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Orbital Magnetic Resonance Imaging of a 36-Year-Old Woman with Leber Hereditary Optic Neuropathy: A Case Report

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Abstract: Leber hereditary optic neuropathy (LHON) is a rare disorder that results in loss of central vision. Although the initial onset of LHON is most commonly seen in patients aged 15-35 years, it may occur at any age. The disorder is more common in men than women and is known to be caused by one of three mitochondrial DNA point mutations: 11778G>A, 3460G>A, or 14484T>C. Whereas the diagnosis of LHON is conventionally based on a patient's clinical presentation, family history, and the results of ophthalmologic examination and genetic testing, it can significantly benefit from early contribution of neuroimaging. We report a case of LHON in a 36-year-old woman with low visual acuity and progressive worsening of vision for 7 months, a family history of LHON, and abnormal central hyperintense signal within the optic nerves on T2-weighted fat-saturated magnetic resonance imaging of the orbits. Some etiopathogenetic and neuroimaging aspects of LHON as well as challenges in diagnosis and treatment of patients with the disorder are also discussed.

Keywords: *Leber hereditary optic neuropathy, T2-hyperintensity, optic nerve, magnetic resonance imaging of the orbit*

Introduction

Leber hereditary optic neuropathy (LHON) (OMIM #535000)[1] is a rare disorder[2] that often results in diverse types of vision loss and may occur at any age, although its initial onset is most commonly seen in patients aged 15-35 years.[3] The disorder is more common in men than women.[3] Although there are still gaps in understanding the etiology of LHON, in approximately 95% of patients,[1] the disorder is known to be caused by one of three mitochondrial DNA (mtDNA) point mutations: most commonly 11778G>A (OMIM 516003.0001), as well as 3460G>A (OMIM 516000.0001), and 14484T>C (OMIM 516006.0001).[1,3] In addition, an autosomal recessive form of LHON, Leber-like hereditary optic neuropathy (OMIM #619382), with a clinical manifestation indistinguishable from that of LHON was recently identified.[4] The pathogenesis of

Key Points

- Radiologists should be familiar with MRI signs of Leber hereditary optic neuropathy (LHON) within and beyond the visual system to be able to contribute to the timely diagnosis and effective treatment of patients with the disorder.
- A nonspecific hyperintense signal within and swelling of the optic nerves and the optic chiasm are commonly detected on T2-weighted MRI in the pregeniculate visual pathway of patients with LHON.
- In conjunction with clinical findings, MRI can help exclude other causes of optic neuropathies in the acute phase of LHON, visualize the tissue loss across the pregeniculate visual pathway in chronic LHON, and evaluate the changes in volume and diameter of the optic nerves following patient treatment.

Abbreviations
- FatSat: fat-saturated (MRI)
- GCL: ganglion cell layer
- HVF: Humphrey visual field
- LHON: Leber hereditary optic neuropathy
- LHON-MS: LHON-multiple sclerosis (phenotype)
- MD: mean deviation
- MRI: magnetic resonance imaging
- MS: multiple sclerosis
- mtDNA: mitochondrial DNA
- OCT: optical coherence tomography
- OU: oculus unitas (both eyes)/oculus uterque (each eye)
- PVD: posterior vitreous detachment
- RGC: retinal ganglion cells
- RNFL: retinal nerve fiber layer
- TSE: turbo spin-echo (MRI)

LHON is related to degradation of retinal ganglion cells (RGCs) within the inner retina, leading to subsequent degeneration of the optic nerve and, ultimately, the loss of vision.[3] The prevalence of LHON is 4.3 per 100 000 worldwide.[2]

From a clinical perspective, the rarity of LHON and the similarity of its clinical manifestations to those of neuromyelitis optica, optic neuritis, neuropathies of various etiologies,[5,6] as well as Harding disease (a multiple sclerosis-like phenotype) and Leigh syndrome (a rare neurodegenrative mitochondrial disorder) associated with LHON,[7] make a conclusive diagnosis of LHON challenging. From a neuroimaging perspective, an early diagnosis is no less difficult because of the genetic variability of the disorder, its rarity, fast progression, frequent association with comorbidities with distinct neural profiles, possible changes following the treatment of the disorder, and technical difficulties in magnetic resonance imaging (MRI) of the optic nerves.[3]

