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Case Report

Leber Hereditary Optic Neuropathy "Plus" with the m.14487 T>C Mutation as the Causality of Hemidystonia: A Case Report

Fumio Takano[a] Kaori Ueda[a] Norio Chihara[b] Mina Arai[a]
Mari Sakamoto[a] Takuji Kurimoto[c] Yuko Yamada-Nakanishi[a]
Makoto Nakamura[a]

[a]Division of Ophthalmology, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan; [b]Division of Neurology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan; [c]Kurimoto Eye Clinic, Osaka, Japan

Keywords
Leber hereditary optic neuropathy plus · Rare mitochondrial point mutation · Dystonia

Abstract
Introduction: Leber hereditary optic neuropathy (LHON) complicated with extraocular symptoms is called LHON plus. We describe a case of LHON plus with a rare mutation, which also caused dystonia. ***Case Presentation:*** An 18-year-old male patient developed symptoms of dystonia at the age of 15 years. Two years later, he noticed decreased visual acuity and central scotoma in the left eye. One month later, the same symptoms occurred in the right eye. Although the optic discs in both eyes revealed mildly redness and edematous change, no abnormal findings were detected on fluorescence fundus angiography and orbital magnetic resonance imaging. Mitochondrial deoxyribonucleic acid (mtDNA) sequencing detected the m.14487 T>C mutation. From clinical course and fundus findings, the case was diagnosed LHON. The optic nerve gradually atrophied and central scotoma remained. ***Conclusion:*** The m.14487 T>C mutation is one of the causative mutations in patients with dystonia or Leigh encephalopathy and a minor mutation in patients with LHON. However, in the present case, ocular symptoms were more severe than systematic symptoms and the disease course was consistent with LHON. For the above reasons, this case can be diagnosed as LHON plus. Whole mtDNA sequencing is important in diagnosing LHON if none of the three major mutations are detected.

Correspondence to:
Kaori Ueda, kueda@med.kobe-u.ac.jp

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Introduction

Leber hereditary optic neuropathy (LHON) is an acute or subacute optic neuropathy caused by point mutations in mitochondrial genes, characterized by decreased visual acuity and central scotoma. Typical LHON is caused by mitochondrial deoxyribonucleic acid (mtDNA) point mutation, followed by mitochondrial dysfunction in retinal ganglion cells [1]. One of three major mutations, m.3460 G>A, m.11778 G>A, or m.14484 T>C, is detected in over 90% of LHON cases, and less than 10% of the point mutations have detected outside of these regions [1].

Some LHON cases complicated by systemic disease are referred to as LHON "plus." Mitochondrial diseases are expected to be related with high-energy requirement tissues, such as heart, brain, or muscles [2]. Previous nationwide survey also reported that cerebrovascular or cardiovascular diseases were more likely to be complicate by LHON [3]. In this report, we describe a case of LHON with dystonia and the rare m.14487 T>C mutation. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000542202).

Case Presentation

An 18-year-old male developed right-sided dystonia symptoms around the age of 15 years. At the age of 16 years, the patient underwent a thorough examination at the Division of Neurology in Kobe University Hospital to determine the cause of his symptoms. Clinical examination revealed right arm rigidity, right hand dominant bilateral postural fine regular tremor in the hands, and right foot inward turning posture when walking. Cerebrospinal fluid analysis showed the following: normal cell count, total protein, and glucose concentration; IgG index of 0.61 (normal); and no cerebrospinal fluid-specific oligoclonal bands. Serum lactic acid and pyruvate levels were 13.5 mg/dL (normal range: 3–17 mg/dL) and 1.25 mg/dL (normal range: 0.3–0.94 mg/dL), respectively. Galactocerebrosidase enzyme levels in lymphocytes and serum levels of very long-chain fatty acids were normal. The patient also had low levels of circulating ceruloplasmin (17.2 g/dL, normal range: 21–37 mg/dL), but normal levels of urinary copper (16 μg/L, normal range: <36 μg/L). Intracranial magnetic resonance imaging (MRI) revealed white matter lesions with high-intensity T2-weighted signals and partial low-intensity T1-weighted signals in the left putamen to the cerebral peduncle (shown in Fig. 1). An ophthalmologic examination revealed no abnormalities in visual function. At that point, the cause of patient's dystonia symptoms and the intracranial MRI lesion had not been determined.

