Photoreceptor changes in Leber hereditary optic neuropathy with m.G11778A mutation

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Abstract

- **AIM:** To evaluate the functional and structural changes of photoreceptors in patients and asymptomatic carriers with Leber hereditary optic neuropathy (LHON) using full-field electroretinography (FERG) and optical coherence tomography (OCT).
- **METHODS:** Individuals diagnosed with LHON at the Renmin Hospital of Wuhan University and their family members were included in this cross-sectional observational study. The FERG a-wave amplitude of affected patients and asymptomatic carriers was analyzed. The thickness of the outer nuclear layer (ONL), inner and outer segment (IS/OS) and total photoreceptors in the macular fovea and parafovea were measured.
- **RESULTS:** This study included 14 LHON patients (mean age: 20.00±9.37y), 12 asymptomatic carriers (mean age: 39.83±6.48y), and 14 normal subjects (mean age: 24.20±1.52y). The FERG results showed that the dark-adapted 3.0 electroretinography and light-adapted 3.0 electroretinography a-wave amplitudes of patients and carriers were significantly decreased ($P<0.001$). The ONL and photoreceptors layers were slightly thicker in patients than in normal subjects ($P<0.05$), whereas they were thinner in carriers ($P<0.05$). There were no differences in IS/OS thickness among the groups ($P>0.05$).
- **CONCLUSION:** Photoreceptors function is significantly impaired in LHON-affected patients and asymptomatic carriers. Meanwhile, photoreceptors morphology is slightly altered, mainly manifesting as a change in ONL thickness.
- **KEYWORDS:** Leber hereditary optic neuropathy; asymptomatic carriers; photoreceptor; electroretinogram;

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INTRODUCTION

Leber hereditary optic neuropathy (LHON) is a primary inherited mitochondrial disease arising from mitochondrial DNA mutations[1]. Over 95% of LHON cases are caused by three primary point mutations, m.11778G>A, m.3460G>A and m.14484T>C[2]. Mutations result in the dysfunction of the mitochondrial respiratory chain complex subunit I[3]. Retinal ganglion cells (RGCs) are rich in mitochondria and are most prone to mitochondrial dysfunction, eventually leading to RGC degeneration and necrosis and optic nerve atrophy[4]. Most LHON patients are male, and LHON typically manifests as acute or subacute painless central visual loss in both eyes simultaneously or successively. Approximately 50% of male carriers and 90% of female carriers do not develop visual loss in their lifetime, referred to as asymptomatic carriers[5]. Photoreceptors are also densely packed with mitochondria. However, previous studies have shown that photoreceptors function and morphology are usually not affected in LHON patients[6-7]. To date, most studies on LHON have focused on RGCs; little attention has been paid to the changes in photoreceptors. Some studies have revealed a decreased amplitude in the full-field electroretinography (FERG) or abnormal photoreceptors thickness on optical coherence tomography (OCT) in LHON patients, indicating abnormal photoreceptors function or structure[8-11]. Notwithstanding, these studies did not deeply address the characteristics and mechanisms of photoreceptors dysfunction and abnormal morphology.

In this study, we analyzed the FERG and OCT manifestations of LHON-affected patients and asymptomatic carriers to explore the characteristics of photoreceptors impairment.

SUBJECTS AND METHODS

**Ethical Approval** This study was approved by the Clinical Research Ethics Committee of the Renmin Hospital of Wuhan University (No.WDRY2021-K018) and followed the tenets of the Declaration of Helsinki. All participants provided written informed consent.
were performed using built-in software. The thicknesses of the analyses of the peripapillary retinal nerve fiber layer (pRNFL) >20 were retained. Automated segmentation and thickness automatic tracking function was adopted, the images were imaged by a 3.4 mm diameter circular scan. A real-time function was imaged by a horizontal B-scan through the fovea, and the optic disc were imaged by Spectralis HRA-OCT (Heidelberg Engineering, Heidelberg, Germany). The macula was imaged optical coherence tomography (OCT) recording equipment (GT-2008V-IV, Chungking, China) according to the standard protocol of the International Society for Clinical Electrophysiology of Vision [12]. The results of the FERG were recorded, followed by the photopic negative response (PhNR), defined as the first negative wave induced in response to dark-adapted 0.01 electroretinography, dark-adapted 3.0 electroretinography, light-adapted 3.0 electroretinography and light-adapted 30 Hz flicker electroretinography were recorded, followed by the photopic negative response (PhNR), defined as the first negative wave after the b-wave [13]. The a-wave and PhNR amplitudes were recorded from the trough to the baseline. The reference value was determined according to the normal value obtained by the Laboratory. Full-Field Electroretinography Recording FERG was recorded using the GOTEC visual electrophysiology instrument (GT-2008V-IV, Chungking, China) according to the standard protocol of the International Society for Clinical Electrophysiology of Vision [12]. The data were expressed as the mean ± standard deviation (SD). t-test was used for group comparisons, and pairwise comparisons were performed with the least significant difference test. P<0.05 was considered statistically significant. RESULTS Demographic Data Demographic data are shown in Table 1. A total of 14 LHON-affected patients (11 males; mean age: 20.00±9.37y; mean BCVA: 1.81±0.56 logMAR; mean disease duration: 26.71±21.34mo), 12 asymptomatic carriers (12 females; mean age: 39.83±6.48y), and 15 normal subjects (12 males; mean age: 24.20±1.52y) were included in the study. There was no statistically significant difference in age and gender between patients and normal subjects (P>0.05). Due to the fact that most of the family members accompanying LHON patients to our hospital are their mothers, the majority of carriers included in this study are middle-aged women. Full-Field Electroretinography The FERG results of the affected patients and asymptomatic carriers are shown in Table 2. Except for PhNR amplitude reduction, the amplitudes of the dark-adapted 3.0 a-wave and light-adapted 3.0 a-wave of patients were both significantly decreased (P<0.001). In addition, the amplitudes of the dark-adapted 3.0 a-wave and light-adapted 3.0 a-wave of carriers were also slightly decreased (P<0.001). However, the amplitudes of the dark-adapted 0.01 a-wave and light-adapted 30 Hz flicker electroretinography of patients and carriers were not significantly decreased (P>0.05).
Macular Optical Coherence Tomography  The ONL, IS/OS and total photoreceptors thicknesses of the macular fovea, nasal parafovea and temporal parafovea in patients, carriers and controls are shown in Table 3 and Figure 1. Compared with controls, the ONL and photoreceptors thicknesses of the macular fovea in patients was increased slightly ($P<0.05$). There were no differences between affected patients and normal subjects regarding the thickness of the IS/OS in the fovea or the photoreceptors in the parafovea ($P>0.05$). The thicknesses of the ONL, IS/OS and photoreceptors of the fovea in asymptomatic carriers were not significantly altered ($P>0.05$). The ONL and photoreceptors layers of the parafovea in asymptomatic carriers were slightly thinner than those in the controls ($P<0.05$), whereas no significant differences were detected in IS/OS thicknesses ($P>0.05$).

