Leber’s hereditary optic neuropathy with diffuse white matter changes mimicking gliomatosis cerebri: illustrative case

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BACKGROUND Leber’s hereditary optic neuropathy (LHON) is a mitochondrial disease characterized by bilateral severe subacute central vision loss and a mutation in the mitochondrial DNA (mtDNA). The findings on cranial magnetic resonance imaging of patients with LHON vary from subtle to multiple white matter changes. However, they rarely present with diffuse infiltrative white matter changes.

OBSERVATIONS The authors reported a case with diffuse white matter changes mimicking gliomatosis cerebri (GC). The histological findings included only mild glial hyperplasia without immunohistochemical positivity, supporting the diagnosis of glial tumors. Analysis of mtDNA obtained from the blood and brain tissue revealed mutation of m.11778G>A in the NADH dehydrogenase 4 gene, which confirmed the case as LHON. Immunohistochemistry of the brain tissue revealed 8-hydroxy-2-deoxyguanosine positivity, suggesting the presence of oxidative stress.

LESSONS LHON is extremely difficult to diagnose unless one suspects or knows the disease. The present case brings attention not only to LHON but also to other mtDNA-mutated diseases that need to be considered with diffuse white matter changes or GC.

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KEYWORDS Leber’s hereditary optic neuropathy; gliomatosis cerebri; mitochondrial disease; mitochondrial DNA

Leber’s hereditary optic neuropathy (LHON) is a mitochondrial disease that predominantly affects men in their second and third decades of life.1 The clinical manifestation is a severe bilateral subacute central visual loss, with prevalence of approximately 1 in 10,000 to 50,000 cases.2-5 The cause of LHON is a mutation at a maternally inherited mitochondrial DNA (mtDNA). Three mtDNA point mutations, such as m.11778G>A in the NADH dehydrogenase (ND) 4 gene, m.3460G>A in the ND1 gene, and m.14484T>C in the ND6 gene, comprised more than 90% of LHON cases,5,6 and there are also rare variants,7 all affecting genes encoding complex I subunits of the mitochondrial respiratory chain.2,6 As a result, the dysfunction of the mitochondria damages retinal ganglion cells, which are highly susceptible to disrupted adenosine triphosphate production and oxidative stress.1

Gliomatosis cerebri (GC) is a rare disease with diffuse neoplastic glial infiltration involving more than two cerebral lobes. The 2007 World Health Organization (WHO) classification of tumors of the central nervous system categorized GC as a specific entity. The latest 2016 WHO classification excluded GC as a specific entity because DNA methylation revealed that GC corresponded to previously defined molecular subgroups of gliomas and did not demonstrate evidence for a distinct GC signature.8 However, we cannot ignore the invasive radiological features of GC, and further study is required to understand this unique tumor.9

We report a case that clinically and radiologically corresponded to the diagnosis of GC, with minimal or some findings of glial hyperplasia histologically. Immunohistochemical analyses did not show

ABBREVIATIONS 18F-FDG = 18F-fluorodeoxyglucose; FLAIR = fluid-attenuated inversion recovery; GC = gliomatosis cerebri; LHON = Leber’s hereditary optic neuropathy; MRI = magnetic resonance imaging; mtDNA = mitochondrial DNA; ND = NADH dehydrogenase; PCR = polymerase chain reaction; PET = positron emission tomography; WHO = World Health Organization.

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positivity in IDH1R132H or TP53, but molecular analysis showed a point mutation at mtDNA of LHON. LHON is a disease primarily affecting the visual system, and it infrequently presents with small white matter lesions on brain magnetic resonance imaging (MRI). We discuss a case of LHON and other mtDNA-mutated diseases with diffuse radiological white matter changes mimicking GC.

