CASE REPORTS

Increased Microcirculation on Optic Nerve Head by Laser Speckle Flowgraphy at Early Stage of Leber Hereditary Optic Neuropathy

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ABSTRACT

Leber hereditary optic neuropathy (LHON) is a mitochondrial disorder predominantly affecting young men. Characteristic features of an early stage of LHON are peripapillary telangiectatic microangiopathy with optic disc hyperaemia and swelling of the retinal nerve fibre layers. We evaluated the microcirculation of the optic nerve head (ONH) by laser speckle flowgraphy (LSFG) in a 79-year-old man and a 36-year-old woman with LHON. The ONH microcirculation of the tissue area was markedly increased in the early stage in both patients. LSFG may be a useful noninvasive method to suspect individuals to have an early stage of LHON.

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Introduction

Leber hereditary optic neuropathy (LHON) is a mitochondrial (mt) disease characterized by subacute, painless reduction of central vision bilaterally.¹ Atrophy of the temporal optic disc begins to be manifested within a few months after the vision reduction, and the optic disc appears pale and the vision is severely reduced within a year. More than 90% of the patients with LHON carry one of three mutations at nucleotide positions 3460 (np3460G > A), 11778 (np11778G > A), and 14484 (np14484T > C) of the mtDNA.¹ The majority of patients are young men in their first to third decade of life at the onset. Clinically, it is difficult to diagnose LHON with a late onset because the patients have minimal or an absence of the typical findings in the optic nerve head (ONH) and retina, such as hyperaemic disc, peripapillary telangiectatic microangiopathy, and swelling of the retinal nerve fibre layer (RNFL).^{2–5} And, the diagnosis of LHON in women is sometimes delayed because of the low incidence.

Recently, optical coherence tomography (OCT) has been used to diagnose LHON by examining the thickness of the circumpapillary retinal nerve

fibre layer (cpRNFL)⁶ and the macular ganglion cell-inner plexiform layer (GCIPL)⁷ at an early stage of LHON. The presence of characteristic OCT findings will allow physicians to justify performing mtDNA analysis for individuals with unknown gradual visual reduction with a central scotoma bilaterally.⁷

Hyperaemic disc and peripapillary telangiectatic microangiopathy are characteristic features in an early stage of LHON.¹ Recent advancements of laser speckle flowgraphy (LSFG) have enabled clinicians to monitor and measure the relative blood flow on the ONH. The output of the LSFG instrument is the mean blur rate (MBR) which represents the relative blood flow rate of the vessels of interest.^{8,9} The MBR can be determined for the total area of the ONH (MA: MBR of total area), the vessel region of the ONH (MV: MBR of vascular area), and the tissue region of the ONH (MT: MBR of tissue area). The MV represents the large vessels on the ONH area, while the MT represents the microvasculature on the ONH.¹⁰ The values of the MBRs have been reported for eyes with glaucoma,¹¹ autosomal dominant optic neuropathy,¹² acute non-arteritic ischaemic optic neuropathy,¹³ and

anterior optic neuritis,¹³ with characteristic findings for each disease.

We report our findings in two patients with LHON; a 79-year-old man with the 11778G > A mutation and a 36-year-old woman with the 3460 G > A mutation. The ocular blood flow on the ONH was determined by LSFG at an early stage of LHON in both patients. Our LSFG findings showed an increase in microcirculation on the tissue area of ONH in both patients. This could represent the telangiectatic microangiopathy of the ONH, which is one of the characteristics of LHON at an early stage.

