LEBER'S HEREDITARY OPTIC NEUROPATHY: A CASE REPORT

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Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disease that primarily affects the optic nerve, causing bilateral vision loss in juveniles and young adults. A 12-year-old boy had complained of blurred vision in both eyes for more than 1 year. His best-corrected visual acuity was 0.08 in the right eye and 0.1 in the left. Ophthalmologic examination showed bilateral optic disc hyperemia and margin blurring, peripapillary telangiectasis, and a relative afferent pupil defect in his right eye. Fluorescein angiography showed no stain or leakage around the optic disc in the late phase. Visual field analysis showed central scotoma in the left eye and a near-total defect in the right. Upon examination of the patient's mitochondrial DNA, a point mutation at nucleotide position 11778 was found, and the diagnosis of LHON was confirmed. Coenzyme Q10 was used to treat the patient.

Key Words: Leber's hereditary optic neuropathy, mitochondrial DNA
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Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disease that causes acute or subacute bilateral vision loss in young adult males. The point mutation at nucleotide position (np) 11778 of mitochondrial DNA (mtDNA) was first identified by Wallace et al in 1988 [1]. Several mtDNA mutations have subsequently been identified. mtDNA mutations result in deficiencies of energy generation within cells, especially in tissues with high energy consumption, such as nerve fiber cells. Clinically, the optic disc shows pseudoedema, peripapillary telangiectasis, and central or cecocentral scotoma. Fluorescein angiography typically shows no fluorescein leakage or stain in the late phase. LHON is easily mistaken for optic neuritis or compressive optic neuropathy. Here, we present a case and describe the clinical characteristics and current therapy for LHON.

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CASE PRESENTATION

A 12-year-old boy had suffered from blurred vision of the right eye for more than 1 year and visual acuity of the left eye had begun to worsen 2 months previously. Despite proper corrective lenses, his visual acuity became progressively more blurred. The patient's best-corrected visual acuity (BCVA) was 0.08 in the right eye and 0.1 in the left. The ocular surface and anterior segment, including the conjunctiva, cornea, anterior chamber, iris, and lens, all appeared to be normal under biomicroscopic examination. Intraocular pressure was also within normal limits. However, a relative afferent papillary defect was noted in his right eye, and bilateral optic disc margin blurring with hyperemia and peripapillary telangiectasis were found upon ophthalmoscopic examination (Figure 1). The patient's medical records revealed no congenital or systemic illness, no drug or substance abuse, and no family history of poor vision. He had undergone bilateral functional endoscopic sinus surgery (FESS) for chronic paranasal sinusitis under general anesthesia 3 months before he came to our department, and subjectively felt a worsening of visual acuity after surgery.

Initially, intracranial lesions or inflammatory or miscellaneous disorders of the optic nerve were suspected.

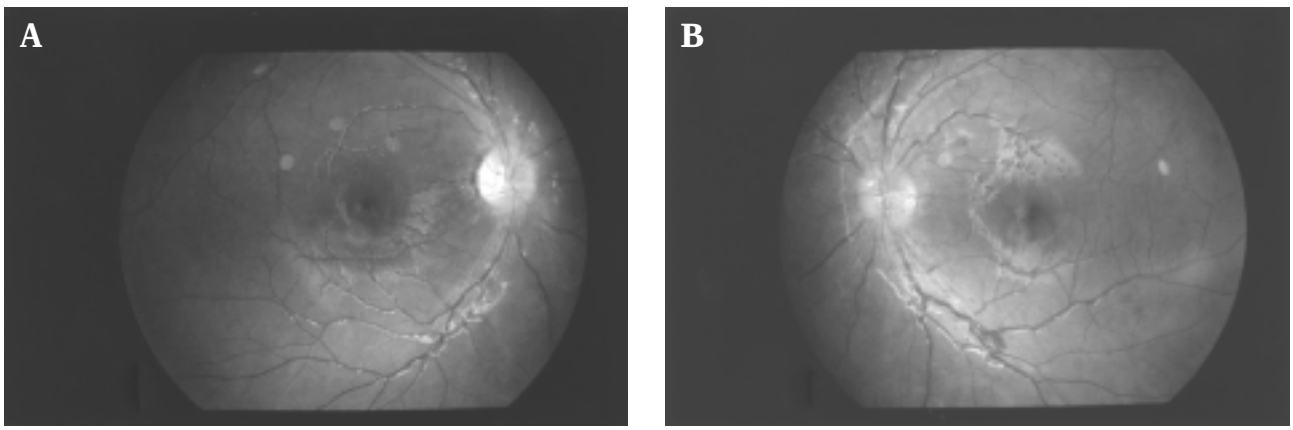

Figure 1. *Fundus photographs of the right (A) and left (B) eyes showing bilateral optic disc hyperemia and margin blurring, peripapillary telangiectasis, and arteriole tortuosity.*

