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Case report

Repetitive brainstem lesions in mitochondrial DNA 11778G > A mutation of Leber hereditary optic neuropathy

Noriyuki Miyaue[a,b,*], Yuki Yamanishi[a], Satoshi Tada[a], Rina Ando[a], Hayato Yabe[b], Masahiro Nagai[a], Masahiro Nomoto[a]

[a] Department of Neurology and Clinical Pharmacology, Ehime University Graduate School of Medicine, Ehime, Japan
[b] Department of Neurology, Saiseikai Matsuyama Hospital, Ehime, Japan

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Dear Editor,

Leber hereditary optic neuropathy (LHON), a maternally inherited disorder, is typically characterized by painless subacute bilateral visual loss in early adulthood. Most LHON patients carry mitochondrial DNA (mtDNA) point mutations affecting complex I of the respiratory chain, including 3460G > A, 11778G > A, and 14448T > C mtDNA mutations. Some LHON cases reportedly present extraocular symptoms, indicating involvement of central nervous system (CNS).

We herein report a case with 11778G > A mtDNA mutation presenting with repetitive brainstem lesions without visual impairment.

1. Case presentation

A 24-year-old man developed an unsteady gait, vertigo, and nausea in the previous 3 months. The patient's mother developed the recurrence of subacute visual loss at an age of 40 years, without recovery. Genetic analysis in the blood sample confirmed her to have a 11778G > A mitochondrial DNA (mtDNA) mutation when the patient was detected as carrying the same mutation at an age of 5 years. His brain magnetic resonance imaging (MRI) revealed symmetrical lesions in the brainstem, including the inferior colliculus (Fig. 1A) when he presented with mild bilateral hearing loss at an age of 19 years, which improved spontaneously. Brain MRI showed no lesions in the brainstem at an age of 21 years (Fig. 1B). Furthermore, neurological examination revealed horizontal nystagmus, mild truncal ataxia, and a positive Romberg sign, but no visual impairment. At an age of 24 years, brain MRI again revealed symmetrical lesions in the brainstem including the vestibular nuclei (Fig. 1C). Hearing tests revealed no hearing loss but an abnormal speech perception, supported by auditory brainstem response (ABR) findings, which showed obscured wave V on both sides. Blood test, including serum thiamine level and anti-aquaporin 4 antibody level, and cerebrospinal fluid analysis yielded normal findings. Exome sequencing identified no causative mutation in his blood sample, except for the 11778G > A mtDNA mutation. We commenced intravenous methylprednisolone treatment, but improvement was not observed.

2. Discussion

This study reports a case with a family history of LHON, presenting with repetitive brainstem lesions. While visual loss is the only clinical symptom observed in most LHON cases, a subset of LHON cases presenting with extraocular symptoms, indicating CNS involvement, has been referred to as “LHON-plus syndrome.”

In terms of manifestation, the present case with repetitive brainstem lesions was also considered for multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD). Coexistence of MS and LHON, known as Harding's syndrome, is reported to occur more frequently than expected by chance [1,2]. Brainstem lesions in most cases with NMOSD are reported to be asymmetrical or unilateral with poorly defined margins [3], while brainstem lesion recurrences are very rare in MS cases.

* Corresponding author at: Department of Neurology and Clinical Pharmacology, Ehime University Graduate School of Medicine, 454 Shidukawa, Tohon City, Ehime 791-0295, Japan.
E-mail address: miyaue@m.ehime-u.ac.jp (N. Miyaue).

