Original Contribution

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Magnetic Resonance Imaging Findings in the Pregeniculate Visual Pathway in Leber Hereditary Optic Neuropathy

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Background: Current research has not provided a consistent and qualitative description of MRI features in Leber hereditary optic neuropathy (LHON). Our study aims to investigate the MRI findings in the pregeniculate visual pathway and discuss their clinical significance in LHON.

Methods: Orbital MRI was retrospectively analyzed for 53 patients with LHON (101 afflicted eyes) admitted to the Department of Neurology, Beijing Tongren Hospital, Capital Medical University, from 2014 to 2019. We described the imaging abnormalities and discussed their associations with the time interval from the onset of vision loss to the performance of MRI (TIOVP), prevalence of m.11778G>A, and best-corrected visual acuity (BCVA).

Results: T2 hyperintense signal (HS) was determined in 82 afflicted eyes, with 34 located in the intraorbital segment (IO) of the optic nerve (ON), 26 in the IO concurrent with intracanalicular segment (ICn), 14 in the IO and ICn concurrent with intracranial segment (ICr) of the ON, 4 in the IO, ICn, and ICr concurrent with optic chiasm (OCh), and 4 in the IO, ICn, ICr, and OCh concurrent with optic tract (OTr). MRI was normal in the remaining 19 afflicted eyes. Among the 6 groups, no statistical differences were found in the TIOVP (P = 0.071), prevalence of m.11778G>A (P = 0.234), and BCVA (P = 0.076). As T2 HS extended, the BCVA gradually decreased. Nineteen of the 54 afflicted eyes revealed contrast enhancement, with the TIOVP ranging from 0.25 to 6 months.

Conclusions: T2 HS was common in the pregeniculate visual pathway in LHON. It was not correlated with the prevalence of m.11778G>A and did not benefit in disease staging. As it extended, the BCVA gradually decreased. Contrast enhancement was relatively rare, always occurring in the subacute stage.

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Leber hereditary optic neuropathy (LHON; OMIM 535000) is a maternally inherited disease characterized by bilateral, painless, subacute, central vision loss, which may happen simultaneously or sequentially (1). The most prevalent primary mitochondrial DNA (mtDNA) mutations responsible for 90%–95% of LHON cases are m.11778G>A/MT-ND4, m.3460G>A/MT-ND1, and m.14484T>C/MT-ND6. Other mtDNA mutations such as m.3635G>A, m.10197G>A, m.14502T>C, m.3736G>A, m.3866T>C, m.10680G>A, m.11696G>A, and m.13513G>A are considered as rare causes of LHON (2–8). Missense mutations in mtDNA genes are known to cause mitochondrial dysfunction with drastic defects in complex I subunits of the mitochondrial respiratory chain and result in the focal degeneration of the retinal ganglion cells (RGCs) and loss of axons within the optic nerve (ON) (9). LHON primarily is a clinical diagnosis, and its clinical features are common to all mitochondrial optic neuropathies.

Several case reports and case series have revealed T2 hyperintense signal (HS) and contrast enhancement on MRI in the pregeniculate visual pathway in patients with LHON (10–17), but it is still unclear with the distribution of these imaging abnormalities based on the small patient cohort. Until now, only a French research has demonstrated that 19 of the 28 cases presented with T2 HS located in the ON and optic chiasm (OCh), and 16 cases showed enlargement of the OCh (15). Hence, the current literature has not

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The authors report no conflicts of interest.

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provided a complete qualitative description of the imaging features in the pregeniculate visual pathway in LHON. Although new imaging techniques such as zero echo time MRI sequences have been developed to enable precise and clinically effective visualization of the visual system in LHON (18), it is still difficult for them to be widely used in clinical practice, and conventional imaging protocols for the pregeniculate visual pathway are still irreplaceable until now. Having this in mind, we report and review the imaging abnormalities in the pregeniculate visual pathway and discuss their clinical significance in patients with LHON.

METHODS

Fifty-three patients with a genetic diagnosis of LHON were enrolled in the Department of Neurology, Beijing Tongren Hospital, Capital Medical University, from January 2014 to December 2019. They all only presented with bilateral or unilateral vision loss. Patients with any other diseases that were known to cause optic neuropathy were excluded. Sequencing of mtDNA fragments was performed targeting the top 19 primary LHON mutations and 35 candidate mutations according to MITOMAP database (https://www.mitomap.org/foswiki/bin/view/MITOMAP/MutationsLHON) and literature review. Our study was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University (Institutional Review Board number: TRECKY2020-112). Each patient signed an informed consent form and was treated in accordance with the tenets of the Declaration of the Helsinki.

