

Case Report

DNAJC30 Mutation in a Patient with Coexisting Leber's Hereditary Optic Neuropathy and Multiple Sclerosis (Harding's Syndrome): A Case Report

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Keywords

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Abstract

Introduction: Patients with Leber's hereditary optic neuropathy (LHON) have a higher risk of developing multiple sclerosis (MS) than the general population. The coexistence of LHON and MS, also known as Harding's syndrome complicates the diagnosis of optic neuropathy, particularly when the underlying genetic mutation is a rare cause of LHON like *DNAJC30*. **Case Presentation:** We present a 26-year-old woman with progressive, sequential, painless, bilateral visual loss which was unresponsive to steroids, and two temporally distinct episodes of neurological disturbance suggestive of central nervous system demyelination. Thorough investigations including serological tests ruled out other causes, including negative neuromyelitis optica and myelin oligodendrocyte protein (MOG) antibodies and nutritional deficiencies. MRI detected areas of demyelination within the spinal cord and brain (infratentorial and periventricular areas). After genetic analysis revealing c.152A>G (p.Tyr51Cys) mutation at the *DNAJC30* gene, LHON was suggested. She was prescribed with idebenone and her visual acuity resolved to normal at 4-year follow-up. **Conclusion:** This case further expands the clinical presentations of *DNAJC30*-related LHON and underscores the importance of considering LHON in patients with demyelinating syndrome presenting with severe bilateral visual loss and presumed optic neuritis unresponsive to steroids.

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Introduction

Leber's hereditary optic neuropathy (LHON) is the most common mitochondrial disease characterized by sequential, painless, and bilateral loss of central vision. LHON is mainly male-dominant with an incomplete penetrance; only 50% of males and 10% of females with a pathogenic variant become clinically symptomatic. It is generally inherited through mitochondrial genome (mtDNA). The most common mutations are m.11778G>A in MT-ND4, m.3460G>A in MT-ND1, and m.14484T>C in MT-ND6 which impair ATP synthesis by disrupting the function of complex I of the electron transport chain, eventually leading to RGC degeneration. These three mutations constitute 90% of LHON cases [1]. Stenton et al. [2] reported an autosomal recessive mode of inheritance for LHON (arLHON) which was caused by mutation in *DNAJC30*, a nuclear encoded gene. c.152A>G (p.Tyr51Cys) mutation at the *DNAJC30* impairs N-module subunits exchange in complex I leading to higher risk of oxidative damage. Their findings highlighted the importance of simultaneous sequencing of the 1-exon gene *DNAJC30* along with mtDNA to bridge the diagnostic gap of LHON [2].

Harding et al. [3] carried out a large case series describing 11 patients with coexisting LHON and multiple sclerosis (MS); therefore, the association is also known as "Harding's syndrome." Despite the LHON which has a higher penetrance in men, Harding's syndrome is more frequent in women [1, 4]. It is suggested that surpassing the high threshold for clinical manifestation in women with LHON could potentially initiate MS pathology [4]. Most of the cases reported with Harding's syndrome carry the three most prevalent LHON-related mutations and there are scarce cases with other mutations.

Herein, we report a 26-year-old woman who was presented with coexisting MS and heterozygous arLHON due to *DNAJC30* mutation. This case report demonstrates the importance of considering LHON as the cause of atypical symptoms for a presumed optic neuritis in a patient with demyelinating disorder and highlights the importance of considering *DNAJC30* gene sequencing in suspected LHON.

The CARE Checklist has been completed for this case report and is attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000545079>).

