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Atypical Leber hereditary optic neuropathy with a 34-year interval between vision loss in both eyes

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ABSTRACT

Purpose: Leber hereditary optic neuropathy (LHON) is an inherited mitochondrial disease characterized by painless vision loss affecting both eyes. The disease usually develops in both eyes within weeks to months of onset. We report a case of LHON who presented with unilateral vision loss in childhood with an interval of more than 30 years between vision loss in the two eyes.

Observation: A 43-year-old man presented with a 1-month history of vision loss in his right eye. At 9 years of age, his visual acuity in the left eye declined, and he had been treated with glaucoma eyedrops bilaterally at his eye clinic. At his first visit to our hospital, his BCVA was 0.15 in the right eye and 0.1 in the left eye, and critical flicker frequency was 16 Hz in the right eye and 15 Hz in the left eye, and he was negative for a relative afferent pupillary defect. The Goldman visual field showed central scotoma in both eyes. Fundus examination revealed slight redness of the right optic disc with meandering retinal small vessels, and the left optic disc had a slight pallor. Fluorescein angiography could not be performed because of liver dysfunction. OCT showed prominent bilateral thinning of the RNFL and retinal ganglion cell layer. Enhancement of the optic nerve was not apparent on orbital gadolinium-enhanced magnetic resonance imaging. Hematologic analysis revealed macrocytic anemia and low levels of vitamin B12 and folate. His mother had a presumptive diagnosis of LHON but did not receive genetic testing. A male cousin also had severe vision loss. Based on the likely family history of LHON, we performed genetic testing, which revealed the 11778 mitochondrial point mutation associated with this condition.

Conclusion and importance: We report a case of LHON with 34 years interval in vision loss in the fellow eye. LHON may develop in the second eye decades after its onset in the first. Detailed medical interviews and scrutiny, such as examination of family history, are warranted in consideration of LHON.

1. Introduction

Leber hereditary optic neuropathy (LHON) is usually manifests between the second and fourth decades of life but occasionally occurs in children and the elderly and develops in both eyes within weeks to months of onset.[1–3] Two large studies[4,5] have revealed a higher percentage of men among Japanese patients with LHON compared to other countries, including Finland, the Netherlands, England, Denmark, and Serbia.[2,6–11] We recently encountered a case of LHON who presented with unilateral vision loss in childhood with an interval of more than 30 years between vision loss in the two eyes. Among previously reported Japanese patients with LHON, none had long interocular intervals as in this case.[4]

2. Case presentation

The patient was a 43-year-old Japanese man. At 9 years of age, his visual acuity in the left eye declined suddenly, without any history of trauma, and he was diagnosed with glaucoma. Although visual acuity and the visual field in his right eye were normal, he had been treated with glaucoma eyedrops bilaterally at his eye clinic. Twelve years ago, central scotoma was detected in his left eye by a Goldman visual field test, which is the oldest such test for which results are available. No scotoma was detected in the Goldman visual field of his right eye 7 years prior to his visit to our hospital. The Humphrey visual field showed a central scotoma smaller than 10° in the right eye both 6 years (Fig. 1A) and 5 months (Fig. 1B) ago. His best corrected visual acuity (BCVA) was

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1.0 in the right eye and 0.1 in the left eye at 1 month before his visit to our hospital. Four years ago, optical coherence tomography (OCT) showed thinning of the retinal nerve fiber layer (RNFL) of both eyes (Fig. 1C). The patient was referred to our hospital because he noticed decreased vision in his right eye. His medical history included liver dysfunction and hypertension. His mother had a presumptive diagnosis of LHON but did not receive genetic testing. A male cousin also had severe vision loss. He is the youngest of four brothers, but none of the other brothers had eye disease. He had been smoking 20 cigarettes a day since age 17 and drank about 1.8 L of sake daily. His diet was irregular and unbalanced. His BCVA was 0.15 in the right eye and 0.1 in the left eye, intraocular pressure was 9.5 mmHg in the right eye and 10 mmHg in the left eye, critical flicker frequency was 16 Hz in the right eye and 15 Hz in the left eye, he showed normal pupillary reflex in both eyes, and was negative for a relative afferent pupillary defect. The Goldman visual field showed central scotoma in both eyes (Fig. 2A). Fundus examination revealed slight redness of the right optic disc with meandering retinal small vessels, and the left optic disc had a slight pallor (Fig. 2B). Fluorescein angiography could not be performed because of liver dysfunction. OCT showed prominent bilateral thinning of the RNFL and retinal ganglion cell layer (RGCL) (Fig. 2C and D). Enhancement of the optic nerve was not apparent on orbital gadolinium-enhanced magnetic resonance imaging. Hematologic analysis revealed macrocytic anemia, liver dysfunction, and low levels of vitamin B12 and folate. Serum vitamin B1, aquaporin-4, and myelin oligodendrocyte glycoprotein antibody titers, leukocyte count, erythrocyte sedimentation rate, C-reactive protein and angiotensin-converting enzyme inhibitor levels, and rapid plasma reagin test were within normal limits. Based on the likely family history of LHON, we performed genetic testing. Genetic testing for mitochondrial DNA mutations at nucleotides 3460, 11778, and 14484 was performed with a biplex invader assay at Bio Medical Lavatory (Tokyo Japan).[12] A mitochondrial point mutation at position 11778, the most common mutation found in patients with LHON, was associated with this condition.[13] The patient is currently taking coenzyme Q10, and his most recent BCVA was 0.02 in the right eye and 0.1 in the left eye.