An "afflicted eye" was defined as an eye with central vision loss and determined time interval from the onset of vision loss to the performance of MRI (TIOVP). Medical records were reviewed to obtain data including sex, age at diagnosis, TIOVP, and the best-corrected visual acuity (BCVA) of the afflicted eyes. Decimal visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR). Orbital MRI was performed for each patient using a standard head coil on a 3-T GE Discovery MR750 scanner (GE Healthcare, Milwaukee, WI). All patients underwent imaging procedures, including precontrast T1 (TR/TE = 456/9 milliseconds) and T2 sequences (TR/TE = 7,500/95 milliseconds) in the axial plane, short tau inversion recovery (STIR) sequences (TR/TE = 606/7.2 milliseconds) in the coronal plane, and contrast-enhanced T1 images in the axial and coronal planes (3-mm thick and 0.5-mm interslice gap). Gadolinium-diethylenetriamine pentaacetic acid was intravenously injected at a dose of 0.1 mmol/kg body weight in 28 patients.

MRI was evaluated blindly and independently by 2 neurologists and 1 neuroradiologist, and it was considered abnormal if they reached an agreement with one of the following criteria:

1. A T2 or T2 STIR HS in any portion of the pregeniculate visual pathway, that is, the intraorbital (IO), intracanalicular (ICn), intracranial segment (ICr), OCh, and optic tract (OTr).
2. Contrast enhancement.

Statistical analyses were performed using IBM SPSS version 26.0 software (IBM, New York, NY). Descriptive statistics were expressed as median (interquartile range, IQR) for nonnormally distributed continuous variables, whereas number and percentage were presented for categorical variables. The Mann–Whitney U test was used to analyze differences in the continuous data. The Fisher exact test and the Kruskal–Wallis test were used to analyze categorical variables. A 2-tailed P value of less than 0.05 was considered significant for all.

RESULTS

Clinical data of 48 men and 5 women with a total of 101 afflicted eyes were included. The median age at diagnosis was 24.06 (IQR 15–32) years (range, 29–56 years). The TIOVP ranged from 0.25 to 120 months, and it was up to 12 months in 10 afflicted eyes. The median TIOVP of all was 2.00 (IQR 1–5) months (range, 0.25–120 months). Forty-eight patients presented bilateral vision loss, and the remaining 5 patients reported unilateral vision loss at diagnosis. The median BCVA was 3.7 (IQR 3.3–4.3) (range, 2.0–5.0). A list of mtDNA mutations is summarized in Table 1.

Imaging Findings

T2 Hyperintense Signal in the Pregeniculate Pathway

T2 HS was present in a total of 82 eyes (81.19%) (Fig. 1). The ON was solely involved in 74 eyes (73.27%), 60 of which (81.08%) showed the sole involvement of the IO (S1) and simultaneous involvement of the IO and ICn (S2). An extensive T2 HS to the OCh and OTr (i.e., S4 and S5) was determined in the remaining 8 eyes (7.92%) (Table 2).

There were no statistically significant differences in both the TIOVP (P = 0.071) and prevalence of m.11778G>A (P = 0.234) among the 6 groups. The TIOVP was 2.335 (IQR 1–4) months in the 19 afflicted eyes with normal MRI, and it was 2.25 (IQR 1–5) months in the 82 afflicted eyes with T2 HS. The difference was not obvious in the TIOVP between both groups (P = 0.900). If further divided into 2 subgroups (≤3 months and >3 months), the distribution of T2 HS was not statistically different between both subgroups (P = 0.161) (Table 2).

The median BCVA gradually decreased among the 6 groups (Fig. 2). It was 0.85 logMAR (IQR 0.4–1.0) in the 19 afflicted eyes with normal MRI and 1.3 logMAR (IQR 0.7–1.7) in the 82 afflicted eyes with T2 HS. A statistically significant difference was found in the median BCVA

TABLE 1. Summarization of mtDNA mutations in 53 patients

Primary mtDNA Mutation	Total No. of Patients	Other Candidate Mutations	Total No. of Patients
m.11778G>A	30	m.11696G>A	1
m.14484T>C	7	m.13513G>A	1
m.3460G>A	4	m.3736G>A	1
m.11778G>A & m.3736G>A	1	m.3866T>C	1
m.11778G>A & m.11696G>A	1	m.10680G>A	1
m.11778G>A & m.12811T>C	1		
m.11778G>A & m.14502T>C	1		
m.3460G>A & m.12811T>C	1		
m.10197G>A	1		
m.14502T > C	1		

between both groups (P = 0.006). Furthermore, the difference was determined between the 19 afflicted eyes with normal MRI and those with T2 HS in S5 (P= 0.017) in which the median BCVA was 2.15 logMAR (IQR 1.94–3.0). The BCVA of the afflicted eyes among the 5 groups was not statistically different (P = 0.076).

