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Case Report

Optic Nerve Head Microcirculation in Eyes with Vogt-Koyanagi-Harada Disease Accompanied by Anterior Ischemic Optic Neuropathy

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Keywords
Anterior ischemic optic neuropathy · Laser speckle flowgraphy · Optical coherence tomography · Optic nerve head microcirculation · Vogt-Koyanagi-Harada disease

Abstract
Anterior ischemic optic neuropathy (AION) is infrequently complicated with Vogt-Koyanagi-Harada (VKH) disease. We quantitatively examined sequential changes in the morphology and circulation hemodynamics, using a C-scan of optical coherence tomography (OCT) and laser speckle flowgraphy (LSFG) in a patient with VKH disease accompanied by AION. A 65-year-old female complained of blurred vision in both of her eyes. The patient presented with optic disc swelling and remarkable choroidal thickening detected by OCT bilaterally. The diagnosis of VKH disease was established based on the presence of pleocytosis detected in the cerebrospinal fluid and hypofluorescent dark dots scattered all around the fundus, detected by indocyanine green angiography. Goldmann perimetry detected visual field defects, similar to superior altitudinal hemianopsia in the right eye and similar to inferior altitudinal hemianopsia in the left eye. The patient was suspected to have developed AION in both eyes. The patient received methylprednisolone pulse therapy, followed by oral prednisolone. With these treatments, the optic disc swelling disappeared. However, optic disc atrophy with visual field defects remained in both eyes. An OCT C-scan showed the ganglion cell complex (GCC) and circumpapillary retinal nerve fiber layer (cpRNFL) thickness getting thinner below the normal range, and LSFG showed the decrease in optic nerve head (ONH) tissue microcirculation. These results supported the occurrence of AION in this patient with VKH disease. The analysis

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of GCC and cpRNFL thickness and ONH microcirculation would be useful for supporting the occurrence of AION in a case of VKH disease.

Introduction

Vogt-Koyanagi-Harada (VKH) disease is a systemic, immune-mediated, inflammatory condition that is considered to be caused by autoimmunity against melanocytes [1]. Acute symptoms at the initial onset include bilateral granulomatous intraocular inflammation, meningitis, and sensorineural hearing loss. Intraocular involvements are characterized by severe posterior segment inflammation, including serous retinal detachment and optic disc swelling, whereas anterior segment inflammation is either absent or mild [1, 2].

Previously, a few cases were reported in which severe visual field defects were seen with disc swelling, indicating that anterior ischemic optic neuropathy (AION) had developed at the onset of VKH disease [3, 4]. Nakao et al. [5] reported 6 patients who showed visual field defects with the retinal nerve fiber layer (RNFL) thickness decrease, suggesting the presence of AION among 15 patients with disc swelling out of 52 VKH disease patients.

Optical coherence tomography (OCT) is a useful tool for visualizing the retinal and the choroidal layers. In VKH disease, choroidal thickness detected by OCT is considered to be a valuable index of disease activity. With active inflammation, the choroid is thickened, and it is decreased (along with the resolution of the inflammation) with the administration of treatment [6]. In addition, OCT can segment the layers of the retina and choroid. It has already been shown that the thinning of the RNFL and the ganglion cell complex (GCC) are characteristic findings seen in optic nerve atrophy, including AION [5, 7].

Laser speckle flowgraphy (LSFG) is a noninvasive imaging modality, capable of quantitatively evaluating ocular blood flow velocity. LSFG targets moving erythrocytes that produce blurring within the speckle pattern, using a diode laser at the wavelength of 830 nm to illuminate the ocular fundus. The mean blur rate (MBR), automatically calculated from variations in the degree of blurring, is a quantitative index of the relative blood flow velocity. The measurement results have a high reproducibility [8]. LSFG is a useful tool for detecting choroidal circulation changes due to inflammation in patients with VKH disease in which the macular MBR is decreased [6]. LSFG can also be used to detect ischemic optic neuropathy in which the MBR of the optic disc tissue is decreased [9].

As mentioned above, OCT and LSFG are useful tools for diagnosing and examining the clinical stage of both VKH disease and AION. This is the first known case report of VKH disease suspected to be accompanied by AION, in which the clinical course could be followed up with OCT and LSFG.

Case Presentation

A 65-year-old female complained of blurred vision in both eyes (OU), which persisted for 1 week. The patient's medical and family histories were unremarkable.