3. Discussion

We experienced a case of LHON with 34 years interval in vision loss in the fellow eye. The patient had noticed a sudden loss of vision and central scotoma in his left eye at 9 years of age without any history of trauma. The possibility of amblyopia was low due to his age and current refraction, with only mild astigmatism in both eyes. Although rare, cases of unilateral LHON and cases with a long interval between disease onset in the two eyes, as in the present case, have been reported. LHON with such onset intervals of 18 and 41 years were thus recently described.[14,15] Common features of these two previous cases and the present case are the 11778 variant of LHON and disease onset in the first eye at an age of less than 10 years. These findings suggest that early onset in the first eye may be associated with a longer interval until onset in the second. A study of the clinical features of LHON with an onset in childhood (younger than 10 years) classified such individuals into four groups: acute bilateral, acute unilateral, slowly progressive, and subclinical.[16] Three children (two with the 11778 mutation and one with a 3460 mutation) among 18 followed up to the age of 25.6 ± 15.1 years (mean ± SD) showed an acute unilateral course. The present case showed childhood onset in the in the left eye, with visual impairment in the right eye not becoming apparent until 34 years later. The Humphrey visual field of the proband at 6 years (Figure 1A) and 5 months (Fig. 1B) before his visit to our hospital shows gradual deterioration of central scotoma in the right eye, suggestive of slow disease progression that finally resulted in a decrease in visual acuity. Mitochondrial DNA mutations in most patients with LHON are found at positions 11778, 14484, and 3460, which occur in over 95% of LHON cases. The mutation at 11778 found in this case is the most common type.[13] Japanese patients with LHON reportedly have a much higher frequency of the 11778 mutation compared to other populations.[2,7,9,13]

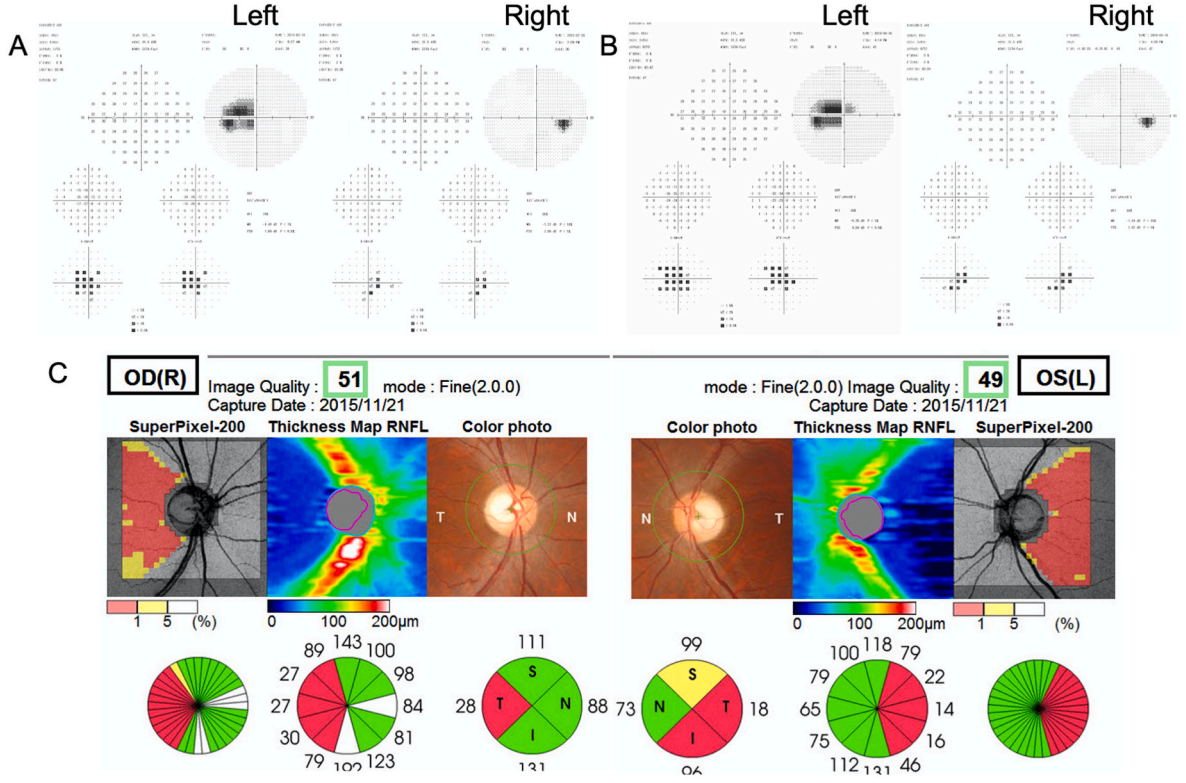

Fig. 1. Humphrey visual field and OCT for the proband before presentation at our hospital. The Humphrey visual field at 6 years (**A**) and 5 months (**B**) before his visit to our hospital showed central scotoma in both eyes. OCT at 4 years before his visit showed thinning of the RNFL in both eyes (**C**).

