Clinical Reasoning:

A 10-year-old boy with bilateral vision loss

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SECTION 1

A 10-year-old previously healthy Caucasian boy was referred for evaluation of bilateral loss of vision with abnormal appearing optic nerves. Two months before the referral, the patient started to exhibit a decrease in vision both at near and at distance with difficulty reading books and difficulty viewing the chalkboard at school. One month prior to the referral, the patient was seen by his primary care physician with a complaint of intermittent headaches, which varied in severity, occurring as frequently as daily. The patient had been taking ibuprofen regularly to alleviate the pain. Vital signs were within normal limits. The patient weighed 53.5 kg and stood 145 cm tall (body mass index 25.4). The patient's family reported that the patient had gained substantial weight over the previous months. MRI and venography of the brain and orbit were unremarkable with no evidence of inflammation, demyelinating disease, or compressive or infiltrative lesions. A lumbar puncture was performed with an opening pressure of 20 cm H₂O with normal cell count, protein, and glucose levels. The patient was started on acetazolamide 250 mg twice a day for a possible diagnosis of idiopathic intracranial hypertension (pseudotumor cerebri) and referred to neuro-ophthalmology for further evaluation.

At the time of neuro-ophthalmology evaluation, the patient continued to report intermittent headaches that had not changed or improved since starting acetazolamide. He denied transient visual obscurations, diplopia, eye pain, tinnitus, numbness, weakness, rash, arthritis, or recent fever or illness. The patient had not taken any other medications over the previous months. There was no relevant past medical or surgical history. His mother had been diagnosed with fibromyalgia and a great aunt had been diagnosed with multiple sclerosis.

There was no family history of ocular disease, including optic nerve pathologies, other vasculitides, or autoimmune or clotting disorders. Neither the patient nor the family was able to indicate whether the bilateral visual changes were simultaneous at onset or sequential.

On examination, best-corrected visual acuity was 20/250 in both eyes. The pupils were symmetric and equally reactive to light with no afferent pupillary defect. Intraocular pressures were 20 mm Hg in both eyes by applanation. Motility and confrontational visual fields were full. The remaining cranial nerves were intact bilaterally. Ishihara color testing revealed 1/11 plates correct in the right eye and 2/11 correct in the left eye. Slit-lamp examination was normal with no conjunctival injection or anterior chamber inflammation. The lenses were clear in both eyes. There were no vitreous cells in either eye. The dilated fundus examination demonstrated bilateral optic nerve elevation, but no hemorrhages or Paton lines. Humphrey visual field examination demonstrated a dense central defect involving the nasal field as well the superior temporal field in the right eye and a dense central defect extending into the inferior field in the left eye (figure e-1 at [Neurology.org](#)). Fundus fluorescein angiography was not performed. B-scan ultrasonography (ultrasound of the inner eye and optic nerve) showed a hyperechoic focus at the optic nerve suggestive of optic nerve drusen (figure e-2). Optical coherence tomography of the retinal nerve fiber layer (RNFL) showed a thickened RNFL bilaterally (figure e-3).

Questions for consideration:

1. What is the differential diagnosis based on these findings?
2. What additional testing would be indicated?

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Table Differential diagnosis of optic neuropathy

Inflammatory (subacute, painless)
Systemic autoimmune disease
Sjögren syndrome
Systemic lupus erythematosus
Wegener granulomatosis
Behçet syndrome
Sarcoidosis
Chronic relapsing inflammatory optic neuropathy
Paraneoplastic
Parainfectious
Genetic/hereditary (subacute, painless)
Leber hereditary optic neuropathy
Kjer type autosomal dominant optic atrophy
Toxic/metabolic (subacute, painless)
Drugs: ethambutol, aminoglycosides, chloramphenicol, linezolid, zidovudine and other antiretroviral drugs
Toxins: smoke, ethanol, pesticides, cyanide, methanol
Nutritional deficiency (vitamins B ₁ , B ₉ , B ₁₂)
Tobacco-alcohol amblyopia
Radiation
Neoplasm (compressive, infiltrative) (subacute, painless)
Optic glioma
Meningioma
Craniopharyngioma
Pituitary adenoma
Lymphoma
Metastases
Compression (subacute, painless)
Pseudotumor cerebri
Abscess
Carotid-ophthalmic artery aneurysm
Thyroid ophthalmopathy
Optic neuritis (subacute/acute, painful)
Multiple sclerosis
Neuromyelitis optica
Viruses
Neuroretinitis
Toxoplasmosis
Bartonella
Syphilis
Lyme disease
Meningitis
Encephalitis
Ischemic optic neuropathy (acute, painless)
Arteritic ischemic optic neuropathy
Nonarteritic ischemic optic neuropathy
Trauma (acute, painful)

SECTION 2

This 10-year-old boy presents with painless, subacute vision loss in both eyes with associated dyschromatopsia and abnormal appearing optic nerves, most notably elevation and RNFL thickening. While B-scan ultrasonography showed findings suggestive of optic nerve head drusen, the patient's clinical course including dramatic vision loss and field changes are inconsistent with a diagnosis of optic nerve head drusen. Fundus examination ruled out retinopathy, and thus we considered the differential diagnosis for bilateral subacute optic neuropathy (table).

At the time of initial presentation, the patient was prescribed a course of oral prednisone for a suspected inflammatory etiology and acetazolamide was continued until follow-up. Workup was unremarkable, including normal serum testing for antinuclear antibody, antineutrophil cytoplasmic antibody, C-reactive protein, erythrocyte sedimentation rate, angiotensin-converting enzyme, lysozyme, rapid plasma reagin, aquaporin 4 immunoglobulin for neuromyelitis optica, and vitamins B₁, B₉, and B₁₂. Visual function remained stable over the next 2 months, during which time the oral prednisone was tapered and acetazolamide discontinued due to lack of improvement.

