

Analysis of Optic Nerve Head Circulation Using Laser Speckle Flowgraphy in a Case of Pediatric Optic Neuritis

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Abstract

Background: To examine the long time course of optic nerve head (ONH) blood flow in a case of pediatric anterior optic neuritis (ON) using laser speckle flowgraphy (LSFG) and optical coherence tomography (OCT).

Case presentation: A 7-year-old Japanese girl presented with a complaint of blurred vision in the right eye, which had a visual acuity of 20 cm/hand motion. The findings of Goldmann visual field test and fundus examination revealed central scotoma and optic disc edema in the right eye, respectively. The results of LSFG demonstrated that the mean blur rate (MBR)-which indicates blood flow-of ONH tissues (MT) was greater in the affected eye (18.8) than in the fellow eye (13.4). In contrast, there was no difference in MBR of arterioles between the two eyes. Vascular cloud (VC)-a parameter measured by the LSFG analysis software and which demonstrates the clarity of the network of vessels in the ONH-in the affected eye (0.26) was lower than that in the fellow eye (0.34), because the run of vessels in the former was unclear owing to inflammation. According to OCT findings, the circumpapillary retinal nerve fiber layer thickness (cpRNFLT) of the affected eye (150 μm) was greater than that of the fellow eye (104 μm). The patient was diagnosed with anterior ON and started on steroid treatment. A week after treatment, the decimal BCVA had recovered to 1.5, and the MT tended to decrease (12.8) with decrease in cpRNFLT (111 μm) in the affected eye. The value of VC gradually increased (0.34) with increase in the clarity of network of vessels in the ONH. Four years after treatment, while there was no difference in MT between the affected (11.0) and fellow (11.1) eyes, the cpRNFLT of the affected eye (78 μm) was lower than that of the fellow eye (106 μm).

Conclusions: This report demonstrates the long-term course of ocular circulation and cpRNFLT in a case of pediatric anterior ON before and after treatment for the first time. Both MT and VC might be useful and effective quantitative indicators of therapeutic efficiency in pediatric anterior ON.

Keywords: *Optic Neuritis; Pediatric; Blood Flow; Optic Nerve; Laser Speckle Flowgraphy; Ocular Circulation*

Abbreviations

BCVA: Best-Corrected Visual Acuity; CFF: Critical Flicker Frequency; cpRNFLT: Circumpapillary Retinal Nerve Fiber Layer Thickness; DBP: Diastolic Blood Pressure; IOP: Intraocular Pressure; IV: Intravenous Drip; LDF: Laser Doppler Flowmetry; LSFG: Laser Speckle Flowgraphy; MBP: Mean Blood Pressure; MBR: Mean Blur Rate; MRI: Magnetic Resonance Imaging; MT: Mean Blur Rate of ONH Tissues; MV: Mean Blur Rate of ONH Vessels; OCT: Optical Coherence Tomography; ON: Optic Neuritis; ONH: Optic Nerve Head; OPP: Ocular Perfusion Pressure; RAPD: Relative Afferent Pupillary Defect; SBP: Systolic Blood Pressure; VC: Vascular Cloud

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Introduction

Optic neuritis (ON) is caused by inflammation of the optic nerve head (ONH); anterior ON is clinically manifested as optic disc swelling [1]. In general, ON is a frequent symptom of acquired demyelinating syndromes in childhood. Pediatric ON has different clinical characteristics relative to adult ON [2]. Clinical characteristics of ON in children include bilateral manifestation, good response to steroid treatment, and occurrence after viral infection (e.g. mumps and measles) [2,3].

Definite diagnosis of ON requires several examinations, including the visual field test and magnetic resonance imaging (MRI). Previously, Maekubo, *et al.* [4] had reported that laser speckle flowgraphy (LSFG, Softcare Co., Ltd., Fukuoka, Japan) could be useful for differentiating between anterior ON in adults and non-arteritic ischemic optic neuropathy. This technique is dependent on the movement of erythrocytes [5] and is useful for investigating blood flow in the ONH [6-9], retinal vessels [10-12] and choroid [13-17]. It also allows measurement of mean blur rate (MBR), an indicator of blood flow [18]. Measurement of ONH blood flow by LSFG has favorable reproducibility [18] and only requires approximately 4 seconds in sitting position.