**Illustrative Case**

A 71-year-old man presented with bilateral vision loss that had been ongoing for 6 months. There was no relevant family history. He experienced progressive vision loss of the central visual field at the right eye and visited an ophthalmologist. MRI was performed to rule out diseases of the central nervous system resulting in diffuse white matter changes (Fig. 1A). Fluid-attenuated inversion-recovery (FLAIR) MRI showed a high-intensity area at the right temporal, occipital, and parietal lobes, the insula, the basal ganglia, the peduncle of the midbrain, the splenium of the corpus callosum, the optic chiasm, and the bilateral optic tracts (Fig. 1A). Gadolinium-enhanced T1-weighted MRI did not reveal an enhanced lesion (Fig. 1B). Radiological reports highly suggested GC. 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) (Fig. 1C) did not reveal any uptake corresponding to this FLAIR high-intensity lesion.

He then presented with progressive vision loss of the left eye. He was treated with intravenous steroid pulse therapy, but no improvement was noted after. There was no papilledema on fundoscopy, and the cerebrospinal fluid analysis was normal. Despite the diffuse white matter changes, the patient did not present with any other neurological symptoms except for bilateral vision loss. The ophthalmologists referred the patient to our department to confirm the histopathology of the brain.

A stereotactic biopsy was performed through the right parietal lobe to obtain tissue from the splenium of the corpus callosum (Fig. 1D). The histological findings revealed mild glial hyperplasia, but atypical cells or demyelination were not demonstrable (Fig. 2A and B). Immunohistochemical analyses showed negative IDH1R132H and TP53 and MIB1 labeling index <1% (Fig. 2C, D, and E, respectively); thus, there were no findings to support the diagnosis of GC or glial tumors. Because of the patient’s progressive bilateral visual loss, the ophthalmologists suspected the possibility of LHON, resulting from the mtDNA mutation of m.11778G>A extracted from the blood (Fig. 3).

We additionally investigated the brain tissue from the stereotactic biopsy, which also resulted in m.11778G>A mtDNA mutation (Fig. 3). Because of the genetic result, the patient did not receive radiation and chemotherapy. We have been following the case for more than 2 years, and no radiological or neurological worsening has been noted (Fig. 1D). Additional immunohistochemistry using 8-hydroxy-2′-deoxyguanosine (8-OHdG, ab48505, Abcam) antibody demonstrated positivity (Fig. 2F), suggestive of cellular oxidative stress. mtDNA has a circular, double-stranded molecule with a length of 16,569 bp. Methods for detecting mtDNA mutations are as follows. Using polymerase chain reaction (PCR), we first amplified the whole length of mtDNA by three pairs of primers: Mito1_F: TTCCATCCACCTCTCTCTCCCTAG and Mito1_R: GAGCCCCATTGTGTGTTGTTAATA; Mito2_F: GTGGGCCTAGCCCTACTAGTCTCAA and Mito2_R: GGGATATTGATTTCACGGAGGATGG; and T27: TTCGCCCACTAAGCCAATCACTT and Mito3_R: GCGGGAGAAGTAGATTGAATTTGAAG. After the confirmation of amplified PCR products and the purification step, we used the following three primers to detect the major three hotspot mtDNA mutations of LHON by Sanger sequencing: M3460P-1_F: TTGTACCCATTCTAATCGCAA; LEBER_SP_F: GGCGCAGTCATTCTCATAAT; and m14484P-1_F: TCTTACCCAACAGCACAATG.

**Discussion**

**Observations**

LHON is a relatively known disease among ophthalmologists; however, it is not as well known among most neurosurgeons and neurooncologists. The present case demonstrated diffuse infiltrative lesions on brain white matter and bilateral optic tracts. Approximately 67.9% of LHON cases present with high-intensity optic chiasm and bilateral optic tracts on T2-weighted MRI; however, 4.1%
to 10% of GC cases also present with such findings. Patients with LHON infrequently present with white matter changes on MRI, but none so far have presented with diffuse infiltrates, such as the present case.