The patient consequently underwent laboratory examination, visual field analysis, fluorescein angiography, visual-evoked potential (VEP) examination, and magnetic resonance imaging (MRI). Blood biochemistry, erythrocyte sedimentation rate (ESR), and heavy metal screening were all within normal limits. Imaging studies revealed no orbital or intracranial lesions, and fluorescein angiography showed no stain or leakage in the late phase (Figure 2), indicating pseudoedema of the optic disc. Visual field examination showed a near-total defect in the patient's right eye and central scotoma in the left (Figure 3). Both eyes showed increased latency on VEP examination and color vision abnormalities. Based on the clinical symptoms and signs, LHON was suspected and mtDNA examination revealed a point mutation at np 11778. As the patient is the only child of the family and his mother had passed away years ago in a traffic accident, it was difficult to trace the pedigree of the mtDNA mutation. However, other family members of the patient's mother are under further investigation.

Six weeks later, the patient subjectively felt a deterioration of vision in both eyes. Visual acuity was 0.03 in the right eye and 0.08 in the left eye, and the visual field defect in the left eye was enlarged. After coenzyme Q10 treatment, visual acuity and visual field remained steady during the follow-up period. Three months after the patient's first visit, his BCVA was 0.03 and 0.08 in the right and left eyes, respectively, although he subjectively felt that his vision had improved. Optic atrophy was noted in his right eye, but peripapillary telangiectasis and disc margin blurring had disappeared in both eyes.

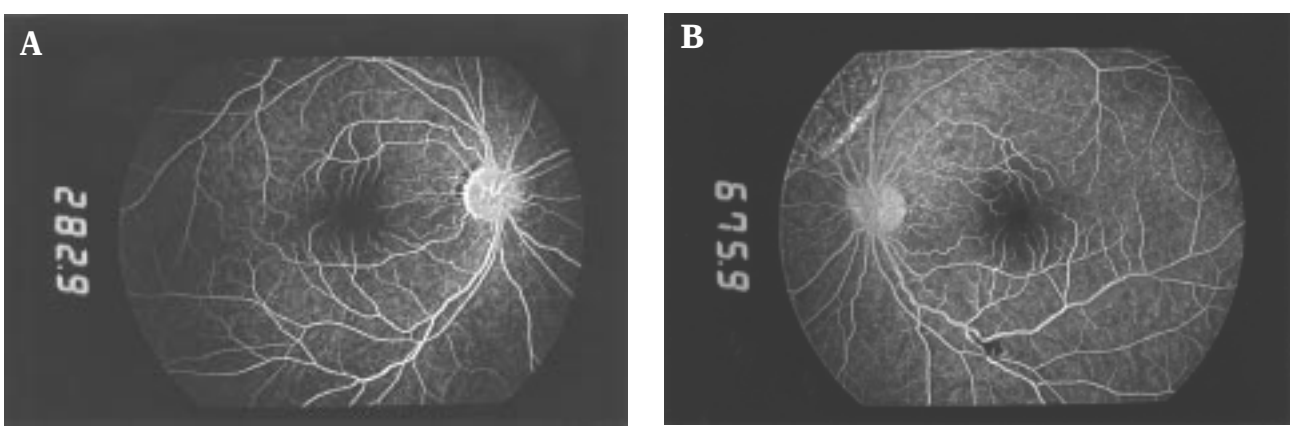

Figure 2. *Fluorescein angiography of the right (A) and left (B) eyes in the late stage showing no stain or leakage of fluorescein around the optic discs.*