Her best-corrected visual acuity (BCVA) was 0.2 in the right eye (OD) and 0.6 in the left eye (OS) with hyperopic refractive error. A slit-lamp examination revealed no abnormal findings in the anterior segment OU. Funduscopic examination showed optic disc swelling OU, and OCT showed remarkable choroidal thickening as well as optic disc swelling OU (Fig. 1a). Fluorescein

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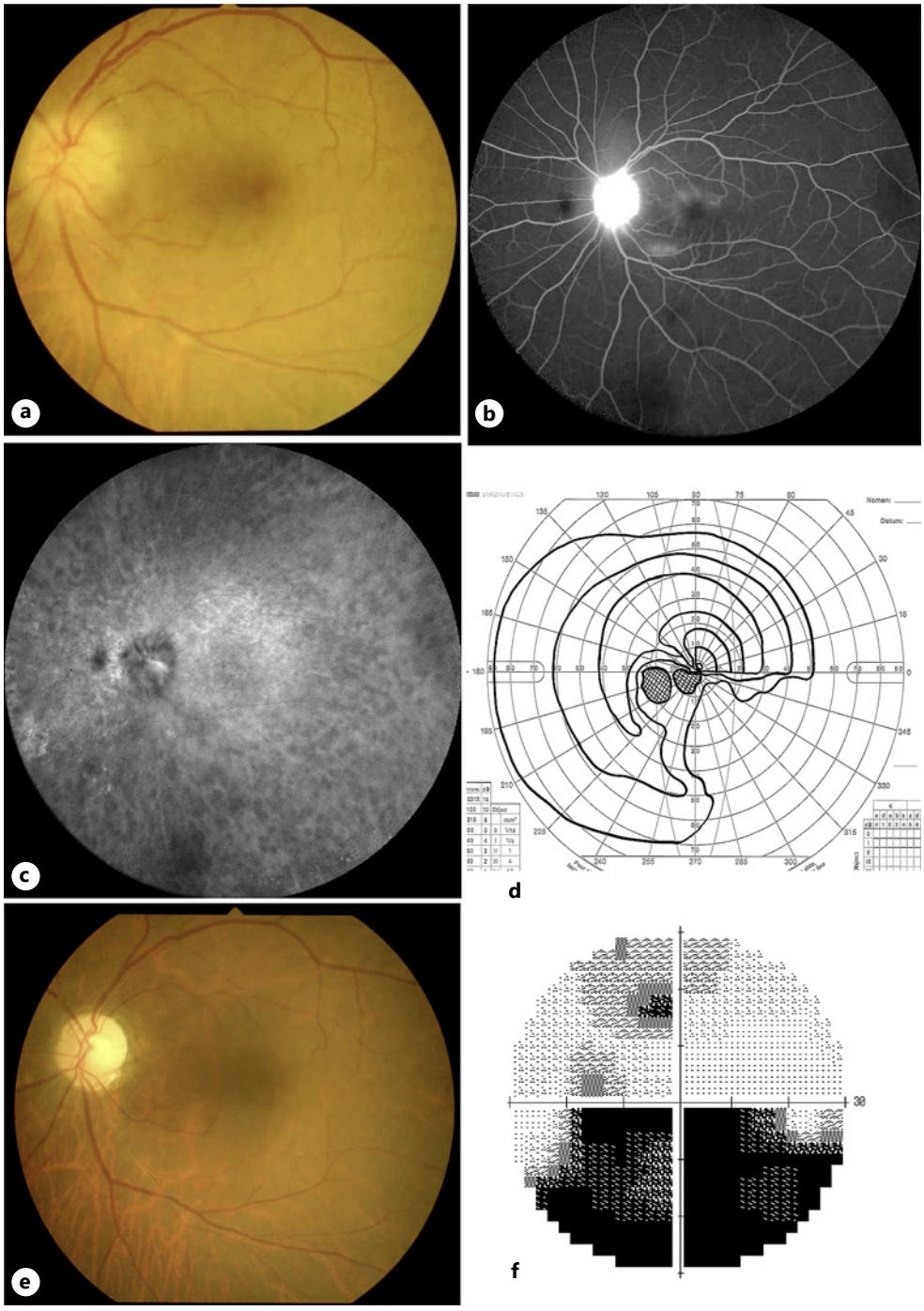