One year and 8 months later, the patient experienced decreased visual acuity in the left eye and visited the ophthalmologist again. The patient had no history of ocular trauma, smoking, drinking, or drug use and no change in dystonia symptoms before or after visual impairment. The patient's older brother also had mild dystonia symptoms, but there were no family histories, including ophthalmologic disease. Decimal visual acuity was RV = 1.0 (1.0 × S + 5.00D), LV = 0.2 (0.2 × S + 5.00D), respectively. The light reflex was prompt and complete in both eyes without relative afferent pupillary defect. The critical flicker frequency was 36.0 Hz in the right eye and 28.5 Hz in the left eye. The visual field showed a small central scotoma in the left eye (shown in Fig. 2a). The optic discs were mildly hyperemic and edematous in both eyes, and the peripapillary capillaries exhibited mild telangiectasia (shown in Fig. 2b). Fundus fluorescein angiography showed no abnormal findings, including leakage of fluorescein from optic disc (shown in Fig. 2c) which suggested no inflammatory findings in the optic disc or retina. All blood test results were within reference ranges. Orbital and intracranial magnification MRI showed no lesions in the visual pathway. One month after the onset of symptoms

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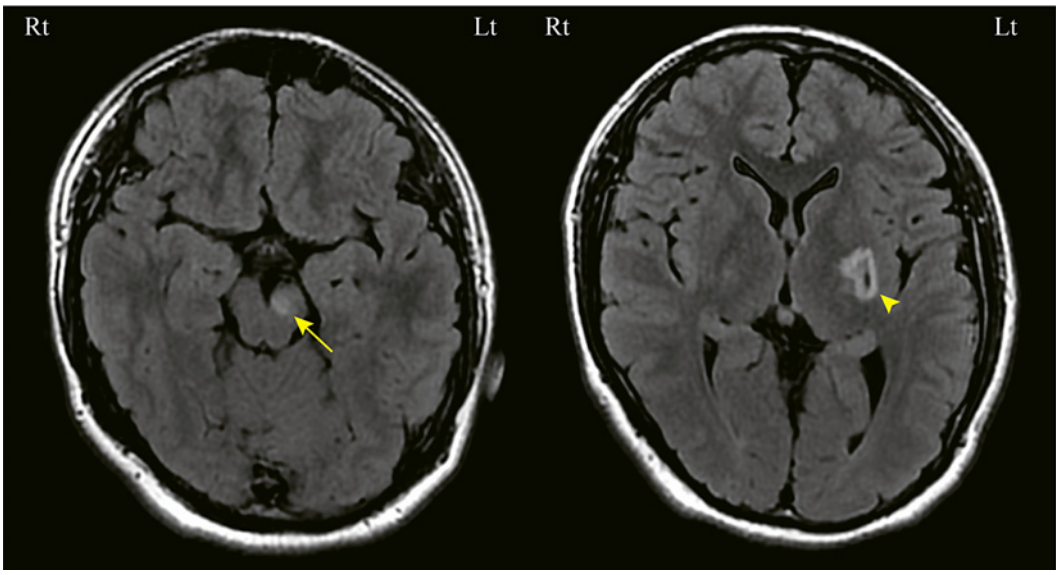

Fig. 1. Head magnetic resonance imaging during a close examination for dystonia. White lesions were detected from the left putamen to the cerebral peduncle (arrow, arrowhead, FLAIR image).