Patients

Case 1

A 79-year-old man noticed a painless gradual decrease in the vision of his right eye beginning in April 2015. This was followed 1 month later by

a decrease in vision in the left eye. He was referred to Kyorin University Hospital from a local eye clinic with unknown bilateral optic neuropathy in June 2015. He was a mild smoker from age 60 to 75 and mild alcohol drinking since age of 20 years. He did not have any family history of serious eye disease. His decimal best-corrected visual acuity (BCVA) was 0.04 in the right eye and 0.2 in the left eye. The intraocular pressure (IOP) was 11 mmHg in the right eye and 9 mmHg in the left eye. A relative afferent pupillary defect (RAPD) was present in the right eye. He had no pain on eye movements. The critical flicker frequency (CFF) was <20 Hz in the right eye and 25 Hz in the left eye. Ophthalmoscopy demonstrated a tigroid fundus which was more apparent in the right eye and no vascular abnormalities in both eyes.

The ONH had a slight temporal pallor in the right eye (Figure 1A) and slight redness in the left eye (Figure 1B). Fluorescein angiography was not

Figure 1. Colour fundus photographs and Laser speckle flowgraphy (LSFG) colour map of the optic nerve head (ONH) in case 1. Fundus photographs show that the optic nerve head has a mild temporal pallor in the right eye (A) and mild redness in the left eye (B) on June 2015. The fundus appears tigroid in both eyes. A colour map of the LSFG image of the ONH is reddish with a slight yellow mottling in the temporal area indicating an increase in the mean blur rate of the tissue area (MT) of the ONH in the right eye (C). The ONH is entirely red in the left eye indicating an increase in the MT at an early stage of LHON (D).

performed because of his advanced age. Goldmann perimetry (GP) showed a central to superotemporal defect in the right eye and a cecocentral scotoma in the left eye. Contrast-enhanced magnetic resonance images (MRI) of the orbits and brain were normal. Routine blood tests were negative. Various auto-antibodies for autoimmune diseases including anti-aquaporin (AQP)-4 antibody ≤ 1.3 U/ml were all within the normal range.

OCT (Zeiss Cirrus, Carl Zeiss Meditec, Dublin, CA, USA) was performed in June 2015, and the results showed a decrease in the cpRNFL thickness in the inferior quadrant of the right eye and an increase in the cpRNFL thickness of the inferior quadrant of the left eye from the normal range. OCT also demonstrated a decrease of the GCIPL thickness in the superotemporal sector and a slight decrease in the inferonasal sector of the right eye, and normal thickness of the GCIPL in the left eye. The OCT findings suggested that his pathological eye conditions were that of LHON and not bilateral optic neuritis or ischaemic optic neuropathy. Then, mitochondrial genetic testing was performed and showed a 11778G>A mutation.

The ocular blood flow on the ONH was measured by LSFG (LFSG-NAVI, Softcare, Fukuoka, Japan) in June 2015. Three parameters of the overall MBR (MA), vessel-area MBR (MV), and tissue-area MBR (MT) are shown in Table 1. The LSFG values of ONH indicated a nearly double increase in the MT values in both eyes at 21.8 arbitrary units (AU) in the right eye and 26.1 AU in the left eye compared to 13.5 ± 2.0 AU in 189 normal eyes of 189 Japanese individuals or 13.9 ± 1.5 AU in 27 eyes of normal individuals ≥ 60 years.¹⁴ On the other hand, the MV values are within normal limits of 43.9 AU in the right eye and 47.4 AU in the left eye compared to 51.8 ± 6.8 AU in 189

normal eyes of 189 Japanese individuals or 48.7 ± 4.2 AU in 27 eyes of normal individuals ≥ 60 years.¹⁴ The colour images of the ONH appeared reddish with a slightly mottled yellowish pattern in the temporal area in the right eye (Figure 1C) and entirely reddish in the left eye (Figure 1D).

In December 2016, his BCVA was 0.01 in the right eye and hand motion in the left eye. The ONH appeared totally pale in both eyes. The MA, MV, and MT values were decreased in both eyes (Table 1).