However, a hyperintense signal within and swelling of the optic nerves and the optic chiasm are commonly detected on T2-weighted MRI in the pregeniculate visual pathway of patients with LHON.[3,8,9] And, although some authors[5,9] suggest that these findings are nonspecific markers of optic neuropathies, when a patient presents with central or ceco-central scotoma, deterioration of visual acuity, dyschromatopsia, reduced contrast sensitivity, thinning of the inferior-temporal retinal nerve fiber layers (RNFL), family history positive for LHON, and/or extraocular features,[6,7] MRI can help exclude other causes of optic neuropathies in the acute phase of LHON,[5] visualize the tissue loss across the pregeniculate visual pathway in patients with chronic LHON, and evaluate the changes in volume and diameter of the optic nerves following patient treatment.[3]

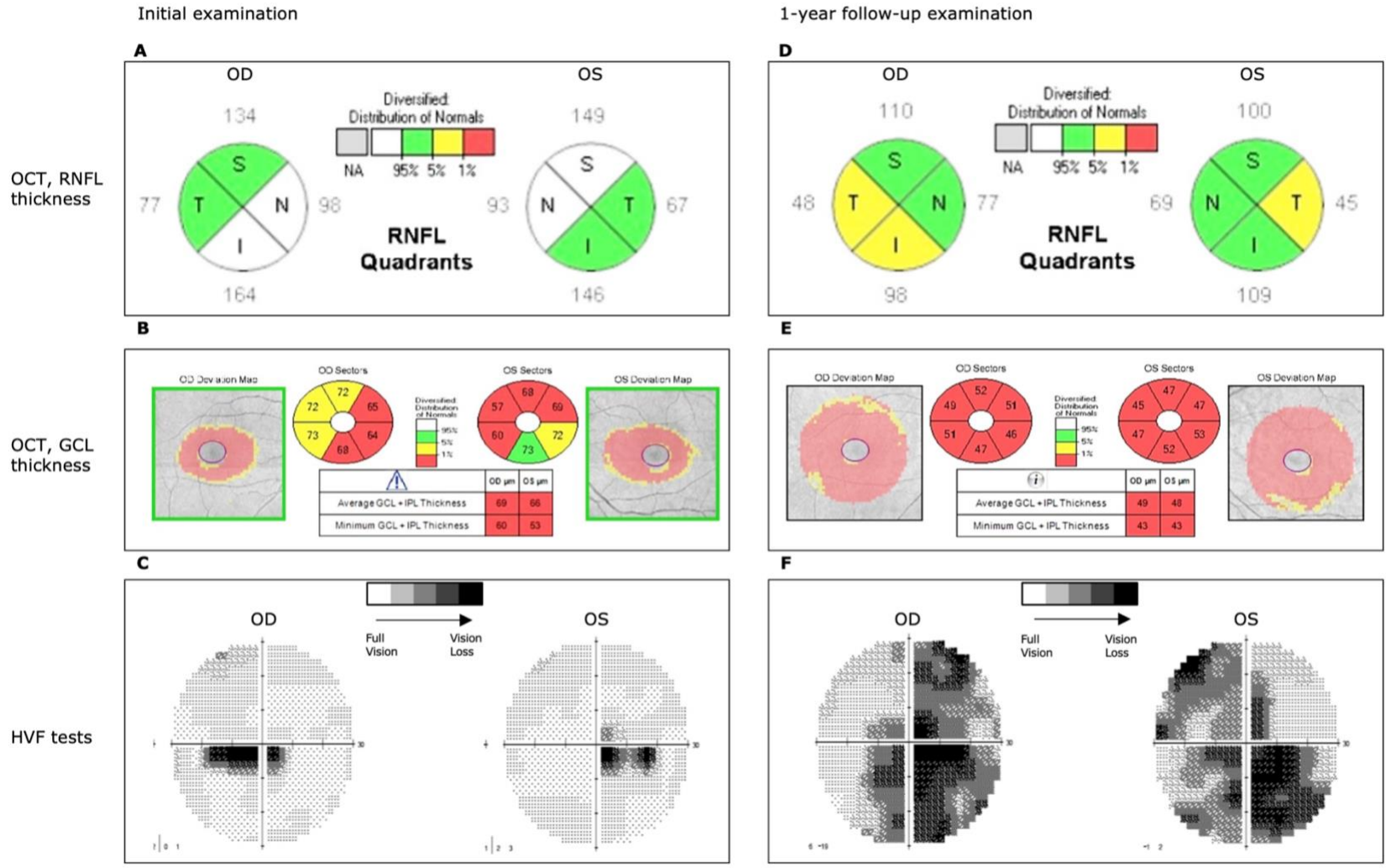
In our patient, on T2-weighted fat-saturated (FatSat) MRI, we observed a pronounced hyperintense signal in the canalicular and the cisternal segments of the optic nerves. Considering the patient's clinical presentation and family history, this MRI finding played an important role in confirming the diagnosis of our patient with LHON.