The LSFG analysis software (Ver. 3.1.79.0, Softcare Co., Ltd.) can calculate several parameters from the MBR of the ONH. It can also distinguish vessels and tissues by means of an automated definitive threshold and analyze the MBRs of ONH vessels (MV - MBR corresponding to retinal arterioles) and tissues (MT - MBR corresponding to capillary vessels). Values of MT obtained by LSFG have been verified by direct comparison with those obtained by the microsphere [19] and hydrogen gas clearance [20,21] methods. Furthermore, the LSFG analysis software can also demonstrate vascular clouds (VC), which indicate the clarity of the network of vessels in the ONH (i.e. the greater the clarity of ONH vessels, the greater the value of VC; Figure 1).

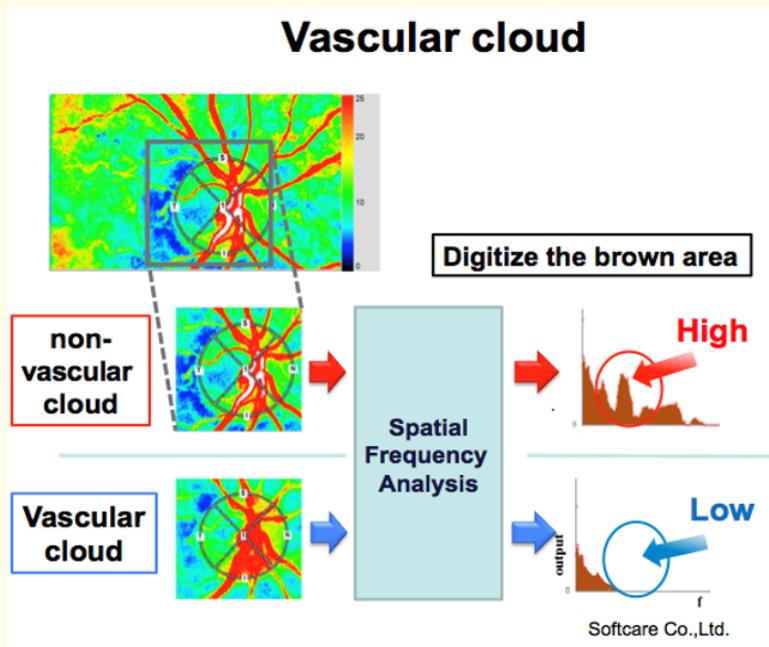


Figure 1: Analysis of vascular cloud (VC) measured using a laser speckle flowgraphy (LSFG) analysis software. An indicator of the clarity of the network of vessels in the optic nerve head (ONH), VC was analyzed using the LSFG analysis software (Softcare Co. Ltd.). After spatial frequency analysis, this software digitizes the brown area and reports the value of the VC. The value of VC is lower in case of non-clouded vessels (i.e. clear vessels in the ONH) and higher in case of clouded vessels.

To the best of our knowledge, no study to date has investigated ONH blood flow in pediatric ON. It is important to assess the effect of ON treatment in children by non-invasive methods. In the present case report, we have used LSFG to demonstrate the 4-year time course of pediatric anterior ON before and after treatment.

Case Presentation

A 7-year-old Japanese girl presented with a complaint of blurred vision in the right eye one week before her first visit. Before the worsening of visual acuity, the patient had fever. She visited the department of ophthalmology at a local hospital and was suspected to have optic disc edema. She was referred to Toho University Sakura Medical Center, Sakura city, Japan (hereinafter referred to as “our hospital”), for detailed examination for optic disc edema in the right eye. She had no history of abnormal birth, allergy, or medical or familial conditions. At her initial visit to our hospital, the visual acuity of the right and decimal best-corrected visual acuities (BCVAs) left eyes were 20 cm/hand motion and 1.5, respectively. The right and left intraocular pressure (IOP) values were 18 and 19 mmHg, respectively. The affected and fellow eyes both exhibited a refractive error of +0.5 diopters (D), which was measured using an auto-refractometer (Kowa Co., Ltd., Tokyo, Japan).