Of the 19 afflicted eyes with normal MRI, 15 eyes (78.95%) presented with BCVA ≥1.0 logMAR. There were 52 afflicted eyes with BCVA ≥1.0 logMAR, and 15 of them (28.85%) showed normal imaging findings. Four of the 49 afflicted eyes (8.16%) with BCVA <1.0 logMAR revealed normal imaging findings.

Contrast Enhancement in the Pregeniculate Pathway

Contrast-enhanced MRI was performed in 54 afflicted eyes. Nineteen of them (35.19%) revealed enhancement in various segments of the pregeniculate visual pathway and thus were classified into the enhancement group (Fig. 3). The remaining 35 afflicted eyes were categorized into the nonenhancement group. In the enhancement group, the median TIOVP was 2 (IQR 1–4.5) months (range, 0.25–6 months) and the median BCVA was 1.37 logMAR (IQR 0.9–1.85). In the nonenhancement group, the median TIOVP was 3 (IQR 1–4) months and the median BCVA was 1.3 logMAR (IQR 0.6–1.7). There were no significant differences in both the TIOVP (Z = 354.500, P = 0.739) and the BCVA (Z = 263.000, P = 0.205) between both groups.

DISCUSSION

LHON was the first disease identified to be associated with mtDNA point mutations and has become one of the most well-known mitochondrial diseases (19). Today, neuro-ophthalmologists, ophthalmologists, and neurologists are all familiar with its clinical presentation and genetic characteristics. However, the knowledge of the imaging manifestations of the pregeniculate visual pathway is relatively limited and inconsistent. In this study, we summarized the imaging findings on conventional MRI in 53 patients with 101 afflicted eyes. T2 HS was detected in 81.19% of the afflicted eyes, with S1 and S2 predominantly involved. However, the S4 and S5 were rarely affected. There were no statistically significant differences in both the TIOVP and the prevalence of m.11778G>A among the various affected segments. The distribution of T2 HS was also not statistically different between afflicted eyes with TIOVP within 3 months and those up to 3 months. Although statistical differences were also not obvious in BCVA among various affected segments, the BCVA was gradually decreased as the extension of the T2 HS. 35.19% of the afflicted eyes revealed minimal enhancement in different segments of the ON, OCh, and OTr.

T2 HS in the pregeniculate pathway had been previously reported in patients with LHON. In 1989, Kermode et al demonstrated T2 HS in the IO of the ON in 8 of the 13 patients with the TIOVP of 3 months–16 years (10). In 1998, Mashima et al detected T2 HS in bilateral ON in 5 patients at the chronic stage (12). However, the OCh and

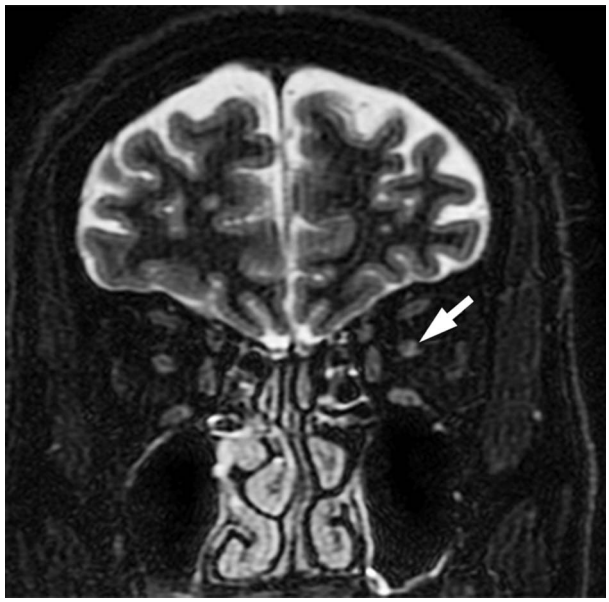

FIG. 1. T2 hyperintense signal on MRI. Orbital MRI performed in a 48-year-old man 6 months after the onset of bilateral visual loss. T2 coronal short tau inversion recovery sequence showed hyperintense signal (*white arrow*) in the intraorbital segment of the left optic nerve.