Question for consideration:

1. Based on these results, how would you narrow your differential diagnosis and what other tests would you pursue, if any?

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All conditions listed are of variable clinical presentations and may differ from these categorizations.

SECTION 3

The most common causes for bilateral symmetric optic neuropathies in the setting of unremarkable laboratories include Leber hereditary optic neuropathy (LHON), dominant optic atrophy, and nutritional and toxic optic neuropathies.

Dominant optic atrophy is characterized by bilateral vision loss that occurs at a young age, typically before age 10, which progresses slowly to a visual acuity between 20/100 and 20/200. A family history is usually elicited.¹ A chronic poor diet can lead to vitamin B deficiencies, with thiamine deficiency being the most common etiology. Several antibiotics can produce mitochondrial optic neuropathies, including ethambutol, aminoglycosides, chloramphenicol, linezolid, zidovudine, and other antiretroviral drugs. Toxins that may contribute to optic neuropathy include ethanol, methanol, pesticides, and cyanide.² In patients with LHON, a maternal family member with vision loss can often be identified.¹

Genetic testing in our patient revealed the presence of the 11,778 (mt-ND4) G→A mitochondrial DNA mutation consistent with a diagnosis of LHON. The patient and his family were counseled regarding the diagnosis, prognosis, and current treatment options. The family was counseled on pursuing genetic testing for the patient's brother and sister.

DISCUSSION LHON was originally described by Dr. Theodore Leber, a German ophthalmologist, in 1871.¹ LHON was the first disorder to be attributed to and is the most common optic neuropathy caused by a point mutation in mitochondrial DNA (mtDNA).¹ The most commonly diagnosed mutation is found at nucleotide position 11,778 (mt-ND4), followed by point mutations at nucleotide positions 14,484 (mt-ND1) and 3,460 (mt-ND6).¹ A total of 90% to 95% of LHON diagnoses are attributable to these point mutations.^{1,2} The mitochondrial mutations affect NADH dehydrogenase subunits of respiratory complex I of the electron transport chain reducing the efficiency of ATP synthesis and resulting in the selective degeneration of susceptible retinal ganglion cells.^{1,2} While the exact mechanism is not understood, heteroplasmy, haplogroup inheritance, mitochondrial mass, hormonal differences, and environmental factors likely play a role.²

No epidemiologic studies have been carried out in the United States, but reports from northern Europe indicate the prevalence of LHON diagnosed by the 3 most common point mutations to be 1 in 31,000–54,000.^{3–6}

LHON is predominantly diagnosed in men (80%–90%) in the second and third decade of life, although cases in patients as young as 2 years and as old as 87 years at diagnosis have been documented.²

The patient typically presents with painless, subacute vision loss in one eye, followed by sequential vision loss weeks later in the other eye. Funduscopy examination during the acute phase of the disease may be normal or may show hyperemia of the optic disc, vascular tortuosity, and RNFL swelling without corresponding leakage on fluorescein angiography around the optic disc. Auxiliary tests to rule out differential diagnoses include visual field testing, optical coherence tomography, visual evoked potentials, MRI, and lumbar puncture.^{1,2}

A clinical diagnosis may be reached with evidence of a maternal family history of vision loss and typical presenting symptoms. The diagnosis can then be confirmed in the majority of cases by direct genetic testing for the common LHON mtDNA mutations.¹

Prognosis is typically poor.² The severity of the phenotype is greater for the 11,778 and 3,460 mutations and milder for the 14,484 mutation.¹ The vision loss is typically permanent but reports have indicated visual improvement in untreated individuals, most frequently with the 14,484 mutation.² Because most LHON mutations are homoplasmic, one of the most important components of treating remains genetic counseling for the family.⁷

Treatment is aimed at restoring the functionality of respiratory complex I and reducing oxidative stress. Idebenone, a member of the quinone family, and structurally similar to coenzyme-Q₁₀, was evaluated in the Rescue of Hereditary Optic Disease Outpatient Study (RHODOS) and demonstrated a trend toward visual improvement, although not statistically significant.⁸ Similarly, EPI-743, a para-benzoquinone, was shown to halt the disease course and reverse vision loss in 4 of 5 patients in an open-label clinical trial.⁹ More recently, gene therapy has moved to the forefront in ongoing clinical trials. Feuer et al.¹⁰ reported an improvement in visual acuity from baseline to 3 months with the use of an adenovirus vector in 5 patients with the 11,778 mutation with no adverse effects.

Despite the lack of a universally accepted treatment, the sequential vision loss in LHON offers a potential therapeutic window to halt the disease progression if recognized early. Ongoing trials promise better understanding of disease pathophysiology as well as the safety and efficacy of various treatment options.

Follow-up. The patient was started on idebenone 600 mg daily. At examination 4 months after initial presentation and 2 months after the diagnosis of LHON, the patient noted a slight subjective improvement in vision. Best-corrected visual acuity was 20/150 in both eyes; color plates improved to 3/11 in both eyes. Examination, including optic nerve appearance, was unchanged.

AUTHOR CONTRIBUTIONS

Dr. Bulwa collected patient information and all relevant investigations including imaging from medical records, performed all literature reviews, drafted/revised the manuscript, and formatted the figures. Dr. Nichols and Dr. Gupta are the principal treating neuro-ophthalmologists, provided patient histories and information on the diagnosis and follow-up, and provided comments and revisions on the manuscript.

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DISCLOSURE

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