The findings of slit-lamp examination revealed no abnormalities in the cornea, lens, or retina. The right eye exhibited moderate mydriasis of the pupil, attenuated direct light reflex, and a positive relative afferent pupillary defect (RAPD). Fundus examination findings showed slight optic disc edema and unclear margins of the ONH in the right eye (Figure 2a). There were no abnormal findings in the ONH in the left eye (Figure 2b). Figure 2 shows the LSFG color map images of the right and left eyes; the fundus image of the ONH of the right eye (Figure 2c) exhibited warmer colors than that of the fellow eye (Figure 2d). The values of MV/MT obtained using the LSFG analysis software were 44.3/18.8 and 45.6/13.4 in the affected and fellow eyes, respectively. The VC value of the affected eye (0.26) was lower than that of the fellow eye (0.34). Blood flow in the ONH has been reported to be associated with change in ocular perfusion pressure (OPP) [22]. Therefore, in order to investigate changes in OPP, the patient was evaluated for intraocular pressure (IOP) and systolic and diastolic blood pressure (SBP and DBP, respectively) at each measurement point; these values were then used for calculating mean blood pressure (MBP) and OPP. First, MBP was calculated using the following equation: $MBP = 1/3 \cdot (SBP - DBP) + DBP$. Then, OPP was calculated as the weighted difference between MBP and IOP using the following equation: $OPP = 2/3 \cdot MBP - IOP$. At initial visit, SBP/DBP were 105/52 mmHg. The difference in OPP between the affected (28.4 mmHg) and fellow (27.4 mmHg) eyes at initial visit was not significant.

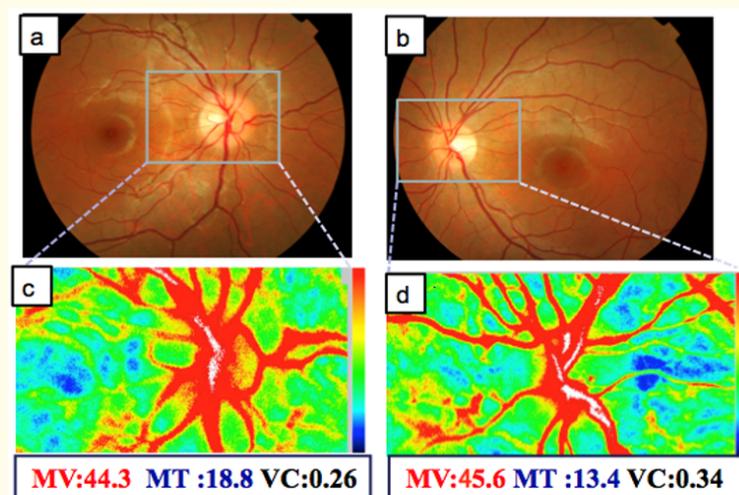


Figure 2: Fundus photography and laser speckle flowgraphy (LSFG) images acquired at the initial visit. Fundus examination findings showed slight optic disc edema and unclear margins of the optic nerve head (ONH) in the right eye (a). There were no abnormal findings in the ONH in the left eye (b). Color maps of the right (c) and left (d) eyes acquired by LSFG at the initial visit show the mean blur rates of arterioles (MV) and ONH tissues (MT) as well as vascular cloud (VC) values in the right (44.3, 18.8, and 0.26, respectively) and left (45.6, 13.4, and 0.34, respectively) eyes.

Circumpapillary retinal nerve fiber layer thickness (cpRNFLT) was determined by optical coherence tomography (OCT; Spectralis® OCT; Heidelberg Engineering Inc., Heidelberg, Germany). The cpRNFLT of the right eye (150 μm ; Figure 3a) was greater than that of the fellow eye (104 μm ; Figure 3b). Goldmann visual field test findings revealed central scotoma (Figure 3c) in the right eye; the critical flicker frequency (CFF) of the right eye remained unmeasured because it was below the threshold. Orbital T2-weighted MR images showed a high-intensity signal in the right optic nerve (Figure 3d). Fluorescein angiography results indicated early hyper-fluorescence leakage in the affected eye (Figure 3e); however, there was no fluorescein leakage or blockade in the fellow eye (Figure 3f).