Case Presentation

A 36-year-old woman presented to an ophthalmologist with a 7-month-long progression of blurry vision in the left eye. The patient reported that for the prior 3 months, her vision was significantly worsening while viewing a computer screen. The patient's vision also appeared to worsen in association with alcohol consumption. Just prior to presentation, the patient experienced acute changes of vision in the right eye and, for the first time since the onset of the symptoms, sought help from a primary care physician who suggested that the symptoms may be due to a retinal injury, for which the patient was referred to an ophthalmologist.

On the initial ophthalmologic examination, the patient's visual acuity was 20/25 OD and 20/70 OS. The patient's contrast sensitivity was reduced, to a greater degree in the left eye, while counting fingers was intact in all quadrants of both eyes on confrontation visual fields testing. The patient did not experience metamorphopsia on the Amsler grid test. The result of an Ishihara 8-plate test was 8/8 in both eyes, indicating no evidence of color blindness. On dilated optical fundus examination, retinal hemorrhage along the inferotemporal arcade was seen and findings that may represent

Figure 1. The Results of Initial and 1-Year Follow-up Optical Coherence Tomography (OCT) and Humphrey Visual Field (HVF) Tests of a 36-Year-Old Woman with Leber Hereditary Optic Neuropathy (LHON)



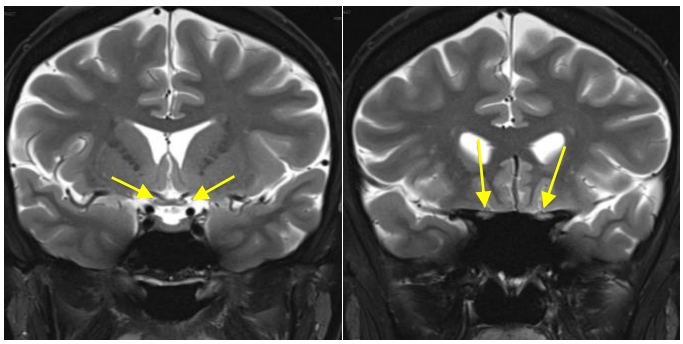
A 1-year comparison of the results of OCT and HVF tests shows only mild losses in thickness of the RNFL (A and D) incongruent with both significant losses in thickness of the GCL (B and E) and substantial expansion of visual fields defects (C and F) in both eyes, the findings suggestive of LHON in general, and LHON type II in particular. (C and F) 30-2 HVF grayscale maps show 1-year progression of visual field defects from a small, dense central scotoma to severe vision losses in both eyes.

Abbreviations: GCL, ganglion cell layer; I, inferior sector; N, nasal sector; OD, right eye; OS, left eye; RNFL, retinal nerve fiber layer; S, superior sector; T, temporal sector.