Case 2

A 36-year-old woman was presented with a 3-week history of a painless gradual decline of the vision in her right eye. She was referred in Tokyo Medical University Hachioji Medical Center from a local eye clinic as a suspect of right optic neuritis in December 2015. She did not smoke or drink alcohol. Her maternal uncle had visual disturbances from his youth. Her decimal BCVA was 0.3 in the right eye and 1.5 in the left eye, and the IOP was 15 mmHg in each eye. The RAPD test was mildly positive in the right eye. She had no pain with eye movements. The CFF was 31 Hz in the right eye and 38 Hz in the left eye. Ophthalmoscopy demonstrated mild optic disc hyperaemia with inferotemporal retinal nerve fibre layer swelling and telangiectatic changes in the right eye (Figure 2A). The left eye appeared normal (Figure 2B). FA revealed a slight staining of the ONH with peripapillary telangiectatic microangiopathy without leakage in the right eye and no abnormal findings in the left eye. GP showed a paracentral scotoma in the right eye and normal in the left eye. Routine blood tests

Table 1. MBR values of entire ONH in Case 1 and Case 2.

	MA (AU)		MV (AU)		MT (AU)		IOP (mmHg)		BP (mmHg)		OPP (mmHg)	
	RE	LE	RE	LE	RE	LE	RE	LE	SBP	DBP	RE	LE
Case 1												
In June 2015	30.7	37.2	43.9	47.4	21.8	26.1	11	9	150	78	57	59
In December 2016	15.4	11.0	23.6	19.2	10.4	7.8	12	10	147	72	53	55
Case 2												
In January 2016	29.5	19.7	47.6	34.6	24.4	15.6	12	11	111	80	48	49

MBR: mean blur rate, ONH: optic nerve head, MA: overall mean blur rate, MV: mean blur rate in vascular area, MT: mean blur rate in tissue area, AU: arbitrary unit, RE: right eye, LE: left eye, IOP: intraocular pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure.

The MV values are 51.8 ± 6.8 AU in 189 normal eyes of 189 Japanese individuals.¹⁴ The MT values are 13.5 ± 2.0 AU in 189 normal eyes of 189 Japanese individuals.¹⁴

were within normal limits and the anti-AQP4 antibody was <1.3 U/ml.

Brain CT and MRI showed no abnormal findings. Three days after her initial visit, she received intravenous corticosteroid therapy for 3 days with a tentative diagnosis of optic neuritis. However, her BCVA was unchanged in the right eye, but the visual fields had worsened in the right eye. Her resistance to corticosteroid therapy and a family history suggesting LHON, and genetic mitochondrial testing showed a 3460G>A mutation in January 2016.

The ocular blood flow at the ONH was measured with LSFG 1 month after the initial visit, in January 2016. The LSFG values of MA, MV, and MT are shown in Table 1. The MT value of the ONH was increased nearly at double to 24.4 AU in the right eye and slightly increased to 15.6 AU in the left eye compared to 13.5 ± 2.0 AU in 189 eyes in 189 normal Japanese subjects or 13.2 ± 2.3 AU in 29 eyes of ages 30–39 years.¹⁴ The MV value

was within normal limits of 47.6 AU in the right eye and slightly decreased in 34.6 AU in the left eye compared to 51.8 ± 6.8 AU in 189 normal eyes of 189 Japanese individuals or 52.6 ± 8.4 AU in 29 eyes of ages 30–39 years.¹⁴ The colour images of the ONH appeared red in the right eye (Figure 2C) and slightly yellow in the left eye (Figure 2D).

She visited another eye hospital for a second opinion from a LHON specialist in February 2016, and returned to the Tokyo Medical University Hachioji Medical Center because of a further decrease in the vision in her left eye from that a month earlier in September 2016. Her decimal BCVA was 0.02 in the right eye and 0.5 in the left eye. Ophthalmoscopy showed a mild temporal disc pallor in the right eye and a reddish disc with peripapillary microangiopathy in the left eye. GP showed a central scotoma in both eyes. In March 2017, her BCVAs were 0.02 in the right eye and 0.01 in the left eye, and the optic discs were entirely pallid in both eyes.