Optic Disc Optical Coherence Tomography  The pRNFL thicknesses of affected patients, asymptomatic carriers and controls are shown in Table 4 and Figure 2. The nasal, superior, temporal, inferior and average quadrant pRNFL thicknesses were significantly decreased in the patients compared with those of asymptomatic carriers and controls ($P<0.001$). None of the quadrant pRNFL thicknesses were significantly different in carriers compared to controls ($P>0.05$).

DISCUSSION  In this study, FERG and OCT were used to evaluate the function and structure of photoreceptors in LHON-affected patients and asymptomatic carriers with the m.11778G>A mutation. Previous studies have shown that LHON usually causes RGC dysfunction, leading to amplitude reduction or prolonged latency of pattern electroretinography, visual evoked potential and PhNR. However, FERG results are usually normal\cite{4,6,14-16}. Some studies have revealed sporadic...
et al. [8] found that among 34 LHON patients, 3 demonstrated a decreased b-wave amplitude. Salomão et al. [9] reported that the thicknesses of the outer layers of the retina, such as the IS, OS and retinal pigment epithelium, was not significantly altered in 16 LHON patients. Nevertheless, Lam et al. [10] found that the thickness of the OS in such patients increased significantly, while the thickness of the ONL+IS did not significantly change. They speculated that the cause of OS thickening in LHON patients might be a compensatory morphological reaction caused by optic atrophy rather than photoreceptors dysfunction.

Although there are few studies on photoreceptors in LHON patients, similar results have been found in other glaucoma-related studies. Many studies have demonstrated that the ONL at the fovea in glaucoma patients is significantly thickened, while the IS/OS thickness at the fovea and the photoreceptors thickness at the parafovea are not significantly different. Histopathology confirmed swelling of the cones. It was speculated that the change in cones resulted from the degeneration of RGCs and necrosis of RGCs, we speculate that the causes of ONL thickening in the fovea of LHON patients are similar to those in glaucoma. Further prospective studies are needed to explore the causes of photoreceptors morphological abnormalities. Studies have shown that most RGCs are only connected to cones, and cone density is highest in the fovea. Therefore, this study mainly observed the abnormal function and structure of cones in LHON patients. In addition, this study found that the thickness of the ONL in the parafovea of asymptomatic carriers was decreased, but the specific mechanism is unclear. Larger sample size studies are required in the future to further investigate the mechanisms underlying ONL thinning.

This study has some limitations. First, the sample size of this study is small, which limits the universality of the conclusions. Second, we manually measured the thickness of the ONL and IS/OS in the macular region, which may have resulted in errors. In conclusion, this study evaluated photoreceptors function...
and structure in LHON-affected patients and asymptomatic carriers using FERG and OCT. The dark-adapted 3.0 electroretinography and light-adapted 3.0 electroretinography a-wave amplitudes were decreased, and thickening of the ONL was observed in the fovea of LHON patients. This result suggests abnormalities in the function and structure of photoreceptors, especially cones. Meanwhile, asymptomatic carriers also showed a slight decrease in the amplitude of the a-wave, indicating subclinical dysfunction. The results of this study show that photoreceptors are affected in LHON to some extent in addition to RGCs. Future prospective studies are required to further explore the mechanisms underlying photoreceptors impairment in LHON-affected patients and asymptomatic carriers.

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