Case Presentation

A 26-year-old woman was referred by a neurologist for progressive, sequential, and bilateral vision loss and blurriness over the course of 1 month starting with and more prominent in the right eye without any painful eye movements. She had a past medical history of clinically isolated syndrome involving the spinal cord. Her sensory symptoms had started 7 years prior to presentation involving her left foot and migrating over a period of weeks to reach a level distal to the waist. Her magnetic resonance imaging (MRI) of the brain and spine had revealed one lesion in the infratentorial region and another in the thoracic spinal cord. Follow-up MRIs identified temporally distinct new enhancing lesions at the C4, C6-C7, T2, and T7-T8 levels. Additional workup revealed negative results for anti-aquaporin-4 and myelin oligodendrocyte protein (MOG) antibodies. She was not receiving any medications at the time of presentation and her history for smoking and alcohol drinking was unremarkable. Her family history was insignificant for hereditary causes of vision loss including LHON.

Neuro-ophthalmological examination revealed a best corrected visual acuity (VA) of 20/100 OD and 20/30-2 OS. Her VA demonstrated gradual improvements during subsequent follow-ups. Ishihara color plates revealed that she was able to read only 1 out of 17 color plates in the right eye and 14 out of 17 color plates in the left eye. There was no relative

afferent pupillary defect. Optical coherence tomography (OCT) demonstrated an average retinal nerve fiber layer thickness of 83 microns OD and 93 microns OS with slight temporal thinning. Dilated fundus exam showed pallor of both optic nerves with cup to disc ratio of 0.2 (Fig. 1, 2).

The differential diagnosis for her visual symptoms included bilateral optic neuropathies, such as optic neuritis or LHON. Nutritional deficiencies were ruled out due to normal complete blood count, B12, folate. She proceeded with prednisone 1,250 mg PO daily for 3 days followed by 60 mg and a taper by 10 mg every 5 days; however, at follow-up visit, she did not report any improvements in her symptoms. Additional workups revealed mild T2 hyperintensities on the right side of the optic chiasm and three new cerebral white matter lesions (splenium; 2 lesions of left parietal periventricular white matter) on MRI. MRI findings and oligoclonal bands detected with lumbar puncture confirmed the diagnosis of MS. On subsequent follow-ups, her Humphrey visual field testing showed bilateral central scotomas in both eyes. Slowly progressive nature, sequential involvement of the eyes, symmetrical central scotomas, symptoms unresponsive to steroids, and hyperintensities in optic chiasm detected by MRI were suggestive of LHON. Dilated fundus exam revealed temporal pallor. The genetic testing for three primary mutations were negative; however, she was heterozygous for c.152A>G variant of *DNAJC30* gene associated with arLHON. She was also tested positive for c.1239C>T variant in *UQCRC1* gene with autosomal dominant pattern of inheritance. She was diagnosed with Harding's syndrome and she was started on idebenone 300 mg PO TDS daily which led to improvements in her symptoms. Her VA demonstrated gradual improvements over yearly follow-ups (her latest corrected VA was 20/40-2 OD and 20/20-2 OS) and OCT metrics and examination remained stable with bilateral temporal pallor. The visual fields and OCTs 4 years after follow-up are shown in figure (Fig. 3).

Discussion

The coexistence of MS and LHON presents diagnostic challenges, particularly when rare genetic mutations are involved. This case report describes a patient with atypical features for optic neuritis, whose diagnostic work-up for differential diagnoses were negative. She was ultimately diagnosed with Harding's syndrome due to a heterozygous c.152A>G mutation in *DNAJC30* gene. The final diagnosis was LHON-MS, also known as Harding's syndrome. To our knowledge, this is the first report of *DNAJC30* mutation in Harding's syndrome; however, the results of this case report cannot be attributed to the general population and more comprehensive case series in this regard are needed.

Previous literature supports that the coexistence of LHON and MS is more than a chance effect as patients with LHON have a higher risk of developing MS [4]. Based on our review of the literature, a total of 88 cases of Harding's syndrome have been reported in the literature. The most common genetic mutations associated with LHON in this syndrome are 11,778 (69.3%), 14,484 (12.5%), and 3,460 (10.2%) mutations. Other rare mutations like 14,325, 3,644, 14,841, 9,041, 9,448, 14,502, 12,811, and 13,967 are also reported [5]. Coexistence of glial fibrillary acidic protein [6] or Leigh syndrome [7] with LHON due to *DNAJC30* mutation has been reported; however, there are no prior reports of *DNAJC30* mutation in Harding's syndrome.