Fig. 1. Photographs, Goldmann perimetry and Humphrey 30-2 visual fields of the left eye at the initial visit (**a**, **b**, **c**, **d**) and after the initiation of systemic corticosteroid therapy at 5 months (**e**, **f**). **a** Color fundus photography showing optic disc swelling in the left eye. **b** Late-phase fluorescein angiography showing multifocal leakages in the posterior pole and optic disc staining. **c** Indocyanine green angiography at the middle phase showing multiple hypofluorescent dark dots scattering all around the fundus. **d** Bilateral visual field defects similar to inferior altitudinal hemianopsia, detected by Goldmann perimetry. After the initiation of systemic corticosteroid therapy at 5 months, optic discs were observed to be slightly pale (**e**), and visual field defects still persisted (**f**).

angiography (FA) showed a slight filling delay of the optic disc OU in the initial phase. In the late phase, FA showed slight leakages from retinal capillary vessels and optic disc staining (Fig. 1b).

Indocyanine green angiography (IA) at the middle phase showed multiple hypofluorescent dark dots (HDDs) scattering all around the fundus (Fig. 1c). Visual-evoked potentials were nonrecordable OU. Goldmann perimetry detected visual field defects similar to superior altitudinal hemianopsia in the right eye and similar to inferior altitudinal hemianopsia in the left eye (Fig. 1d). The cerebrospinal fluid cell count was 11/μL, indicating pleocytosis. The diagnosis of incomplete VKH disease was established according to the criteria proposed by the International VKH Disease Committee [10], based on the presence of bilateral characteristic ocular findings and cerebrospinal fluid pleocytosis, but without integumentary findings. In addition, the patient was suspected to have AION OU from the results of the Goldmann perimetry.

The patient received intravenous methylprednisolone that was initially administered at 1,000 mg/day for 3 consecutive days (pulse therapy). Oral prednisolone was then initiated and tapered with the following schedule: 10 days at 40 mg/day, 10 days at 30 mg/day, 10 days at 25 mg/day, 1 month at 20 mg/day, 1 month at 15 mg/day, 1 month at 10 mg/day, 1 month at 5 mg/day, and 1 month at 2.5 mg. The therapy was then stopped.

The patient's optic disc swelling disappeared with the therapy. However, her optic discs became slightly pale, and her visual field defects still persisted OU (Fig. 1e, f). Five months later, the BCVA was 0.3 OD and 0.6 OS. The IOP values were within the range of 9–16 mm Hg OD, 9–14 mm Hg OS during the follow-up period. No recurrence has been observed so far.

Methods

Choroidal Thickness Measurements

The OCT (RS-3000 Advance®; Nidek, Gamagori, Japan) measurements were performed OU at the initial visit, at weeks 1, 2, and 3, and at 1, 4, 5, and 12 months after the initiation of the treatment. The central choroidal thickness (CCT) was determined by manually measuring the distance at the fovea from the outer border of the hyperreflective line, corresponding to the retinal pigment epithelium, to the outer border of the choroid, using a horizontal scan through the fovea (scan length, 12.0 mm). Two authors (Y.Y. and Y.H.), uninformed of the patient's clinical information, independently evaluated the OCT images. The CCT reaching >800 μm was defined as 800 μm because the inner scleral border could not be visualized with OCT.

GCC and RNFL Thickness Measurements

The OCT C-scan GCC thickness and circumpapillary (cp) RNFL thickness were measured at the initial visit and at weeks 1, 2, and 3, as well as at 1, 4, 5, and 12 months. GCC thickness values were automatically calculated and compared to the normative database by software equipped with OCT (Fig. 2a, c, e, g). The mean GCC thickness was calculated from 8 sectors segmented around the macula (6 mm × 6 mm), which excluded the fovea sector (1 mm × 1 mm). The disc circle scan pattern captured an image of a circle with a 3.45-mm diameter around the disc that allowed cpRNFL thickness analysis, compared to those in the normative database (Fig. 2b, d, f, h). The red color zone depicted an extremely thinning area, which represented an abnormal to normal database percentage of <1%. The yellow and white thickened zones represented an abnormal to normal database percentage of <5%. The green area depicted a relatively normal area, evaluated as being between 5% and 95% in a population of normal eyes.

Macular and Optic Disc Circulation Measurements

LSFG measurements using LSFG-NAVI (Softcare, Fukuoka, Japan) were performed to quantitatively examine the choroidal and optic nerve head (ONH) blood flow velocity.