TABLE 2. Distributions of T2 HS based on orbital MRI

Involved Segments	T2 HS (Afflicted Eyes, %)	Mutation Type		TIOVP	
		m.11778G>A (+)	m.11778G>A (−)	≤3 mo	>3 mo
Normal	19 (18.81)	11	8	13	6
S1	34 (33.67)	25	9	26	8
S2	26 (25.74)	17	9	15	11
S3	14 (13.86)	4	10	8	6
S4	4 (3.96)	4	0	1	3
S5	4 (3.96)	2	2	4	0

S1, sole involvement of the IO; S2, simultaneous involvement of the IO and ICn; S3: simultaneous involvement of the IO, ICn, and ICr; S4, simultaneous involvement of the IO, ICn, ICr, and OCh; S5, simultaneous involvement of the IO, ICn, ICr, OCh, and OTr.

OTr were not evaluated in both studies because of inadequate spatial resolution on MRI. In 2017, Christelle Blanc et al found that T2 HS was determined in 19 of the 28 cases (67.9%) within 1 year of onset of vision loss, with 3 located in the ICn concurrent with ICr and 16 in the ICn and ICr concurrent with OCh (15). Cui et al reported T2 HS in 6 of the 16 patients with rare primary mutations within 3–6 months (4). Hence, it indicated that T2 HS in the pregeniculate visual pathway was frequently detected in patients with LHON, and they were disease stage independent. The presence of T2 HS could not exclude the possibility of LHON.

In both Kermode's study and our patients, the IO was the segment most frequently affected by T2 HS among different portions of the ON on MRI (10). In comparison, the ICn segment was less frequently involved in our study. Before 2017, T2 HS in the OCh or OTr was only reported in a few case series (13,14,16,20). However, Christelle Blanc et al revealed the predominance of an extension from the ON to the OCh in patients with BCVA <1.0 logMAR, without sole involvement of the IO or ICn (15). As shown in both Kermode's and our study, this difference was not caused by the TIOVP and prevalence of m.11778G>A. Although statistical differences in BCVA were not obvious among the affected segments, the BCVA was demonstrated to be gradually decreased as the extension of the T2 HS in our patients, which suggested that the lower the BCVA, the more likely the extension of the T2 HS to the ICr, OCh, and OTr successively. Therefore, the prevalence of T2 HS in the ICr and OCh in Kermode's patients may be explained by the higher percentage of afflicted eyes with lower BCVA in comparison with ours. Consequently, when T2 HS occurs in the OCh or OTr, especially in the acute/subacute stage, it should be avoided to misdiagnose LHON as neuromyelitis optica spectrum disorder. Only 8.16% of the afflicted eyes with BCVA <1.0 logMAR revealed normal imaging findings. However, Filippi et al did not detect any macroscopic lesion in the ON in 18 of the 20 afflicted eyes of 10 patients with LHON with BCVA <1.0 logMAR (21). This discrepancy may be caused by the application of low-field MRI system (operating in the range of 1.5 T) and the higher BCVA compared with our patients.

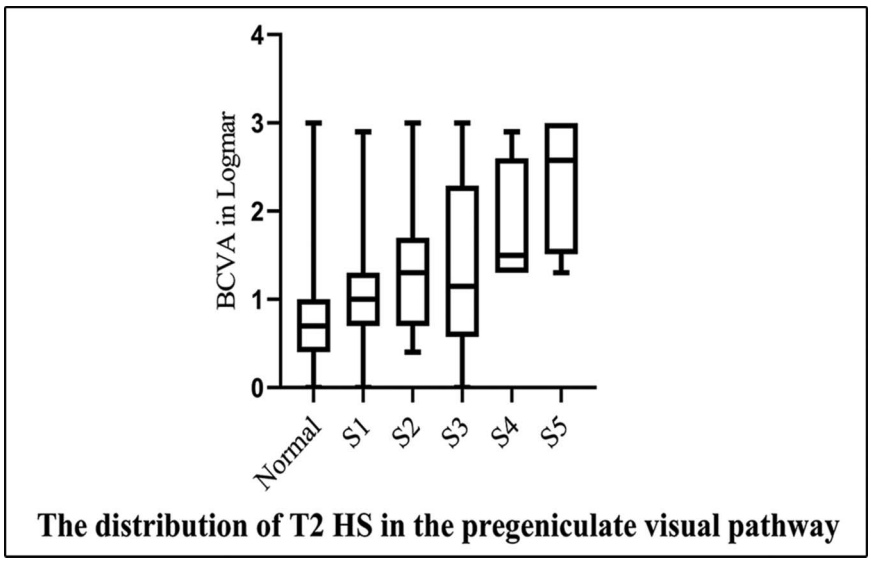

FIG. 2. The BCVA of the 101 afflicted eyes among the six groups.