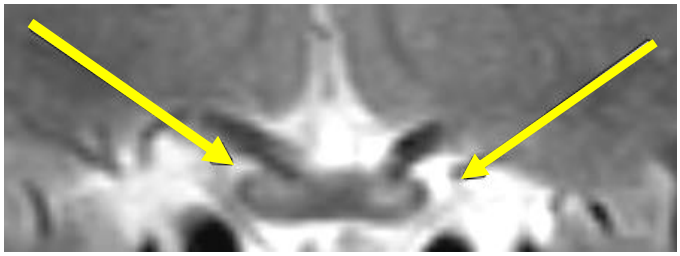
Figure 2. T2-Weighted Fat-Saturated (FatSat) Turbo Spin Echo (TSE) Magnetic Resonance Imaging (MRI) of the Orbits of a 36-Year-Old Woman with Leber Hereditary Optic Neuropathy

A T2-weighted FatSat TSE MR image, coronal view, optic chiasm level

B T2-weighted FatSat TSE MR image, coronal view, optic nerves level



C T2-weighted FatSat TSE MR image, coronal view, optic chiasm level, close-up



(A-C) T2-weighted FatSat TSE MR images of the orbits show abnormal central hyperintense signal in the canalicular and cisternal segments of the optic nerves (A, B, and C, arrows). (C) Image shows a close-up view of the optic chiasm (C, arrows) with central hyperintense signal.

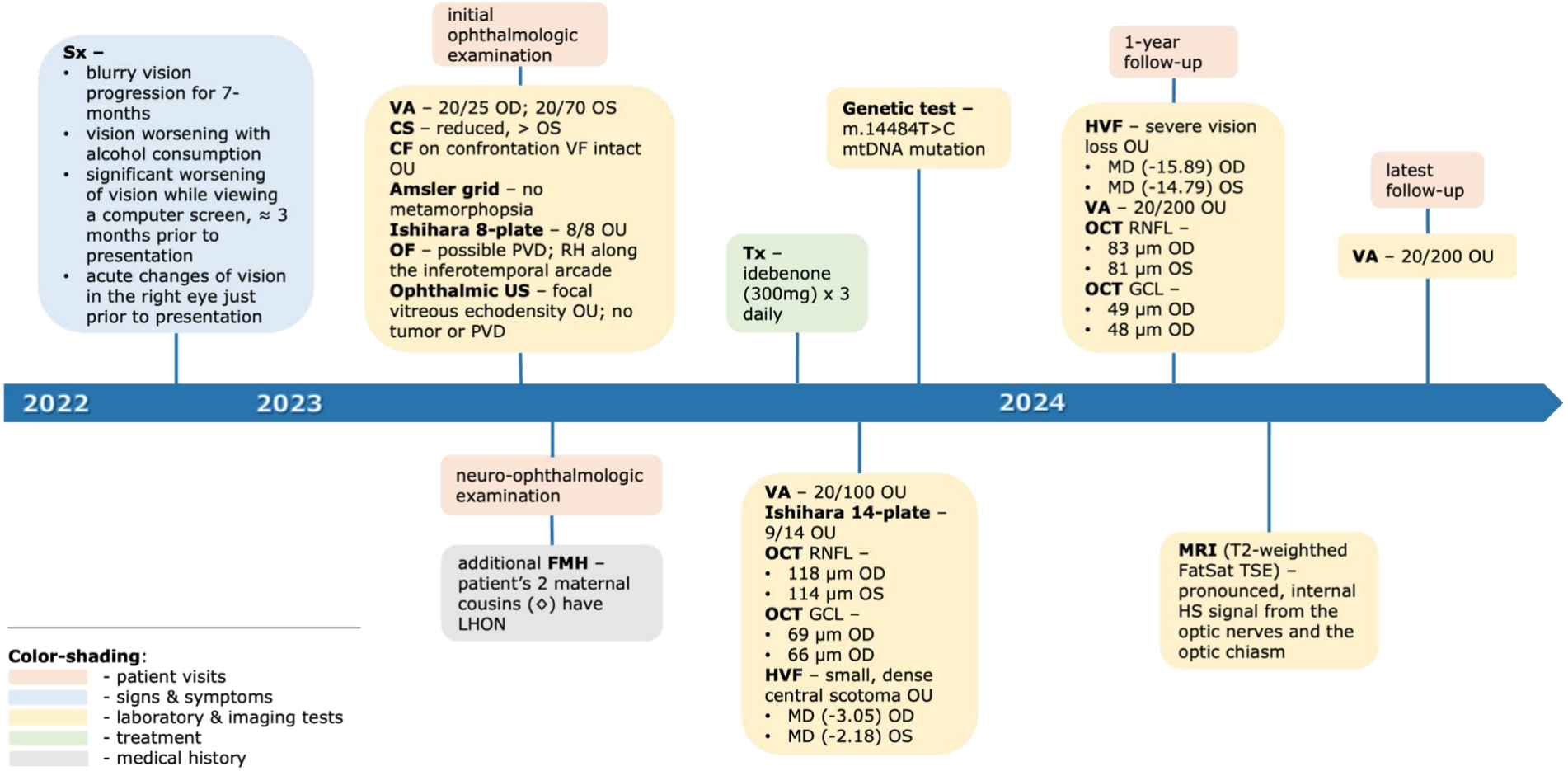
a posterior vitreous detachment (PVD) were noted.

