT. No head-to-head study between OCT and ultrasound has been conducted.

Even if OCT were a sensitive detector of buried drusen, are there not cases in which the optic discs are congenitally elevated without drusen? I have many such patients in whom ultrasound and CT are negative for drusen, yet the discs are clearly elevated and detailed brain imaging and lumbar puncture opening pressures are normal. In such cases, would OCT distinguish congenital from acquired optic disc elevation? We do not know.

In this case, I would not order OCT. I would request a B-scan ultrasound. If it were absolutely positive for buried drusen, I would do no further testing. If it were negative, I would order brain MRI or follow for clinical change, depending on my mood.

If you had told me 40 years ago that in 2011 we would still not have a reliable OBJECTIVE means of assessing visual function, I would have been incredulous. And now we are offered a highly sensitive way to measure RNFL thickness. It should be a terrific help in diagnosis. But somehow, it almost never is. When it has already been performed before I see the patient, I typically ignore it. But then, I barely know how to use a cell phone.

CME ANSWERS
1. b
2. d

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