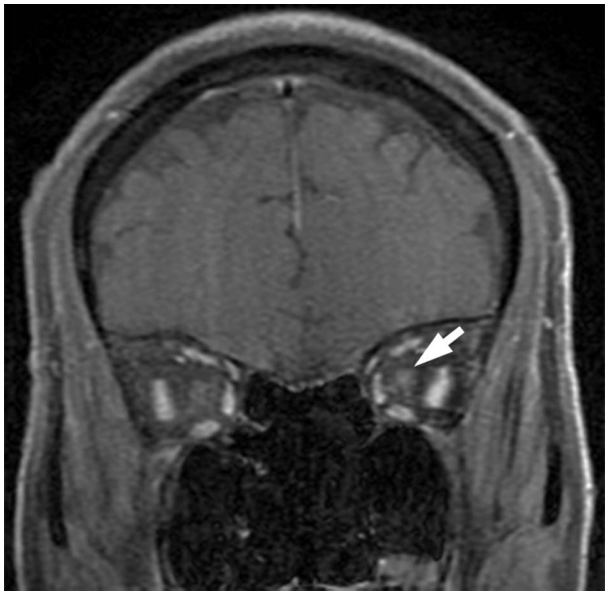

FIG. 3. Contrast enhancement of the optic nerve on MRI. Orbital MRI in a 16-year-old boy with bilateral visual loss, occurring 1 month apart. Coronal contrast-enhanced MRI revealed minimal enhancement in the left optic nerve (*white arrow*).

In our study, contrast enhancement in the pregeniculate visual pathway occurred in 35.19% of the afflicted eyes with the TIOVP within 6 months. However, it had only been documented in a few patients with the TIOVP within 3 months (12,16,17,20). This may indicate that such enhancement did not frequently occur in LHON, and it may be always correlated with the subacute stage. We did not find the difference in both the BCVA and TIOVP between the afflicted eyes with and those without nerve enhancement. Hence, the occurrence of nerve enhancement was not positively correlated with the degree of visual impairment, and it should be differentiated from optic neuritis in the early stage.

Although BCVA $\geq$1.0 logMAR was determined in about 90 percent of the afflicted eyes with normal MRI, only 28.85% of the afflicted eyes with BCVA $\geq$1.0 logMAR revealed normal imaging findings. This was further confirmed by Rizzo's study in which conventional MRIs appeared normal in 6 of the 22 patients with LHON with BCVA $\geq$1.0 logMAR (22).

The retrobulbar ON is composed of myelinated nerve fibers, which are the axons of the RGCs, interstitial glial cells (oligodendrocytes, neuron glial 2 cells, astrocytes, and microglia), and the fibrovascular septa of the pia mater (23). Previous histopathological reports of LHON had described a dramatic decline of the RGCs and axonal loss. Demyelination, fibrillary gliosis, and fibrocytic scarring were also shown in a few cases at autopsy (24–26), which may be an indication of the damage to the interstitial glial cells caused by mitochondrial dysfunction and thus the underlying explanation for the T2 HS in LHON. Besides, the optic nerve has occasionally been found to consist of scattered degeneration dust associated with macrophages, which is an indication of minimal inflammatory changes (24,26). Contrast enhancement may be explained by not only such inflammatory components but also the disruption of the blood–brain barrier.

CONCLUSIONS

Our retrospective study demonstrated that T2 HS in the pregeniculate visual pathway was common in LHON, especially with BCVA $<$1.0 logMAR. It was not correlated with the prevalence of m.11778G$>$A and did not benefit in disease staging. Although no statistical difference existed, the BCVA gradually decreased as the extension of T2 HS. Contrast enhancement was relatively rare, always occurring in the subacute stage. Although further perspective work needs to be performed to confirm these imaging features in larger cohorts, our imaging findings may offer some evidence for the diagnosis of LHON, the evaluation of visual impairment, and further understanding of the pathophysiology of this optic neuropathy.

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