There was no evidence of retinal detachment, the optic nerve head appeared within normal limits, and there was no relative afferent pupillary defect. Fluoresceine angiogram showed no neovascularization or macular edema. An ophthalmic ultrasonography showed focal vitreous echodensity in both eyes with no tumor or PVD. The ophthalmologist suggested that the presence of retinal hemorrhage may be due to Valsalva maneuver. The patient was referred to a neuro-ophthalmologist to be further evaluated for potential optic neuropathy.

Despite the fact that the patient did not have a history of tobacco smoking or heavy drinking, based on the patient's clinical presentation and the results of initial ophthalmologic tests, a neuro-ophthalmologist suspected that the patient had environmentally triggered, type II, Leber hereditary optic neuropathy (LHON). Further history-taking revealed that two of the patient's maternal cousins have LHON. Subsequently, the patient was given idebenone (300mg) three times daily. Genetic testing revealed that the patient has m.14484T>C mtDNA mutation, confirming the presence of LHON. On a following ophthalmologic examination, the patient had a visual acuity of 20/100 OU. A repeated color blindness test on a more comprehensive Ishihara 14-plate set revealed a score of 9/14 in each eye. Optical coherence tomography (OCT) (Zeiss Cirrus 5000 HD-OCT; Carl Zeiss Meditec) showed no signs of atrophy of the retinal nerve fiber layer (RNFL) (average RNFL thickness, 118 µm OD; 114 µm OS) (Figure 1A). However, Humphrey visual field (HVF) test showed a small, dense central scotoma in both eyes [mean deviation (MD), -3.05 OD; -2.18 OS] (Figure 1C). This structure-function mismatch (relatively preserved RNFL despite significant VF deficits) was suggestive of LHON type II, according to the neuro-ophthalmologist. In addition, OCT showed notable thinning of the ganglion cell layer (GCL) in both eyes (average GCL thicknesses, 69 µm OD; 66 µm OS), which was also consistent with the early phase of LHON, where the GCL thinning may precede thinning of the RNFL.

After taking idebenone for approximately one year, the patient returned for follow-up to the neuro-ophthalmology clinic, where OCT showed only mild losses in the RNFL (average RNFL thickness, 83 µm OD; 81 µm OS) (Figure 1D) compared with more severe losses found on HVF test (MD, -15.89 OD; -14.79 OS) (Figure 1F). At this time, OCT showed significant thinning of the retinal GCL (average GCL thickness, 49 µm OD; 48 µm OS) (Figure 1E). The patient's visual acuity was 20/200 OU. To understand the severity of the patient's disease, magnetic resonance imaging (MRI) of the brain and the orbits was performed for the first time. The MRI of the orbits was performed with administration of 5.9 mL of gadobutrol, 1 mmol/mL, utilizing the institution's protocol with imaging sequences as follows: a) precontrast study: T1-weighted thin axial view, b) contrast study: T2-weighted FatSat turbo spin-echo (TSE) thin coronal view, c) postcontrast