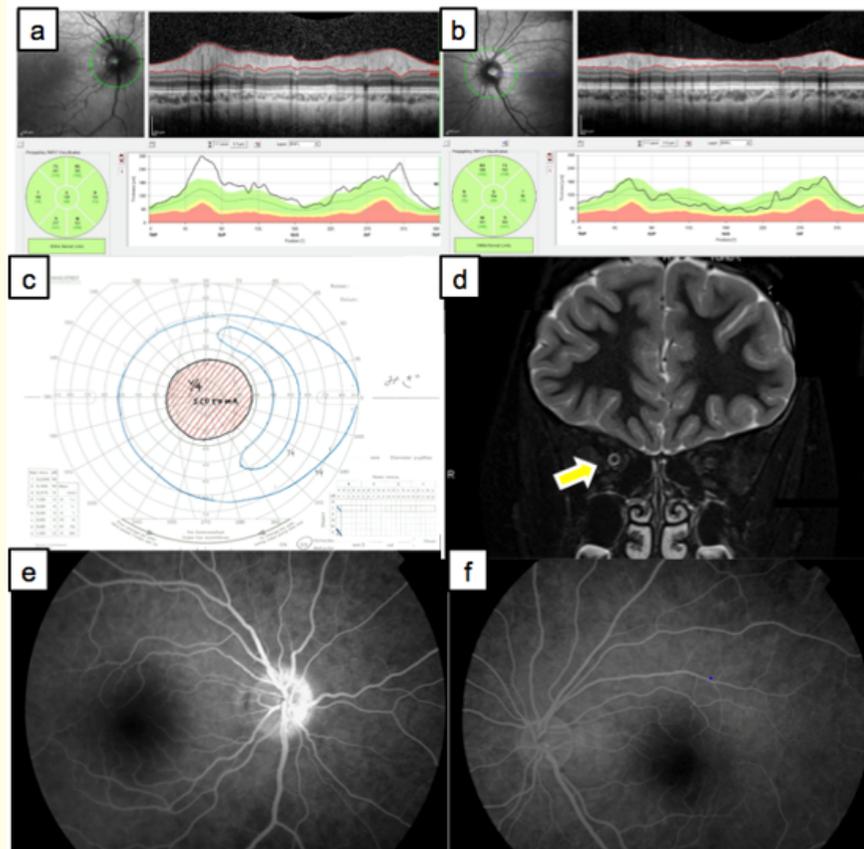


Figure 3: Findings of ophthalmological examination at the initial visit. Optical coherence tomography (OCT), Goldmann visual field test, magnetic resonance imaging (MRI), and fluorescein angiography findings of the affected eye at the initial visit are shown. Circumpapillary retinal nerve fiber layer thickness (cpRNFLT) was determined by OCT (Spectralis® OCT). The cpRNFLT of the right (affected) eye (150 μm , a) was greater than that of the left eye (104 μm , b). Goldmann visual field test findings revealed central scotoma (c) in the right eye, which remained unmeasured because its critical flicker frequency was below the threshold. Orbital T2-weighted MR images showed a high-intensity signal in the right optic nerve (d). Fluorescein angiography findings demonstrated early hyper-fluorescence leakage in the right eye (e); however, there was no fluorescein leakage or blockade in the left eye (f).

On the basis of these clinical findings, the patient was diagnosed with pediatric anterior ON, and treatment was commenced. Recovery after intravenous (IV) steroid administration has been reported to be more rapid than that after placebo or oral steroid administration in the first 15 days after onset [2]. Therefore, in the present case, the patient was hospitalized and treated by intravenous (IV) injection of 900 mg methylprednisolone (30 mg/kg) for 3 days. Following this high-dose methylprednisolone treatment, the patient was placed on oral prednisolone treatment (25 mg/day), the dosage of which was decreased gradually. A week after treatment, the decimal BCVA of the affected eye had rapidly improved to 1.5, and the optic disc edema had also improved. A month after treatment, Goldmann visual field test findings revealed that the central scotoma had disappeared (Figure 4a), and value of flicker in the affected eye now showed a value of 38. The cpRNFLT of the right eye had decreased to 103 μm (Figure 4b). The findings of MRI (Figure 4c) and fluorescein angiography (Figure 4d) revealed high-intensity signal or no leakage in the optic nerve.