in the left eye, similar symptoms, decreased visual acuity and central scotoma, appeared in the right eye. LHON was suspected from the clinical course and results of examinations. As three major points of mutations, m.3460 G>A, m.11778 G>A, and m.14484 T>C, were negative, the entire mitochondrial DNA sequence was performed to search for rare mutations. The m.14487 T>C mutation (91% of heteroplasmy) was detected, which was a causative mutation of dystonia and Leigh encephalopathy. About 1 year after the onset of the ophthalmologic symptoms, the patient's optic nerves completely atrophied in both eyes (shown in Fig. 3a, b). His symptoms stabilized with decimal visual acuities of RV = 0.04 (0.07 × S + 5.50D) and LV = 0.08 (0.09 × S + 4.50D) with central scotoma in both eyes (shown in Fig. 3c), as well as dystonia symptoms did not exacerbate overtime.

Discussion

In this case, the patient developed from dystonia, leading to the diagnosis of LHON plus. Although this is a rare case, we believe it is a very educational case to consider the differential disease of dystonia.

As whole sequencing of mitochondrial gene mutations becomes more widespread, the number of reported cases of rare mutations, such as the present case, will increase. Several LHON cases with rare mutations have been reported [4]. The m.14487 T>C is a known causative mutation for Leigh encephalopathy and dystonia [5–7]. On the other hand, few papers reported this mutation point as the rare mutation of LHON [8]. Optic atrophy in Leigh's encephalopathy is thought to progress slowly in both eyes simultaneously, whereas optic nerve lesions or symptoms in typical LHON cases develop rapidly in one eye at a time with the interval of several weeks. In cases of Leigh encephalopathy with severe systemic symptoms, it may be difficult to follow up visual function in some cases, and when such cases are complicated by optic atrophy, it is difficult to distinguish them from LHON. However, in the present case, the systemic symptoms were mild and stabilized, which enabled the ophthalmological follow-up. In addition, the clinical course of the disease helped distinguish between these two

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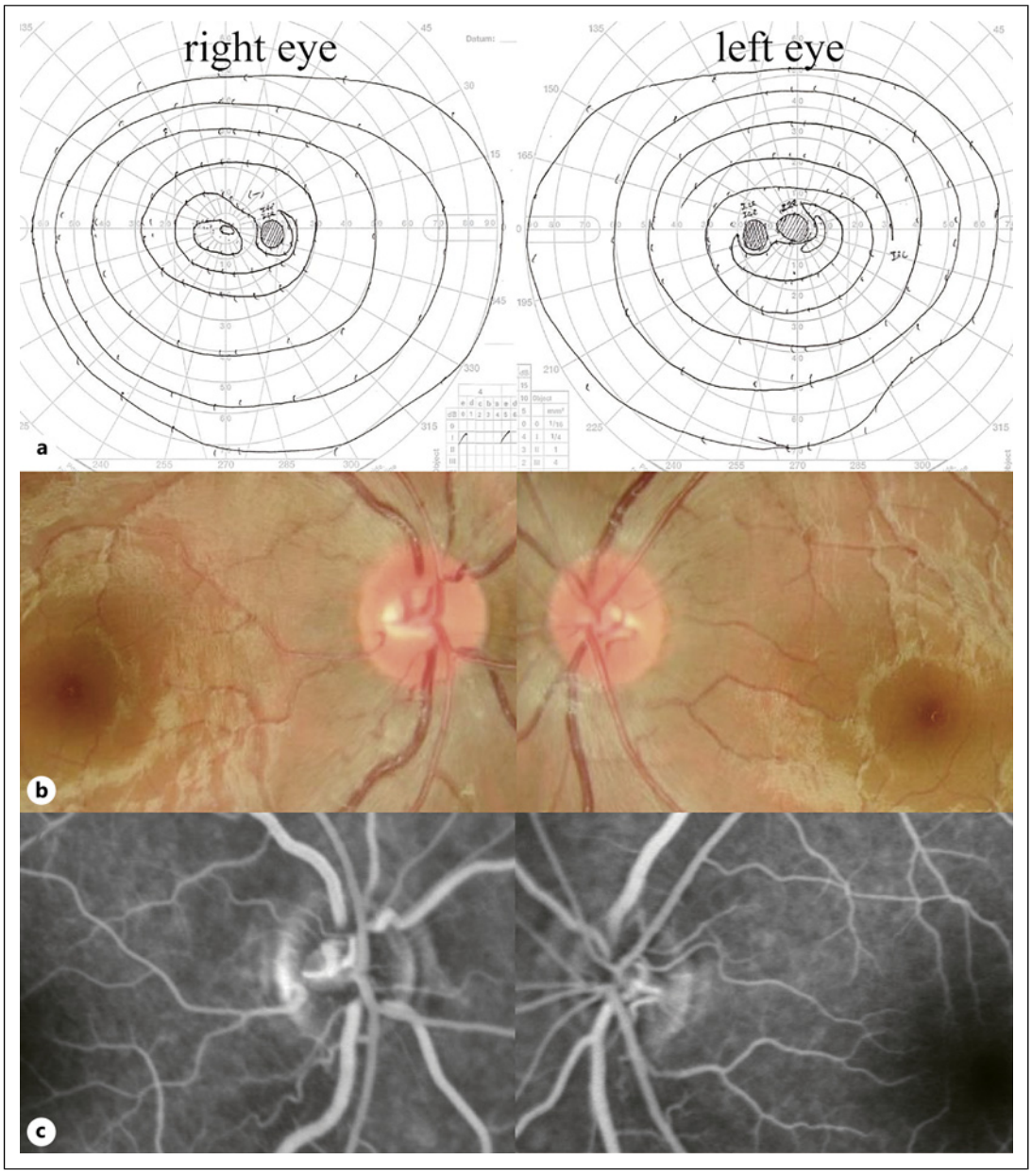