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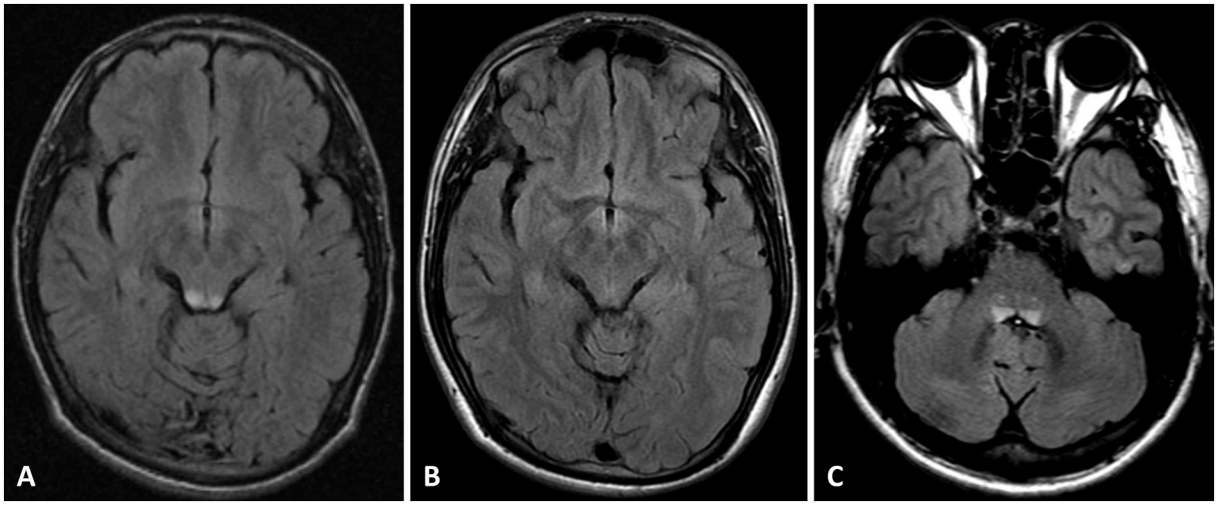

Fig. 1. Brain MRI: (A) 19-year-old fluid attenuation inversion recovery (FLAIR) image showing bilateral hyperintensities of the inferior colliculus; (B) 21-year-old FLAIR image showing disappearance of the previous lesions of the inferior colliculus; (C) 24-year-old FLAIR image showing bilateral and symmetrical hyperintensities of vestibular nuclei.

Bilateral brainstem lesions in the patient, as revealed on brain MRI, resembled those found in Leigh syndrome (LS), which is a progressive neurodegeneration disorder characterized by psychomotor retardation and bilateral lesions in the basal ganglia, thalamus, and brainstem. The onset of LS is typically during infancy or early childhood, with only few reported cases of adult onset. To date, only four cases presenting LS-like symptoms with 11778G > A mtDNA mutation have been described [4–6]. McFarland et al. [4] reported two similar cases with dystonia episodes in infancy, which progressed to involve their trunk, face, and all four limbs. Brain MRI demonstrated symmetric changes in their putamen with no evidence for optic atrophy in either eye. Fruhman et al. [5] reported a case of a 5-year-old girl who developed lethargy, fatigue, difficulty in walking, and weight gain with an initial normal brain MRI. However, her lethargy aggravated with drowsiness, and subsequent brain MRI revealed abnormalities in the hypothalamus, medial thalami, periaqueductal region, dorsolateral medulla, and cerebellar nodules. Administration of carnitine and coenzyme Q10 resulted in improvement in her symptoms; however, the symptoms worsened one month later The subsequent brain MRI showed no significant change in the signal abnormalities; however, she showed no visual disturbance. As with the cases presenting LS-like symptoms with the 11778G > A mtDNA mutation, the present case showed no visual impairment [4,5}. A recent study reported a case with another mitochondrial point mutation wherein bilateral brainstem lesions were revealed by MRI before a sudden loss of vision [7]. Thus, the present case may also develop visual impairment in future.

The inconsistencies between clinical manifestations and MRI findings were reported in cases of LS [8]. In the present case, results of hearing tests and ABR implied inferior colliculus malfunction but brain MRI revealed no residual lesions. Since MRI can only detect damage at a macroscopic level, not a cellular level, there can be a time-lag between MRI findings and clinical features, for example the early stage of stroke in mitochondrial encephalopathy, lactic acidosis, and stroke syndrome (MELAS). In addition, patients with LHON, including those with coexistence of 11778G > A mtDNA mutation with no evident symptoms, were reported to show neural abnormality in central auditory pathways, especially speech perception [9]. Bilateral brainstem lesions are reportedly common in cases with mitochondrial complex I deficiency [10]. Based on our findings, LHON cases may report central auditory pathway dysfunction, including the inferior colliculus, without showing any prominent abnormalities in auditory function.

In conclusion, we described a case with a mtDNA mutation typically associated with LHON, presenting repetitive brainstem lesions supported by both clinical findings and neuroimages. Our case report suggests that LHON cases can show brainstem lesions without visual impairment, and auditory pathways may be involved in cases with the 11778G > A mtDNA mutation, regardless of abnormalities shown by brain MRI.

Declarations of interest

None.

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