DNAJC30 is primarily expressed in the nervous system, including cortex, cerebellum, brain, and the retina. It is located in the inner mitochondrial membrane and serves as an essential chaperone protein in the complex I repair mechanism of electron transport chain preventing the oxidative stress caused by reactive oxygen species (ROS) [2]. While most LHON cases are caused by mtDNA mutations, the concept of arLHON has been introduced recently.

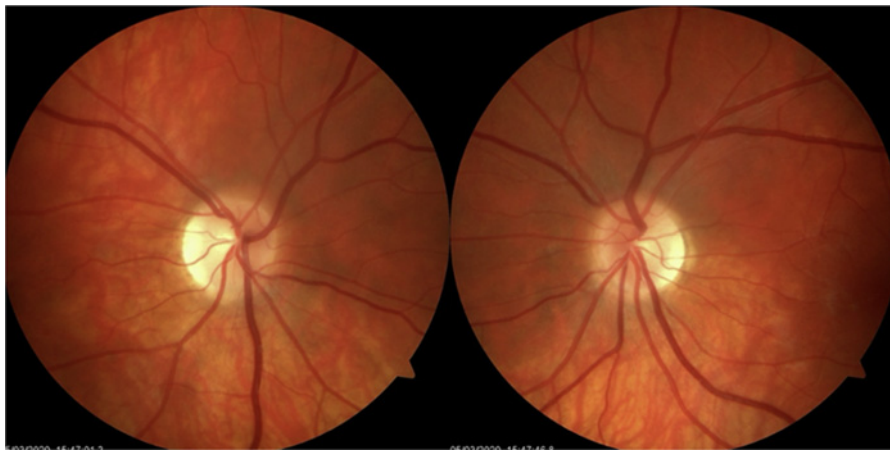


Fig. 1. Fundus photo of the patient at the first assessment. There is bilateral temporal atrophy at optic nerve head.

There are several genes associated with arLHON; however, DNAJC30 screening has greater importance as its p.Tyr51Cys variant is the most common mutation leading to arLHON [2]. In a Polish cohort, arLHON due to mutation in DNAJC30 was more frequent than mtLHON with 41 homozygous and 5 compound heterozygous cases [8].

Clinical presentations of the patient described in this case report were milder than the LHON cases in the literature, potentially explained by her heterozygous *DNAJC30* mutation. She developed symptoms at age 26. In a case series of 46 Polish patients with *DNAJC30* gene variant, the average age of onset was 19 with symptoms indistinguishable from mtLHON [8]. In the study by Stenton et al. [9], the median age of onset of arLHON was 19 years and earlier than mtLHON [2]. Although arLHON is a male-dominant disease, being female combined with LHON is a major risk factor for developing MS [10].

The interval between disease presentation in subsequent eyes in presented case was 3.5 weeks, consistent with data from Kieninger et al. [11] who reported a median time interval of 3.5 weeks between the first and second eye involvement in patients with c.152A>G variant of DNAJC30 with bilateral onset in 40%. Other studies have noted intervals up to several years [10].

Interestingly, our patient did not have any family history of LHON. Major et al. [7] proposed that families carrying *DNAJC30* may go undetected for several generations due to the male predominance and low penetrance of this variant.