Case report timeline



Abbreviations: ◇, diamond, individual whose sex is not specified; CF, counting fingers; CS, contrast sensitivity; FatSat, fat-saturated; FMH, family medical history; GCL, ganglion cell layer; HS, hyperintense; HVF, Humphrey visual field; LHON, Leber hereditary optic neuropathy; MD, mean deviation; MRI, magnetic resonance imaging; OCT, optical coherence tomography; OF, optical fundus; OU, oculus unitas (both eyes)/oculus uterque (each eye); PVD, posterior vitreous detachment; RH, retinal hemorrhage; RNFL, retinal nerve fiber layer; Sx, symptoms; TSE, turbo spin-echo; Tx, treatment; US, ultrasonography; VA, visual acuity.

study: T1-weighted FatSat thin coronal view, and d) postcontrast study: T1-weighted FatSat thin axial view. The findings showed a pronounced internal hyperintense signal from the optic nerves on T2-weighted FatSat TSE sequence (Figure 2). These findings signified edematous changes caused by longstanding cellular damage. In follow-up visits with an ophthalmologist, the patient demonstrated stable vision loss with visual acuity 20/200 OU.

Discussion

This case report exemplifies the characteristics of LHON as well as the importance of neuroradiologic evaluation of patients with this entity. Because LHON is one of the rare disorders[2] that can cause vision loss, it is not readily considered in the differential diagnosis.

The diagnosis of LHON is conventionally based on a patient's clinical presentation, family history, and the results of ophthalmologic examination, and might be confirmed by genetic testing.[6,7] Magnetic resonance imaging may provide evidence of optic nerve damage in patients with chronic LHON,[3,6,9] as the cellular impairment caused by a mitochondrial gene mutation that heavily affects retinal ganglion cells (RGCs) may be associated, although nonspecifically,[5,9] with a hyperintense signal within the posterior portion of the optic nerves and in the optic chiasm on T2-weighted images.[3,8,9] In our patient, who by the time of MRI had significant thinning of GCL, we observed a hyperintense signal in the canalicular and cisternal segments of the optic nerves as well as in the optic chiasm.

Another nonspecific MRI feature that is often observed along the optic nerves in patients with chronic LHON is increased mean diffusivity with reduced fractional anisotropy on diffusion tensor imaging, which seemingly correlates with the loss of specific RGCs and, consequently, with the severity of damage of the optic nerve fibers and reduction of central visual acuity.[3] In addition, in some patients with LHON, MRI may reveal chiasmal enlargement,[3,5,9] swelling of the optic nerve during the acute onset of LHON,[3] and/or loss of chiasmal volume in a chronic phase of the disorder.[3]

Furthermore, in conjunction with clinical findings, MRI can be effectively used for differential diagnosis of LHON to distinguish this disorder from neuromyelitis optica spectrum disorder, optic neuritis, neuropathies of various etiologies,[5,6] as well as Harding disease and Leigh syndrome associated with LHON.[7] Specifically, in younger patients, in cases of demyelinating optic neuritis that is often associated with multiple sclerosis or neuromyelitis optica,[5,6] T2-weighted MR images of the optic nerve(s) or the optic chiasm typically show a hyperintense signal similar to that seen in cases of LHON.[5,6] However, unlike in cases of LHON, this hyperintense signal is characteristically seen in the acute phase of the disease, along with various lesions suggestive of demyelination in the white matter.[5] In patients with orbital infection, ischemic disease, or vasculitis resulting in optic neuropathy/neuritis and vision loss, MRI may show high signal in the paranasal sinuses and the orbital fat, within the optic nerve, or in a vessel's lumen, respectively, on T2-weighted fat-suppressed images.[5] However, in these cases the lesions are often seen unilaterally,[5] although careful clinical examination is necessary here as most of the patients with LHON may have unilateral visual defect at first presentation.[6] As patients with LHON may present with unilateral or bitemporal hemianopia, more frequently in the late phase of the disorder,[6,10] MRI can help exclude compressive optic neuropathy caused by a mass effect (eg, pituitary macroadenoma or craniopharyngioma) on the optic chiasm.[5]