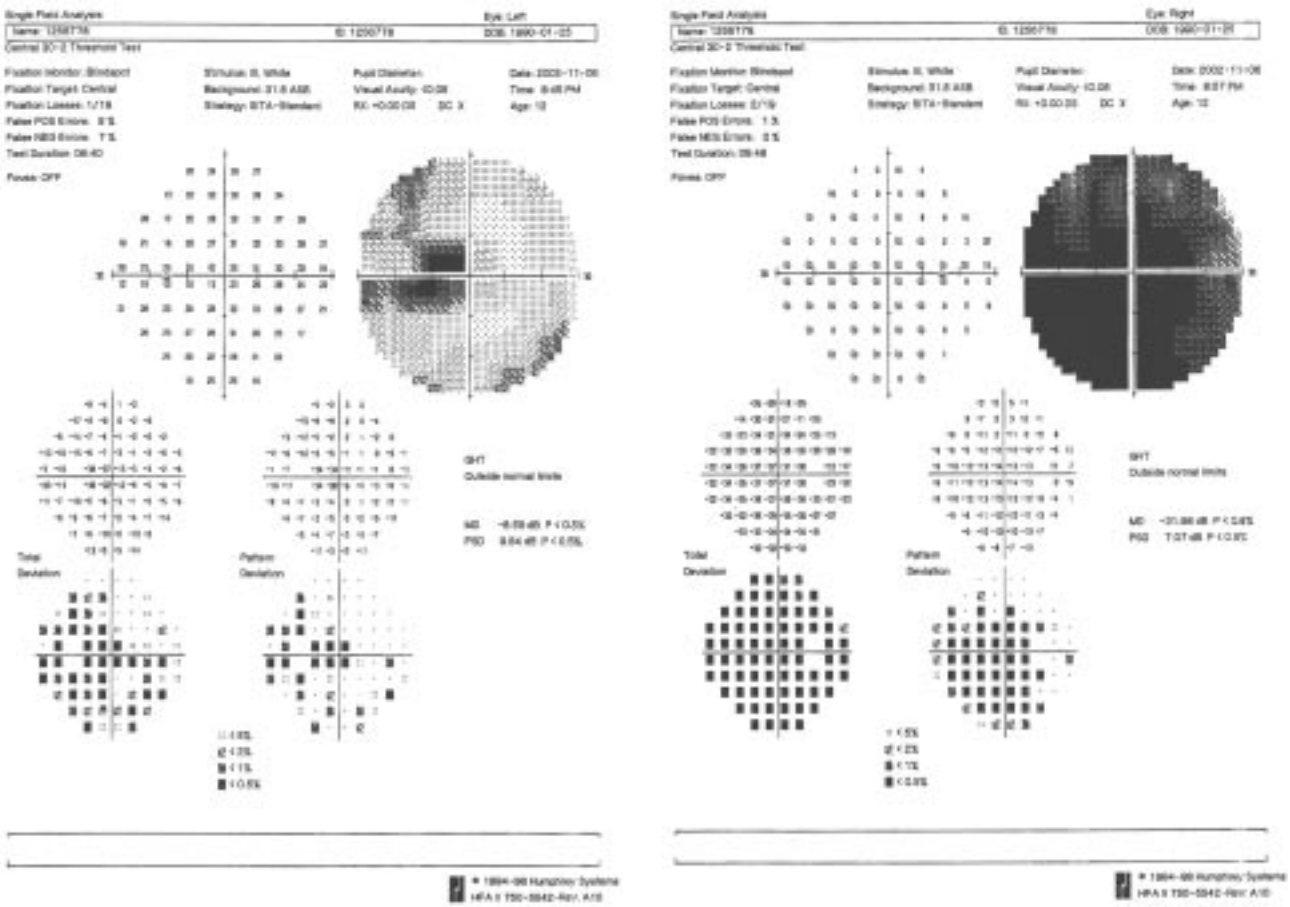

Figure 3. *Humphrey visual fields of the right and left eyes showing near-total defect in the right eye and central scotoma in the left eye.*

Discussion

LHON, a maternally inherited mitochondrial disease, was first identified by Wallace et al in 1988 [1], although it had been described more than 100 years earlier (Von Grafe [2], Leber [3]). In northeast England, the estimated prevalence of LHON is 1 in 25,000 [4].

The first point mutation identified in mtDNA was a single guanine to adenine transition mutation at np 11778. Since then, several mutations in mtDNA have been discovered [5]. However, only mutations at nps 11778, 3460, and 14484 have been proposed as primary mutations [6], which alone can cause optic neuropathy. These three primary mutations account for more than 95% of the LHON pedigree in the study by Mackey et al [7]. In addition to primary mutations, there are secondary mutations [5], which together with primary mutations might play a role in predisposing patients to optic neuropathy. Moreover, a mixture of mutant and normal mtDNA molecules within a cell gives rise to heteroplasmy, as first described by Lott et al in 1990 [8]. Heteroplasmy results in differences between individuals of the same family. That is, some will be predisposed to vision loss and others will not. However, in recent studies, no clear difference in disease severity was found between heteroplasmic and homoplasmic patients [9,10].