MRI findings included hyperintensity in the right side of the optic chiasm and cervical and thoracic spinal cord, splenium, and left parietal periventricular white matter. Roomets et al. [12] described a 11-year-old female patient with subacute vision loss with BCVA of 20/400 OU at presentation with homozygous variant for p.(Tyr51Cys) mutation in DNAJC30 and the only abnormality on MRI was hyperintensities in the posterior portions of optic nerves and optic chiasm as well as chiasm enlargement on T2 sequence. In the case series by Stenton et al. [2] involving 22 individuals, MRI did not detect any abnormalities in 19 of 22 patients. In a study all of the patients with LHON-MS and MS had hyperintense white matter lesions on T2 sequence of MRI while only 26% of patients with LHON had this finding [13]. Rościszewska-Żukowska and Bartosik-Psujek [14] observed regional brain atrophy 8 years after symptoms onset. Küker et al. [15] suggested that there might be characteristic lesions for LHON-MS detected by MRI as LHON-MS-related lesions were less bright on T2-weighted images. These lesions were less visible on T1-weighted images when compared to typical MS in addition to dissimilarities in the pattern of distribution. The lesions differed from typical Dawson's

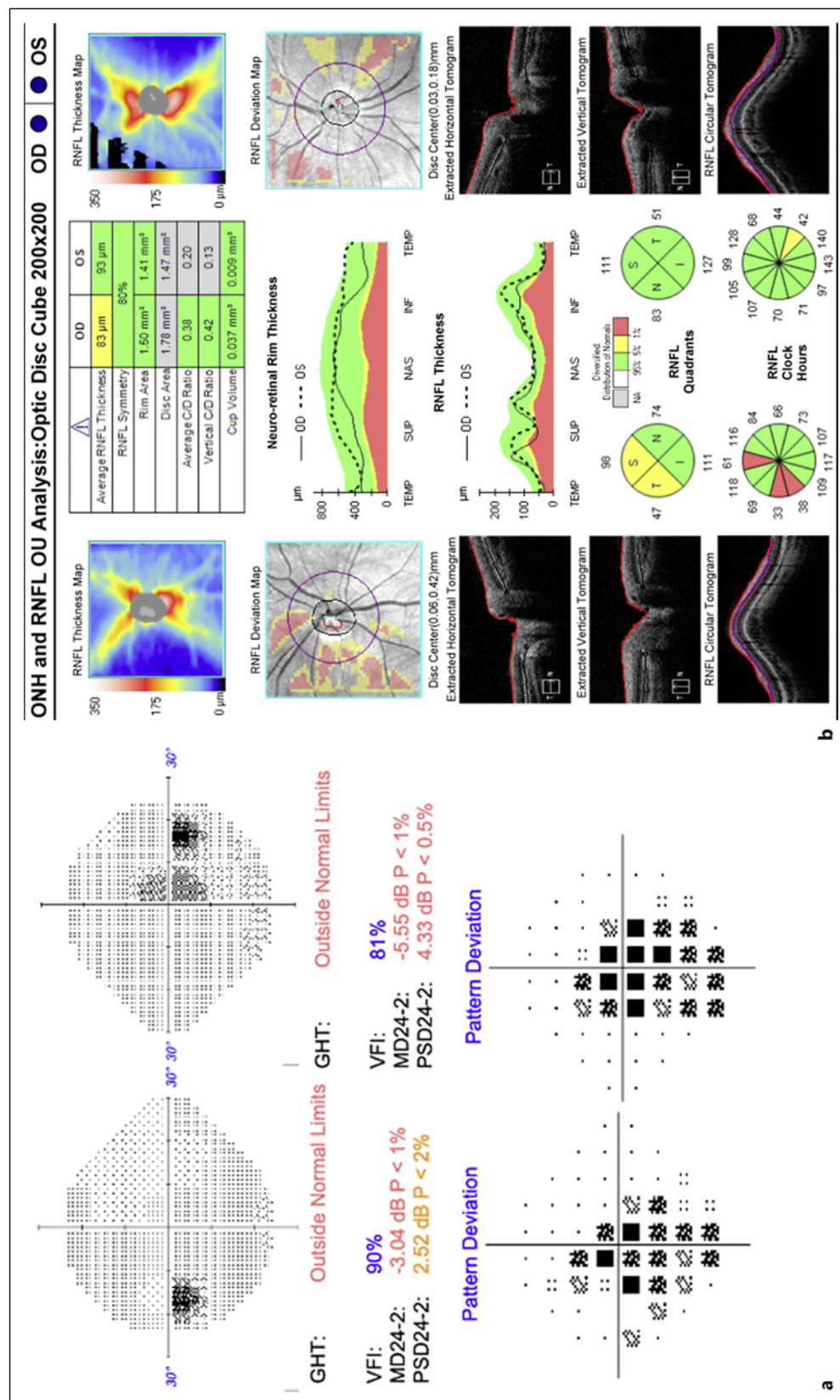


Fig. 2. Humphrey 24-2 SITA-Fast visual field (VF) (a) and optical coherence tomography (OCT) (b) at first visit. VF demonstrated bilateral central scotomas. The stimulus size was III and the mean deviation was -5.55 dB OD and -3.04 dB OS. The visual field index was 81% OD and 90% OS. OCT of retinal nerve fiber layer (RNFL) demonstrated slight temporal thinning, particularly in OD.