LSFG results were examined 5 consecutive times at the initial visit and also at 1, 2, and 3 weeks, as well as at 1, 4, 5, and 12 months after treatment. Information has been available online on the mechanism by which LSFG operates, along with its measurement method [11].

On the color map, a circle band was set at the macula in each eye (Fig. 3a, c, e, g) and ONH (Fig. 3b, d, f, h). Since the origin of the macular MBR is derived from the choroid (because of the macula lacking retinal vessels), the macular MBR indicates choroidal blood flow velocity. The blood circulation of ONH was evaluated with the ONH tissue MBR: the MBR of the whole ONH area minus the MBR of the ONH vascular area. The positions of circle bands were determined manually as being in exactly the same place as those used at the baseline, by comparing the fundus photographs and the LSFG color map images. Each MBR was automatically calculated, using LSFG Analyzer software (Softcare v 3.0.47). Sequential changes in the average MBR were evaluated as the changing rates of the average MBR to the baseline values, as previously described, since MBR is a quantitative index of the relative blood flow velocity.

Perfusion Pressure Measurements

As previously demonstrated [12], within a certain range, the relationship between choroidal blood flow and ocular perfusion pressure (OPP) is linear in healthy subjects with normal eyes. To exclude the possibility of such physiological responses from the results, the patient's blood pressure and intraocular pressure (IOP) were measured to calculate the OPP. The mean blood pressure (BPm) was calculated from systolic blood pressure (BPs) and diastolic blood pressure (BPd) readings, according to the following equation: BPm = BPd + 1/3 (BPs−BPd). OPP was calculated using the following equation: OPP = 2/3 BPm−IOP.

Results

CCT Changes

The marked thickening of the choroid seen at the initial visit had recovered to the normal range with the therapy within 2 weeks and was maintained until 5 months later (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000520036).

GCC and cpRNFL Changes

Changes of the GCC thickness and the cpRNFL OS are shown in Figure 2 (those of them OD, in online suppl. Fig. 2). The GCC thickness was almost normal at the initial visit. However, it changed and was observed as being thin in the macular area OU 2 weeks later. It continued to become thinner (Fig. 2a, c, e, g, i).

The cpRNFL thickened at the initial visit and recovered to a normal range 1 month later. However, it changed and became thin, measuring below the normal range at 5 months (Fig. 2b, d, f, h, j).

Fig. 2. The OCT C-scan images showing the GCC thickness map (**a**, **c**, **e**, **g**) and cpRNFL thickness map in the left eye during follow-up (**b**, **d**, **f**, **h**). The OCT provides thickness maps in which green indicates that the thickness is within the normal range; yellow and white indicate an increased abnormality below the 5% level; and red points to a decreased abnormality below the 1% level. The GCC thickness map indicated almost normal findings at the initial visit (**a**); the appearance of thinning area at 2 weeks later (**c**); a gradual spread over the whole macular area 1 month later (**e**) and 5 months later (**g**). The graph in (**i**) shows the change of the GCC thickness in both eyes. The cpRNFL thickness map showed peripapillary RNFL thickening at the initial visit (**b**) and at week 2 (**d**). The thickness changed to almost normal at 1 month (**f**), and then it showed thinning at 5 months (**h**). The graph in (**j**) shows the change in cpRNFL thickness in both eyes. GCC, ganglion cell complex; cpRNFL, circumpapillary retinal nerve fiber layer. *(For figure see next page.)*