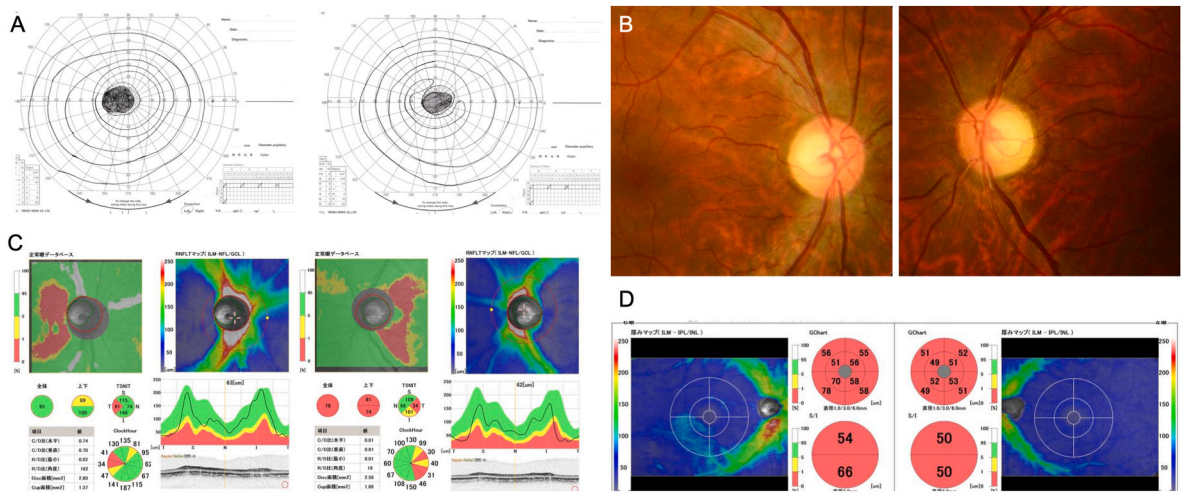

Fig. 2. Ophthalmic examinations at our hospital. The Goldman visual field showed central scotoma in both eyes (**A**). Fundus photographs revealed slight redness of the right optic disc, with meandering retinal small vessels, as well as a slight paleness of the left optic disc (**B**). OCT showed bilateral thinning of the temporal RNFL (**C**) and retinal ganglion cell layer (**D**).

OCT has found RNFL thickening in early-stage LHON and a reduced RNFL thickness in atrophic LHON with a duration of more than 6 months.[17] Thinning of the RNFL in all areas was found at 12 months after disease onset.[18] In the present case, OCT revealed temporal thinning of the RNFL in the right eye at least 4 years before the onset of vision loss (Fig. 1C). Only the temporal region of the RGCL in the right eye showed thinning at his first visit to our hospital (Fig. 2C). No progression of the nerve fiber layer defect over 4 years is also an atypical feature of this case. As the RNFL in the right eye was already thinning at the time of the first visit to our hospital, the patient may have developed LHON for more than 6 months before the visit. However, it took a long time for the symptoms, such as vision loss and visual field disturbance, to appear. Although is not clear when the onset of the disease occurs, such a long duration for symptoms to appear is atypical. This may be related to lifestyle, serum vitamin B1, and other factors.

This case had long-term data of OCT and visual field because the patient had been followed up as glaucoma before the onset of vision loss in the right eye. Further studies are needed to investigate long-term relationship of OCT, visual acuity, and visual field in more patients with LHON.

Vision loss in LHON is thought to be triggered by various factors including anemia, vitamin B12 deficiency, trauma,[19] high intraocular pressure,[20] and excessive smoking and alcohol use.[21] In the present case, heavy drinking and smoking, accompanied by anemia and vitamin B12 deficiency,[22] may thus have triggered the onset of vision loss in the right eye. Conversely, a prolonged lowering of intraocular pressure by glaucoma eyedrops might have delayed LHON onset in the right eye.

4. Conclusions

Ophthalmologists should thus be aware that LHON may develop in the second eye decades after its onset in the first. Detailed medical interviews and scrutiny, such as examination of family history, are warranted in consideration of LHON.

Patient consent

Consent for publication: Written informed consent for publication of clinical details and clinical images was obtained from the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

KS: acquisition, analysis and interpretation of data. Manuscript draft, review of the literature, SI: acquisition of data, review of the literature, KF: acquisition, analysis and interpretation of data, manuscript draft, review of the literature.

Declaration of competing interest

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