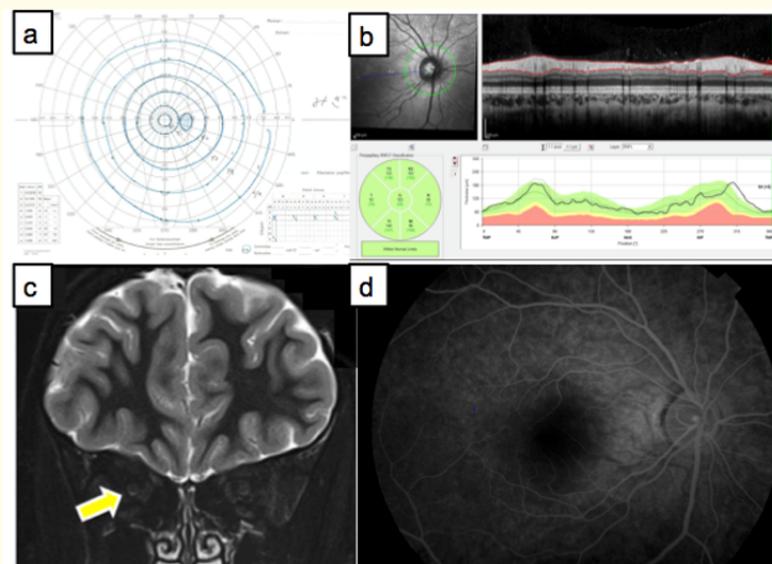


Figure 4: Findings of ophthalmological examination at 1 month after treatment. Goldmann visual field test, optical coherence tomography (OCT), magnetic resonance imaging (MRI), and fluorescein angiography findings of the affected eye at the 1-month follow-up are shown. Goldmann visual field test findings revealed that the central scotoma in the affected eye had disappeared (a). According to OCT findings, the circumpapillary retinal nerve fiber layer thickness had reduced (103 μm) relative to the value at the initial visit. The results of (b) MRI and (c) fluorescein angiography (d) revealed the absence of high-intensity signal or leakage in the optic nerve.

Figure 5 shows the time course of changes in fundus photography and LSFSG findings-including ONH blood flow, MV, MT, and VC-in the affected eye. Although the value of MV in the affected eye had not changed significantly after treatment, the MT value had rapidly decreased by a week after treatment, and the VC value tended to increase with improvement in optic disc edema (i.e. with increase in sharpness of the OHN margin). A year after treatment, the MT value had gradually decreased to approximately 10.8, and the VC value had increased to approximately 0.39. At 4 years after treatment, there was no substantial difference in MT and VC values between the affected (11.0 and 0.41, respectively) and fellow (11.1 and 0.4, respectively).