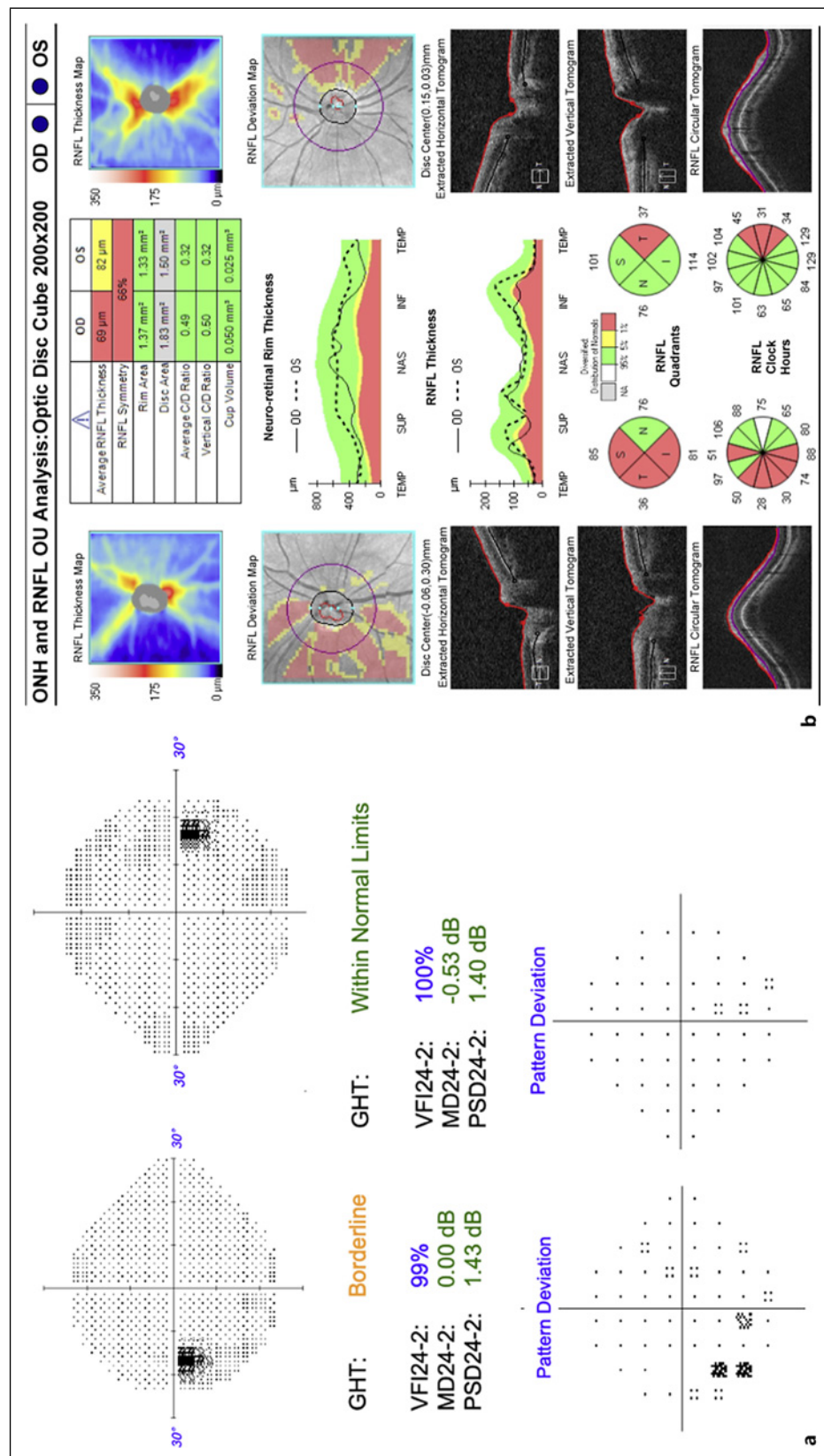


Fig. 3. Humphrey 24-2 SITA-Fast visual field (VF) (**a**) and optical coherence tomography (OCT) (**b**) after 4 years. VF demonstrated improvements with mean deviation -0.53 dB OD and 0.00 dB OS. The visual field index was 100% OD and 99% OS. OCT of retinal nerve fiber layer (RNFL) demonstrated bilateral thinning.

fingers in MS, extending along the white matter tracts and high signal regions around the anterior horns of the lateral ventricles. Beckmann et al. [10] did not report any differences in clinical manifestations, age at onset, disease course, and MRI and CSF findings of patients with LHON-MS from MS.

This patient demonstrated favorable outcomes and significant VA improvements with idebenone treatment, consistent with previous literature. Stenton et al. [9] observed a better long-term prognosis for arLHON with VA improvements in 77% of idebenone-treated and 69% of untreated patients. In addition, 17% of the patients developed complete visual recovery in at least one eye. They suggested that although statistically insignificant, idebenone-treated patients had an 8% higher recovery rate [9]. Response rates were higher in *DNAJC30* mutation-related arLHON compared to mtLHON with idebenone-treated arLHON patients showing an 80.6% response rate [2]. In another study, a response rate of 77% was observed with idebenone-treated arLHON [9]. The VA in the presented patient improved over a course of 4 years. The median time of VA improvement in untreated arLHON was 25.8 (30.3) months and 19 months in another study [2, 11]. In contrast to our findings, Rościszewska-Żukowska and Bartosik-Psujek [14] reported unfavorable outcomes in a 22-year-old female patient with primary presentations of painless, subacute vision loss combined with impaired color vision. They supported this might be because of the dominant role of the neurodegenerative process in LHON-MS [14]. However, in the study by Beckmann et al. [10] patients with LHON-MS demonstrated significant improvements with idebenone.

In conclusion, this case report describes a patient with arLHON phenotype harboring c.152A>G (p.Tyr51Cys) variant of *DNAJC30* gene. Our findings contribute to the growing body of evidence on the importance of screening for non-mitochondrial genetic mutations especially *DNAJC30* testing as the most common cause of arLHON for a timely diagnosis and management of the patients presented with bilateral and atypical features of optic neuropathy particularly in a setting of underlying demyelinating disorder.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. The patient provided written informed consent for the publication of this case report and accompanying images.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Sara KamaliZonouzi: writing – original draft, methodology, validation, investigation, preparation, and visualization. Jonathan Micieli: supervision, conceptualization, validation, reviewing, and editing.

Data Availability Statement

The data supporting this study's findings are not publicly available due to privacy and security reasons but can be obtained from the corresponding author upon reasonable request.

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