Among the primary mutations, the most prevalent, np 11778, accounts for 50% to 70% of all LHON patients [7,8, 11]. In Chinese patients, the ratio is much higher, with np 11778 mutations accounting for 92% of LHON patients, as reported by Yen et al [12,13]. The np 3460 and np 14484 mutations have rarely been reported in Asian LHON patients; the np 11778 mtDNA mutation in our case is consistent with the findings of Yen et al.

The percentage of male predominance is about 71% to 82% for np 11778. Most (70%) patients with np 11778 LHON will develop vision loss between 10 and 30 years of age, and the average interval between the two eyes is

1.8 months [11,14]. Although X-linked factors have been proposed to cause different rates of predominance between male and female patients, no definite linkage has been found [15].

Clinically, in the acute stage, LHON exhibits peripapillary microangiopathy, optic disc pseudoedema, no detectable staining or leakage around the optic disc during fluorescein angiography, central or cecocentral visual field defect, dyschromatopsia, and delayed response in VEP. In the end stage, optic atrophy occurs.

Our case had several of the characteristics mentioned above. However, many cases do not manifest all of these typical features. Newman et al reported that only 58% of patients show classic features of np 11778 LHON [14]. In cases without microangiopathy, Hung et al suggested that VEP is a good indicator for predicting onset of optic neuropathy and vision loss [16].

The visual outcome of LHON has been investigated in several studies [14,17–20]. For np 11778 mutations, as in our patient, the final visual acuity in 98% of patients is less than 20/200, and the average duration of progression of vision loss in each eye was 3.7 months [14]. Prognosis of LHON is dependent on the primary mtDNA mutation [11,14]. It has been reported that the np 11778 mutation is associated with poor visual outcome, whereas np 3460 and np 14484 mtDNA mutations are associated with better visual prognosis [14,19,20]. Visual outcome is best in patients with np 14484 mutations, with 71% of all patients having a final visual acuity of at least 6/24. However, Riordan-Eva et al found no difference in visual prognosis between patients with np 11778 and np 3460 [11]. Visual outcome is independent of secondary mutation [11,17,18]. This may be due to the interaction between undiscovered genetic and environmental factors. It has been proposed that environmental factors, including exposure to certain substances, and tobacco and alcohol consumption, may predispose LHON patients to vision loss [21,22]. However, later studies have disputed these opinions [23].

Although it has been reported that visual prognosis is correlated with age at onset and that there is a favorable visual outcome for childhood LHON [11,17,24], in our case of early childhood onset, BCVA was 0.03 in the right eye and 0.08 in the left eye.

There is no effective clinical treatment for LHON patients to recover normal visual acuity. Many studies have tried to increase mitochondrial energy production. However, their effectiveness remains controversial. It has been reported that idebenone treatment alone, or in combination with vitamin B2 and vitamin C, shortens the period of visual recovery. Unfortunately, there is no significant difference in final visual acuity [25,26]. Huang et al reported significant progress in BCVA within 4 months in a patient with np 11778 mutation treated with coenzyme Q10 [27]. Currently, our patient is undergoing coenzyme Q10 therapy (90 mg/d), but the actual clinical effect requires further investigation. Regarding gene therapy, considerable progress has been made in animal experiments and it might be a possible solution to LHON. However, there are still many difficulties to overcome before it can be applied in clinical practice [28].

The case we present here had several typical symptoms and signs to suggest LHON. However, in many other cases in regular clinical practice, the diagnosis of LHON may not be made due to the absence of a compatible family history or typical clinical appearance. In addition, whether surgery plays a role in predisposing a patient to the onset of LHON is unknown. We strongly suggest that if young adult patients have abnormal optic disc appearance or vessel changes around the disc with unexplained vision loss, genetic counseling should be seriously considered.

References

1. Wallace DC, Singh G, Lott MT, et al. Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science* 1988;242:1427–30.
2. Von Grafe A. An abnormal case of hereditary amaurosis. *Arch Fr Ophthalmol* 1858;4:266. [In German]
3. Leber T. About hereditary and congenital optic neuropathy. *Albrecht Von Grafes Arch Ophthalmol* 1871;17:249–91. [In German]
4. Chinnery PF, Johnson MA, Wardell TM, et al. The epidemiology of pathogenic mitochondrial DNA mutations. *Ann Neurol* 2000;48:188–93.
5. Brown MD, Wallace DC. Spectrum of mitochondrial DNA mutations in Leber's hereditary optic neuropathy. *Clin Neurosci* 1994;2:138–45.
6. Howell N. Primary LHON mutations: trying to separate "fruyt" from "chaf". *Clin Neurosci* 1994;2:130–7.
7. Mackey DA, Oostra RJ, Rosenberg T, et al. Primary pathogenic mtDNA mutations in multigeneration pedigrees with Leber's hereditary optic neuropathy. *Am J Hum Genet* 1996;59:481–5.
8. Lott MT, Voljavec AS, Wallace DC. Variable genotype of Leber's hereditary optic neuropathy patients. *Am J Ophthalmol* 1990;109:625–31.
9. Juvonen V, Huoponen K, Syvanen AC, et al. Quantification of point mutations associated with Leber's hereditary optic neuroretinopathy by solid-phase minisequencing. *Hum Genet* 1994;92:16–20.