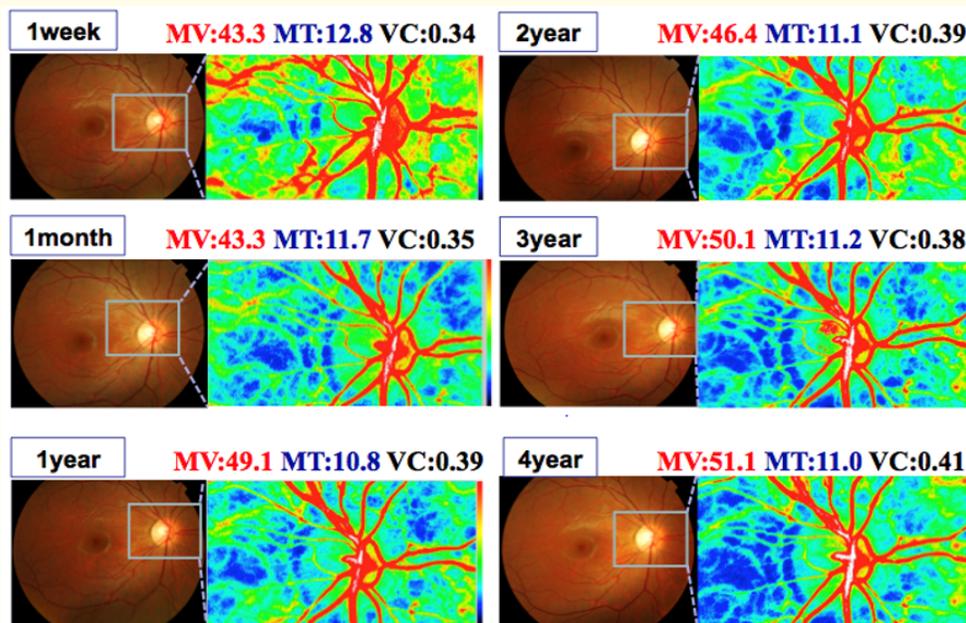


Figure 5: Time course of changes in ophthalmological findings in the eye with anterior optic neuritis. Fundus images and laser speckle flowgraphy color maps of the right eye at 1 week, 1 month, and 1, 2, 3, and 4 years after the initial visit are shown. The optic disc edema had almost resolved by a week after treatment. The mean blur rates of arterioles (MV) and optic nerve head tissues (MT) and the vascular cloud (VC) values are shown.

Figure 6 shows the time course of changes in cpRNFLT. The cpRNFLT of the affected eye decreased gradually with treatment, and there was no bilateral difference in cpRNFLT (affected and fellow eyes, 103 and 104 μm , respectively) a month after treatment. The cpRNFLT of the affected eye continued to decrease. At 4 years after treatment, the cpRNFLT of the affected eye (78 μm) was lower than that of the fellow eye (106 μm). The OPP of the affected eye remained unaltered over the duration of follow-up.

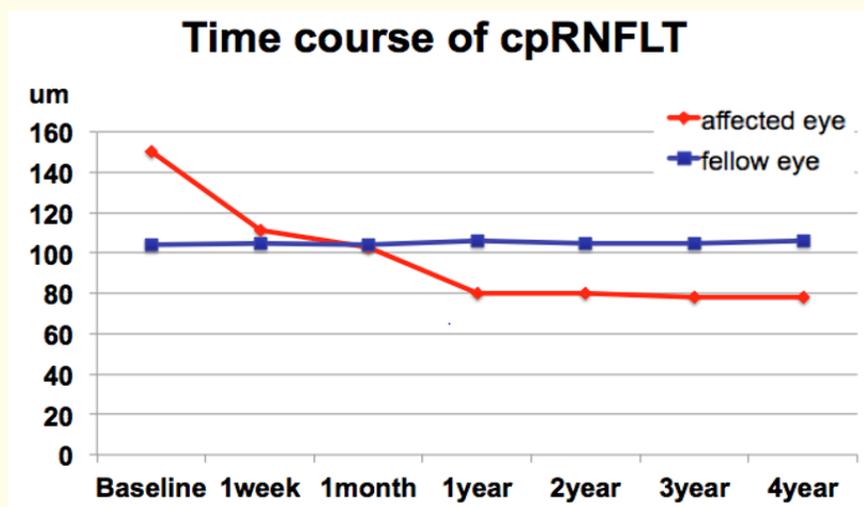


Figure 6: Time course of changes in circumpapillary retinal nerve fiber layer thickness (cpRNFLT). The time course of changes in cpRNFLT over the 4-year follow-up period is shown. The cpRNFLT values in the right and left eyes at the initial visit were 150 and 104 μm , respectively; the corresponding values at 1 week, 1 month, and 1, 2, 3, and 4 years after the initial visit were 111 and 105; 103 and 104; and 80 and 106; 80 and 105; 78 and 105; and 78 and 106 μm , respectively.

Discussion

This report has demonstrated the long-term course of ONH blood flow in a case of pediatric anterior ON for the first time. In the present case, before treatment, the affected eye exhibited greater blood flow in ONH tissues than did the fellow eye; this increased blood flow gradually reduced and normalized after steroid treatment. Furthermore, the value of VC-obtained using the LSFG analysis software-gradually increased with a rise in sharpness of the ONH margin.