Patients with LHON showed significantly reduced volume of the optic chiasm, optic tracts, white matter in the optic radiation, and other subcortical brain structures, which could be detected using diffusion tensor MRI, 3T MRI, or 7T MRI. However, such studies assessed patients with LHON with disease duration over 10 years, indicating that atrophic changes would appear in a chronic phase. Case reports demonstrated chronological changes from swollen to atrophic optic tracts over time; therefore, a swollen structure may be an initial change in LHON. The present case had diffuse white matter changes with thickening of the splenium of the corpus callosum. Thickened splenium has never been reported in patients with LHON and may indicate glioma-like change, but the tissue obtained from the splenium was negative for histological features of gliomas. We presume that the splenium of the corpus callosum will be atrophic in a later phase during follow-up. LHON-related genetic mutations causing mitochondrial dysfunction can induce occult white matter changes in the brain. Because LHON is a disease in young adults, older patients with longer incubation time will transform the occult white matter changes to visible changes.

Epidemiologically, neuroepithelial tumors, including all grades of gliomas, are more frequently observed in men. In terms of survival, male patients with glioblastoma and grade 3 gliomas present with shorter survival than female patients. Therefore, although still controversial, male patients with malignant gliomas had worse survival. As with other gliomas, GC is also frequently observed in men. Contrary to other malignant gliomas, two studies showed that male patients with GC have more prolonged overall survival. In these studies, 36.4% to 39.5% of the GC cases were diagnosed based on clinical and radiological methods alone without a histological diagnosis. On the contrary, other studies demonstrated no survival difference between sexes in patients with GC, all of whom had histologically confirmed GC. As our case presented, a male preponderance nonmalignant disease with diffuse white matter changes can be misdiagnosed as GC, possibly explaining the prolonged survival in men. Although radiological findings are typical for GC, a histological analysis should be conducted to rule out LHON.

FIG. 2. Histological findings. A and B: Hematoxylin and eosin staining showing mild glial hyperplasia. C and D: Negative for immunohistochemical staining of IDH1R132H and TP53. E: MIB1 labeling index is less than 1%. F: Positive for immunohistochemical staining of 8-hydroxy-2'-deoxyguanosine. (Original magnifications: A: ×100; B, C, and F: ×400; D and E: ×200.)

FIG. 3. The result of Sanger sequencing from the blood, brain tissue, and reference as a normal control (arrows). mtDNA from the blood and brain tissue showed m.11778G>A mutation.
We assessed the tumor tissue obtained from brain biopsy to investigate for mtDNA mutation. Because m.11778G>A mutation was detected from the mtDNA of the blood, the same mutation was detected from the mtDNA of the brain. To assess the mitochondrial dysfunction, we immunohistochemically evaluated 8-OHdG, a marker of cellular oxidative stress.\(^{36}\) Corresponding to the previous report with increased 8-OHdG from leukocyte DNA of patients with LHON, the brain tissue showed positivity for 8-OHdG antibody, indicating the presence of oxidative stress in the brain. Kovács et al. also histologically demonstrated oxidative stress in the brain white matter of a patient with LHON as upregulation of mitochondrial manganese superoxide dismutase but used autopsy cases.\(^{37}\) LHON is a disease of the visual system in which histological assessment is difficult; thus, the histological findings of the present case were essential to understand the pathophysiology of the disease. In addition to the three major mtDNA mutations of LHON (m.11778G>A, m.3460G>A, and m.14484T>C), 46-point mutations have been reported as mtDNA mutations in patients with LHON.\(^{7}\) Most of them encode mtDNA genes of ND4L, ND4, ND5, and ND6. Yeung et al. analyzed the mtDNA in glioblastoma and found that ND4L, ND4, ND5, and ND6 were also frequently mutated in mtDNA.\(^{38}\) LHON and glioblastoma presented with the same mutated genes, but they did not share the mutated reference positions. Unlike other mitochondrial diseases, LHON shared mutated genes with glioblastoma, genetically potentiating LHON to mimic GC.

**Lessons**

We presented a case of LHON with diffuse white matter changes mimicking GC. Histological diagnosis is essential to exclude the possibility of GC but is not enough to diagnose LHON. Without the detection of mtDNA mutation of m.11778G>A, it would have been difficult to exclude the diagnosis of GC and possibly would have led to unnecessary treatment involving radiation and chemotherapy. Our case suggested that diffuse white matter changes in a man should be differentially diagnosed as LHON or mitochondrial diseases, which can be confirmed with mtDNA mutation findings.

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