10. Harding AE, Sweeney MG, Govan GG, et al. Pedigree analysis in Leber's hereditary optic neuropathy families with a pathogenic mtDNA mutation. *Am J Hum Genet* 1995; 57:77–86.
11. Riordan-Eva P, Sanders MD, Govan GG, et al. The clinical features of Leber's hereditary optic neuropathy defined by the presence of a pathogenic mitochondrial DNA mutation. *Brain* 1995;118(Pt 2):319–37.
12. Yen MY, Yen TC, Pang CY, et al. Mitochondrial mutation in Leber's hereditary optic neuropathy. *Invest Ophthalmol Vis Sci* 1992;33:2561–6.
13. Yen MY, Wang AG, Chang WL, et al. The spectrum of mitochondrial DNA mutations in Chinese patients. *Jpn J Ophthalmol* 2002;46:45–51.
14. Newman NJ, Lott MT, Wallace DC. The clinical characteristics of pedigrees of Leber's hereditary optic neuropathy with the 11778 mutation. *Am J Ophthalmol* 1991;111:750–62.
15. Juvonen V, Viikki J, Aula P, et al. Reevaluation of the linkage of an optic atrophy susceptibility gene to X-chromosomal markers in Finnish families with Leber's hereditary optic neuropathy (LHON). *Am J Hum Genet* 1991;53:289–92.
16. Hung HL, Kao LY, Huang CC. Clinical features of Leber's hereditary optic neuropathy with the 11778 mitochondrial mutation in Taiwanese patients. *Chang Gung Med J* 2003;26:41–7.
17. Nikoskelainen E, Huoponen K, Juvonen V, et al. Ophthalmologic findings in Leber's hereditary optic neuropathy, with special reference to mtDNA mutations. *Ophthalmology* 1996;103:504–14.
18. Oostra RJ, Bolhuis PA, Wijburg FA, et al. Leber's hereditary optic neuropathy: correlation between mitochondrial genotype and visual outcome. *J Med Genet* 1994;31:280–6.
19. Johns DR, Smith KH, Miller NR. Leber's hereditary optic neuropathy. Clinical manifestations of the 3460 mutation. *Arch Ophthalmol* 1992;110:1577–81.
20. Johns DR, Heher KL, Miller NR, et al. Leber's hereditary optic neuropathy. Clinical manifestations of the 14484 mutation. *Arch Ophthalmol* 1993;111:495–8.
21. Chalmers RM, Harding AE. A case-control study of Leber's hereditary optic neuropathy. *Brain* 1996;119(Pt 5):1481–6.
22. Tsao K, Aitken PA, Johns DR. Smoking as an aetiological factor in a pedigree with Leber's hereditary optic neuropathy. *Br J Ophthalmol* 1999;83:577–81.
23. Kerrison JB, Miller NR, Hsu F, et al. A case-control study of tobacco and alcohol consumption in Leber hereditary optic neuropathy. *Am J Ophthalmol* 2000;130:803–12.
24. Swartz N, Savino PJ. Is all nondefinable optic atrophy Leber's hereditary optic neuropathy? *Surv Ophthalmol* 1994; 39:146–50.
25. Mashima Y, Hiida Y, Oguchi Y. Remission of Leber's hereditary optic neuropathy with idebenone. *Lancet* 1992;340:368–9.
26. Mashima Y, Kigasawa K, Wakakura M, et al. Do idebenone and vitamin therapy shorten the time to achieve visual recovery in Leber hereditary optic neuropathy? *J Neuroophthalmol* 2000; 20:166–70.
27. Huang CC, Kuo HC, Chu CC, et al. Rapid visual recovery after coenzyme q10 treatment of leber hereditary optic neuropathy. *J Neuroophthalmol* 2002;22:66.
28. Guy J, Qi X, Pallotti F, et al. Rescue of a mitochondrial deficiency causing Leber hereditary optic neuropathy. *Ann Neurol* 2002;52:534–42.