Regarding ocular circulation in eyes with ON, a previous study involving LSFG analysis of adult acute anterior ON reported that the MBR in the ONH of affected eyes was significantly higher than that of fellow eyes [4]. These results are in agreement with the present findings. In the present case, the LSFG analysis software was used to distinguish arterioles (for calculating MV) and capillary vessels (for calculating MT) in the ONH. Although there was no substantial difference in MV between the affected and fellow eyes, the value of MT in the affected eye was substantially higher than that in the fellow eye. Taking into account these clinical findings as well as the fact that MT indicates blood flow in microvessels or branches of short posterior arteries or the ring of Zinn-Haller in the lamina cribrosa [23,24], we believe that capillary blood flow to the lamina cribrosa in eyes with pediatric anterior ON might be increased mainly because of hyper-permeability due to inflammation.

In the present case, blood flow in ONH tissues decreased gradually after treatment with high doses of glucocorticosteroids. At 4 years after treatment, there was no difference in MT between the affected and fellow eyes. Glucocorticoids have been reported to play a role in constricting and regulating microcirculation [25]. These findings together suggest that capillary vessels dilated because of inflammation can be constricted and normalized by steroid treatment. However, a previous study involving laser Doppler flowmetry (LDF) analysis reported that high-dose prednisolone treatment of adult anterior ON might only cause a small increase in ONH blood flow [26]. This discrepancy in findings between the present and previous studies might have resulted from differences in wavelength between LSFG and LDF. The wavelength of the laser diode used for LSFG (830 nm) [20] is longer than that used for LDF (670 nm) [26] and the value of superficial ocular blood flow (i.e. blood flow in ONH arterioles) determined by LDF is greater than that determined by LSFG. Considering these findings, we hypothesize that, in eyes with pediatric anterior ON, steroids would have a greater effect on microvessels dilated because of inflammation than on arterioles. Nevertheless, steroid treatment has some effect on blood flow in arterioles (i.e. MV) in eyes with anterior ON, although the exact mechanism is unknown.

In contrast to the value of MT, the value of VC tended to increase with elevation in the clarity of the vessels in the ONH after treatment in this case; there was no bilateral difference in VC at 4 years after treatment. These clinical findings indicate that VC might be a good quantitative indicator for assessment of treatment effects in eyes with acute anterior ON. Further studies with more cases will be needed to elucidate whether VC is useful indicator for assessment of therapeutic effect in patients with anterior ON in adult or children.

In the present case, the cpRNFLT of the affected eye decreased gradually over the 4-year follow-up period, even after improvement of visual acuity. It has been reported that RNFL represents the most proximal region of the afferent visual pathway, and changes in RNFLT represent changes in optic nerve axonal integrity because of absence of myelin [27]. In a study by Costello, *et al.* [27] RNFL thinning was observed in the majority of adult patients with ON, and it tended to occur within 6 months of onset of ON. In another investigation, RNFL thinning in eyes with ON was found to persist for over 2 years [28]. In the present case, within a month post-treatment, the cpRNFLT in the affected eye had become thinner than that in the fellow eye. This finding is consistent with those of previous studies. In addition, a novel finding in the present case was that, despite recovery of visual acuity, the RNFL thinning continued till 4 years after treatment. It is not yet clear whether there is an association between loss of RNFL and decrease in blood flow in ONH tissues in eyes with pediatric ON. Further studies with more cases and other disease are needed to evaluate the possibility that LSFG could be useful not only for the assessing the treatment effects but also for helping in the differential diagnosis of inflammatory and non-inflammatory pathologies affecting the optic nerve head such as optic neuritis and papilledema caused by an elevation of the intracranial pressure.

Conclusions

This report is the first to demonstrate the time course of ONH blood flow in pediatric anterior ON. Non-invasive methods such as LSFSG might be useful for assessing the treatment effects of ON in children over a long-term follow-up period.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Written informed consent was obtained from the patients' parent for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Availability of Data and Materials

All data generated or analyzed during the present study are included in this published article.

Competing Interests

The authors declare that they have no competing interests.

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