Figure 2. Colour fundus photographs and Laser speckle flowgraphy (LSFG) colour map of the optic nerve head (ONH) in case 2. Fundus photographs show mild optic disc hyperaemia with inferotemporal retinal nerve fibre layer swelling and telangiectatic changes in the right affected eye (A) and normal appearance in the left subclinical eye (B) in December 2015. The LSFG images of the ONH is entirely red indicating an increase in the MT in the right affected eye (C) at an early stage of LHON and yellow in the left subclinical LHON eye indicating a slight increase in the MT (D).

Discussion

This is the first study with LSFG to invest the blood flow on the ONH in the patients with an early stage of LHON. LSFG is useful for detecting changes in the ocular blood flow of the microvasculature in the ONH in the same individual because the MBR is a relative value.⁸ The MBR can be affected by the IOP but not by the systolic blood pressure in normal individuals.¹⁴ The MV value is affected by the age and sex of the examinee, while the MT is independent of age or sex.¹⁴ Thus, it should be possible to use the MT values to compare individuals and to make comparisons with the MT values of normal eyes.¹⁴ The software of LSFG also displays the relative blood flow rate in colours maps with gradation based on the MBR values from 0 (black) to 25 (red) in a standard setting. The images are red when the ocular blood velocity is fast or the blood flow is high, i.e., the MBR value is high. The MBR value over 25 also represents red in colours maps. Thus, red colour images of LSFG represent high ocular blood flow that indicates more than 25 MBR values. In contrast, the images appear green to blue when the ocular blood velocity is low or the blood flow is low, i.e., the MBR value is low. The yellow colour between red and green indicates intermediate level of blood flow between the high and low rates.

In Case 1, the right eye was the first to manifest the characteristics changes of LHON followed 1 month later by the left eye. We were able to confirm the different onset times of the two eyes by the fundus photographs, OCT, and LSFG: the MT values increased to 21.8 AU in the right eye and more to 26.1 AU in the left eye. The LSFG colour images of the ONH at the early stage of LHON were red except for yellow mottling in the temporal area of the right eye, and completely red in the left eye. The image of the temporal area of the disc in the right eye indicated a decrease of the vasculature of that area. Although the fundus photographs in an early stage did not show the typical findings in Case 1, LSFG demonstrated an increase in blood flow of microvasculature of the tissue region (MT value) of ONH. In Case 2, the MT values increased to 24.4 AU in the right eye and

slightly increased to 15.6 AU in the left eye. Clinically, Case 2 did not develop LHON in the left eye when the right eye had the characteristics of the disease, showing nearly normal findings of fundus photographs and LSFG of the left eye. Seven months later from January 2016, the left eye developed LHON. The higher MT values on ONH of LSFG in our two patients may represent characteristic feature of an early stage of LHON.

The MBR of the ONH were found to be slightly increased in eyes with anterior optic neuritis¹³ but were reduced in eyes with glaucoma,¹¹ autosomal dominant optic atrophy,¹² and acute non-arteritic ischaemic optic neuropathy.¹³ Higher MBR values with entirely red LSFG images have not been reported so far in other optic neuropathies. The MT represents the ONH microvasculature, while the MV represents the large vessels on the ONH.¹⁰ Therefore, higher MT values in our two patients indicate an increase in blood flow in the microvasculature in the tissue area of the ONH, not in the large vessels. This may be related to the telangiectatic microangiopathy which is a characteristic finding in eyes with an early stage of LHON.

In conclusion, LSFG is a useful method for detecting alterations in the blood flow of the microvasculatures on the ONH in optic neuropathies noninvasively. Our findings indicate that an increase in the MT value is a characteristic finding for an early stage of LHON. In patients with subacute bilateral loss of visions and central scotomas, OCT and OCT angiography^{15,16} are reported to be important noninvasive methods to diagnose suspected LHON patients. In addition, LSFG can be a useful method to examined individuals suspected to have LHON. Further studies with more cases are required to confirm whether the high MT value on the ONH is specific for LHON at an acute stage.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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