Fig. 2. Ophthalmologic findings immediately after the onset of LHON. **a** The visual field shows a left central scotoma. **b** The optic disc is hyperemic with telangiectasia. **c** Fluorescein fundus fluorescence angiography shows no leakage of fluorescence in either eye.

diseases. The ophthalmological symptoms developed in one eye, followed by the other eye after an interval of 1 month, and the patient showed no relative afferent pupillary defect, which was characteristic in LHON. The fundus image revealed characteristic mild papilledema without leakage of fluorescein, which was also typical finding in LHON. The m.14487 T>C mutation is unique in that the mutation content is 91%, which is close to homoplasmy. High mutation rate is usually related to the severity of the disorder, and this case had only mild dystonia and ocular symptoms. A detailed examination of the right-sided dystonia symptoms and the left putamen region on the MRI did not reveal any alternative diagnoses, including cerebral infarction or other metabolic abnormalities.

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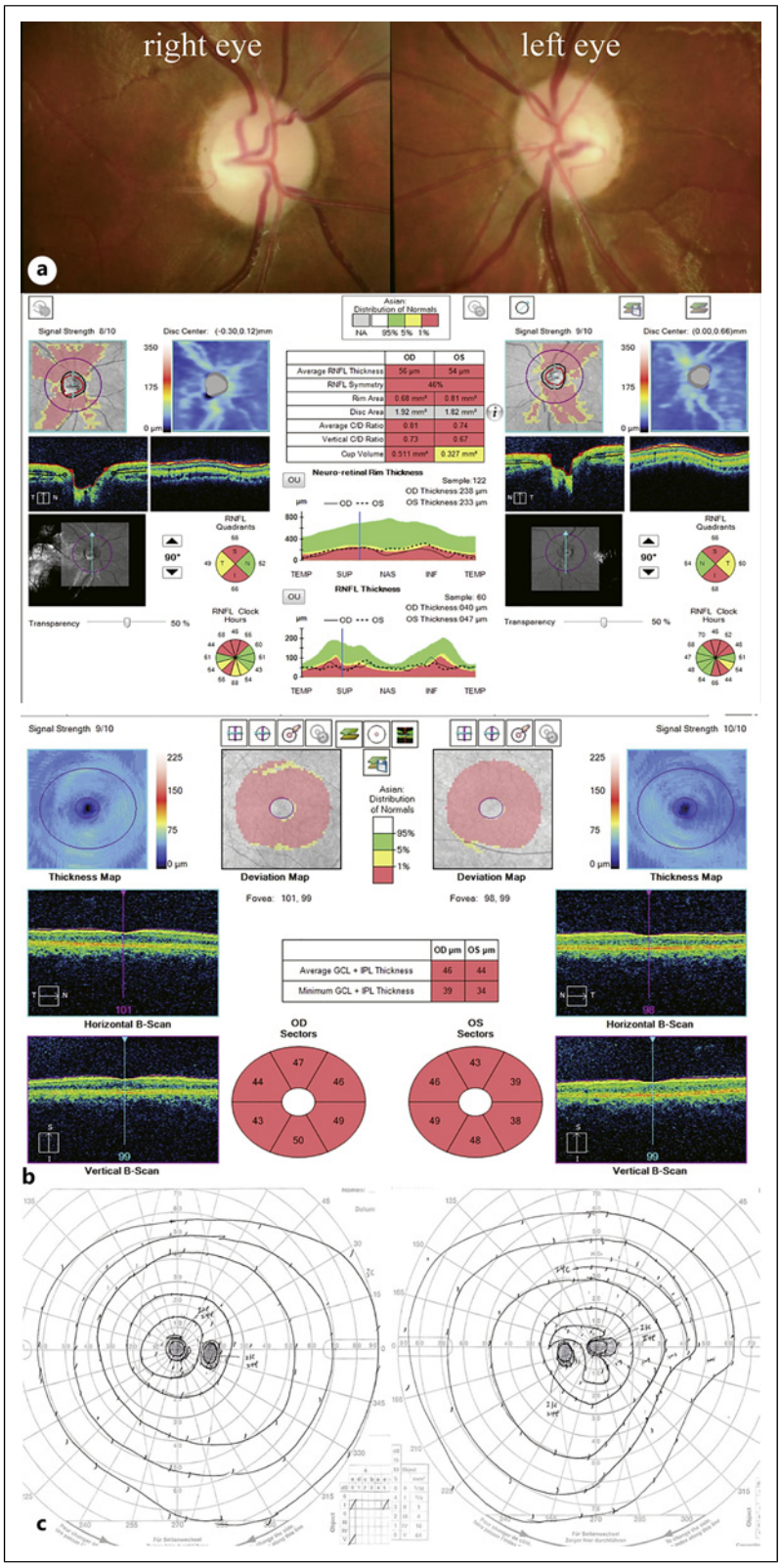

Fig. 3. Chronic phase, 1 year after the onset of the case. **a** The optic disc became atrophic in both eyes. **b** OCT showed thinning of the inner layer of the retina. **c** Central scotoma remained in both eyes.

LHON combined with systemic disease is referred to as LHON "plus." Most patients with LHON only develop visual dysfunction because LHON mainly affects the retinal ganglion cells. However, in a nationwide survey conducted in Denmark, patients with LHON had a higher incidence of central/peripheral nerve disease, cardiovascular disease and alcohol-related disorders as LHON plus, and a significantly increased mortality rate [3]. LHON itself is not associated with mortality, but it can have serious life-threatening effects depending on the complicating disease as LHON plus. The widespread use of whole sequencing will increase the detection of rare mutations in mitochondrial genes, such as this case.

Statement of Ethics

Written informed consent was obtained from the patient and parent for publication of all clinical course and data. This report does not include any identifying information of the patient. This case report was conducted in accordance with the Declaration of Helsinki. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest.

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Author Contributions

F.T., K.U., N.C., M.A., and M.S. examined the patients. K.U. wrote the manuscript. N.C., M.A., M.S., T.K., and Y.Y.N. reviewed and edited the manuscript. M.N. supervised the cases.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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