Case Report:

Leber Hereditary Optic Neuropathy in a 60-Year-Old Man with Vitamin B12 Deficiency

LHON should be considered as a diagnosis in patients, regardless of age, with unexplained bilateral optic neuropathy and central vision loss.

By Darby D. Miller, MD, Craig E. Geist, MD, and Charles J. Macri, MD

A 60-year-old man developed Leber Hereditary Optic Neuropathy (LHON) in the context of B12 deficiency. Ophthalmic exams, over time, revealed worsening central vision and bilateral optic disc pseudoedema. Orbit and brain MRI demonstrated enhancement of the left optic nerve sheath. Despite a well-characterized LHON missense mutation, years of antiretroviral therapy, colorectal cancer with chemotherapy, and a case of MRSA pneumonia, the patient experienced no visual loss until becoming vitamin B12 deficient. This case serves as an important reminder that LHON should be considered as a diagnosis in patients, regardless of age, with unexplained bilateral optic neuropathy and central vision loss.

Introduction
Leber Hereditary Optic Neuropathy (LHON) is a rare mitochondrial disorder that typically results in severe and permanent vision loss in adult males beginning in the second decade of life. Three point mutations, G3460A, G11778A, and T14484C, account for the vast majority of cases, and cause impairment of complex I-dependent ATP synthesis. Several precipitants of LHON have been described in the literature, including antiretroviral therapy, anemia, and B12 deficiency.1-3

Case Report
A 60-year-old man presented to neuro-ophthalmology complaining of over two-weeks of blurry vision and difficulty reading. Three weeks prior to presentation, he was hospitalized for a blood transfusion due to anemia (Hb 10.9 g/dl). He reported blurry vision in the left eye within a few days after the transfusion, at which point he saw an
optometrist, who referred him to a neurologist that same day. Neurological examination was significant for bilateral optic disc pseudopseudema. Although several blood tests and cerebrospinal fluid analyses were negative, his vitamin B12 level was low (258 ng/ml). Two months previously, B12 level was normal (848 ng/ml). In addition, an MRI revealed unilateral enhancement of the left optic nerve sheath (Fig. 1a), suggesting optic neuritis. The patient was then hospitalized for a three-day course of intravenous methylprednisone, which did not result in any visual improvement.

His past medical history was noteworthy for a diagnosis of HIV at age 33. He had received antiretroviral therapy for several years and was currently taking tenofovir, emtricitabine, and nevirapine. At neuro-ophthalmology examination, his CD4 count was 314 and viral loads were undetectable. His past medical history was also significant for colorectal cancer diagnosed five years earlier. He received chemotherapy and was in remission. Two months prior to vision loss, he was hospitalized for MRSA pneumonia requiring intubation for four weeks. He recovered from the pneumonia and was discharged home on supplemental oxygen. His family history included a maternal uncle and male cousin who both had early vision loss due to unknown etiologies.

During initial neuro-ophthalmology examination, he reported “hazy” vision and difficulty in reading. His corrected visual acuity declined from a baseline of 20/50 in both eyes to 20/100 in the right eye and 20/400 in the left. Optic disc pseudopseudema and blurred disc margins were noted bilaterally (Fig. 1b). He had no evidence of HIV retinopathy. A repeat MRI again demonstrated enhancement of the left optic nerve sheath. A Humphrey Visual Field (HVF) test revealed bilateral centrocecal scotomas (Fig. 1c). A repeat lumbar puncture and several blood tests were negative, and his CD4 count and viral load remained stable. Another three-day course of intravenous methylprednisone was completed, which again did not result in any visual improvement. A temporal artery biopsy was also performed which was negative for giant cell arteritis.
The following visit, visual acuity further declined to 20/200 in the right eye and to counting fingers at four feet in the left. Optic disc pseudodema and blurred disc margins worsened bilaterally. In light of a strong maternal family history for central vision loss, LHON was considered, with an atypical presentation, as a possible etiology. Genetic testing revealed two mitochondrial mutations seen in LHON: G11778A, a pathogenic mutation, and G15257A, a non-pathogenic mutation. Over the next month, his central vision continued to deteriorate bilaterally, and he progressed to legal blindness.

Discussion
This case is unusual because of the late age at presentation and the two mutations associated with LHON. A case report describes a patient with the same two missense mutations whose visual loss began at age 18. However, the 15257 mutation, although seen in LHON, is not pathogenic. Nevertheless, there are possible explanations for the late presentation.

First, in a subset of patients with the G11778A mutation, a protective effect has been hypothesized for those with mtDNA of haplogroup F or H.

Second, approximately 15 percent of LHON patients are heteroplasmic, meaning both mutant and wild type mtDNA coexist within the individual, and heteroplasmy can reduce the risk of vision loss. However, this patient’s heteroplasmy and haplogroup statuses are unknown.

Despite a pathogenic LHON mutation, several years of antiretroviral therapy, colorectal cancer with chemotherapy, and a severe case of MRSA pneumonia, this patient experienced no visual loss. In this case, the probable precipitant of visual loss was the vitamin B12 deficiency, in the background of a pathogenic LHON mitochondrial mutation. Vitamin B12 deficiency is a documented LHON precipitant and has been shown to cause mitochondrial toxicity as a result of inhibition of the TCA cycle.

Unfortunately, correction of vitamin B12 levels did not result in any visual improvement, and bilateral visual loss consistent with LHON occurred. This case emphasizes the importance of testing for LHON in patients, no matter their age, with unexplained bilateral optic neuropathy with central vision loss.

Darby D. Miller, MD is a resident in the Department of Ophthalmology at The George Washington University School of Medicine.

Craig E. Geist, MD is Professor of Ophthalmology and Chairman in the Department of Ophthalmology at The George Washington University School of Medicine.

Charles J. Macri, MD is Professor of Obstetrics & Gynecology; Director, Division of Maternal Fetal Medicine in the Department of Obstetrics and Gynecology at The George Washington University School of Medicine.

This study is not industry-sponsored.

Dr. Darby Miller reports no disclosures.

Dr. Craig Geist reports no disclosures.

Dr. Charles Macri reports no disclosures.