Because some patients with LHON may manifest extraocular features (LHON 'plus' syndromes), including multiple sclerosis, movement disorders, cardiac arrhythmias, peripheral neuropathy, nonspecific myopathy, and dementia, evaluation of these patients with MRI may be necessary,[3,7,11] although screening for LHON should be decided on a case-by-case basis.[11] One of the LHON 'plus' syndromes that requires the attention of radiologists is the LHON-multiple sclerosis (LHON-MS) phenotype, Harding syndrome. This condition can be misrecognized as multiple sclerosis (MS) because of similar clinical manifestation with bilateral, sequential vision loss and the appearance on T2-weighted MR images as discrete and disseminated demyelination areas with high signal intensity, mainly in the periventricular white

matter.[1,5,7] However, ocular pain that typically occurs in MS is not characteristic for LHON-MS, the loss of vision, uniquely for the latter, is often unilateral, and lesions in LHON-MS are less bright than those in MS on T2- weighted images and may have a distinctly different distribution.[11] Knowledge of these clinical and imaging characteristics of LHON-MS and the ability to recognize optic nerve damage on advanced MRI sequences early can help expedite accurate diagnosis and treatment to prevent vision loss in patients with the disorder.

Another LHON 'plus' syndrome is the result of association of LHON-phenotype with Leigh syndrome (OMIM #500017), a rare neurodegenerative mitochondrial disorder that is characterized by psychomotor regression, peripheral neuropathy, hearing loss, hyperreflexia, cerebellar ataxia, spasticity, hypotonia, ophthalmoparesis, and optic atrophy.[1,7] In these cases, in addition to hyperintense signal within the optic nerve and the chiasm seen on T2-weighted images in patients with LHON, MRI may often show multiple hyperintense signals in the brainstem and bilateral, symmetric radiolucencies in the basal ganglia.[1]

Although LHON can be challenging to diagnose, it can be effectively treated, especially early in its course, with idebenone, the only approved treatment for the disorder to date.[3] In patients with LHON and dysfunctional complex I of the mitochondrial respiratory chain, idebenone bypasses the complex I, stimulates adenosine triphosphate production, and thus promotes vision recovery, especially if taken within less than one year since the disorder onset.[3,7] The efficacy of treating patients with idebenone can be evaluated on MRI, as it has been shown that treated patients with LHON have greater volume and diameter of the optic nerves compared with those of untreated patients.[3]

Finally, it is worth mentioning that there are thought to be two clinically distinct types of LHON: Type 1 that is triggered genetically and sub-acute, occurs at about age 20, and results in extensive losses in the RNFL and the visual fields, and Type II that is triggered environmentally and insidious, occurs after age 40, typically associated with smoking tobacco and/or heavy alcohol consumption, and results in an extensive loss of the visual fields but partly preserved RNFL.[12] Based on our patient's medical and social history and the results of clinical evaluation, we believe that the patient experienced LHON Type II.

Because the initial clinical presentation and the results of ancillary tests in cases of LHON might not be clear enough for making an accurate diagnosis, some authors[8,9] recommend the early use of MRI to help exclude other causes of optic neuropathies. We believe that in our patient this would be a valid diagnostic approach as it could help facilitate an early and deeper inquiry into the patient's family history, infer the diagnosis, and increase a likelihood of better treatment outcomes.

Conclusion

As MR imaging has become a necessary tool in the diagnosis and treatment of patients with visual abnormalities, understanding the imaging features of LHON becomes a valuable asset for facilitating early diagnosis and treatment. Although LHON is a rare condition, it should be considered by a radiologist during evaluation of the brain and the orbits of patients with sudden or severe vision loss. The most common characteristic of LHON on T2-weighted MRI is abnormal central hyperintense signal within the optic nerves, specifically in the prechiasmatic segment, indicating loss of the myelin and the axonal cells in the optic nerves. A patient's family history can provide a radiologist with additional insight into potential presence of LHON. There is an effective treatment for LHON, and making an early diagnosis is necessary to prevent severe vision loss from advanced optic nerve damage.

Author Contributions

Conceptualization, J.E.C. and J.A.; Acquisition, analysis, and interpretation of data, J.E.C., S.C., and J.A.; Writing – original draft preparation, J.E.C.; Review and revisions J.E.C., S.C., and J.A.; Supervision, J.A. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

None to report.

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