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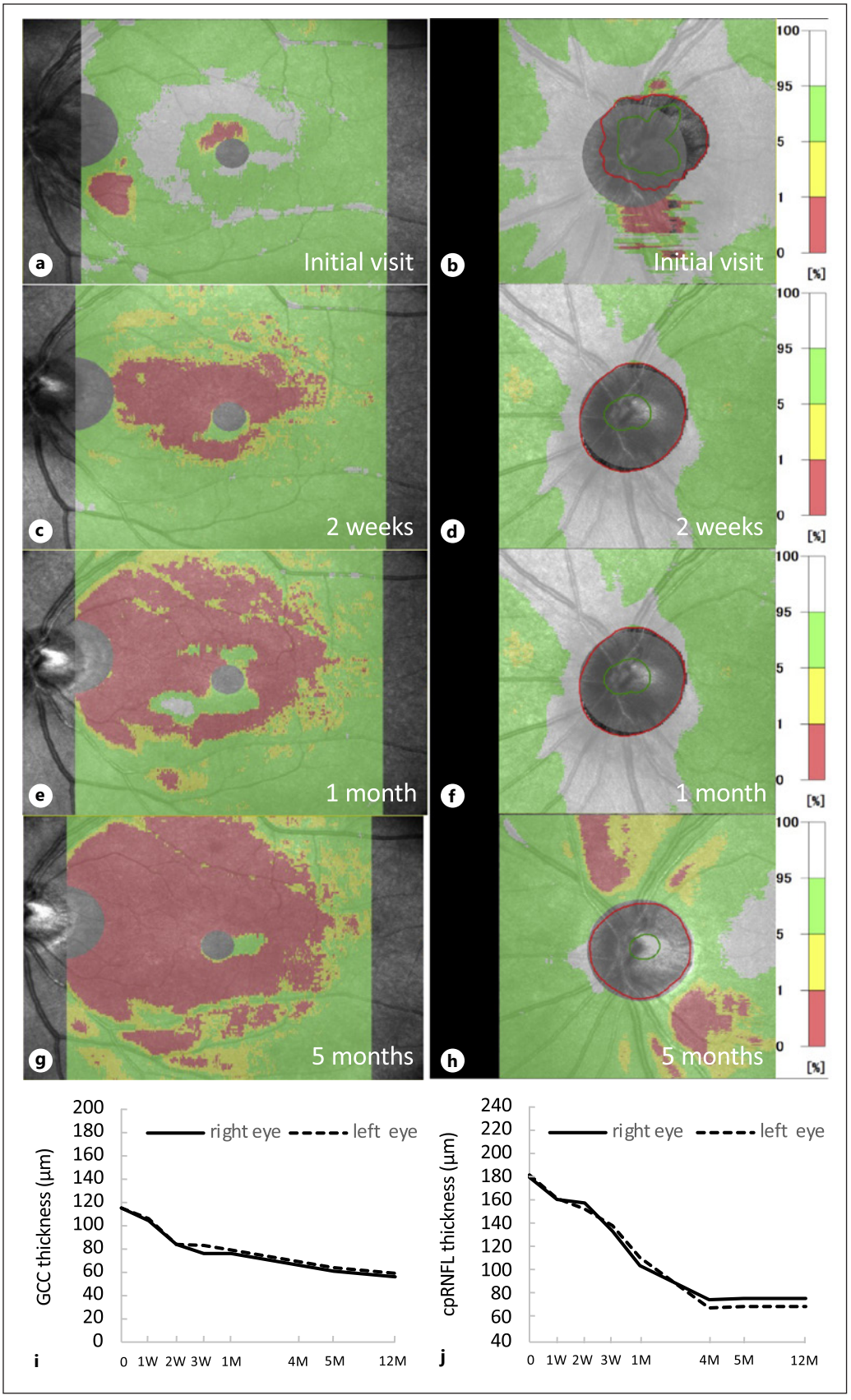

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Macular and ONH Tissue MBR Changes

LSFG was performed in 2 areas: the macula and ONH. Changes of the macular and ONH tissue MBR OS are shown in Figure 3 (those of them OD, in online suppl. Fig. 3). The MBR values in the macular area were low at the initial visit, and they gradually increased with the treatment OU (Fig. 3a, c, e, g, i).

Blood flow velocity at the ONH was evaluated with the tissue MBR. In comparison with the tissue MBR values at the initial visit, the values gradually decreased OU with the treatment (Fig. 3b, d, f, h, j). OPP was unaltered OU during the follow-up period.

Discussion

In this study, we quantitatively evaluated changes of the choroid and ONH blood flow velocity using LSFG and changes of the retinal layer thickness using OCT in a patient with VKH disease accompanied by AION. Findings obtained at the onset, including the remarkable choroidal thickening detected by OCT and multiple HDDs seen in IA bilaterally, along with the presence of pleocytosis, confirmed the diagnosis of VKH disease. The decreased macular MBR at the onset indicating the inflammatory impairment of choroidal circulation increased along with the treatment similar to the clinical course in typical VKH disease. Thus, LSFG is commonly used to detect the impairment of "choroidal circulation" in VKH disease; however, we performed LSFG to detect the impairment of "ONH circulation" in the patient. In addition to the OCT findings (the GCC and cpRNFL thinning), LSFG could show the decrease of the ONH tissue MBR indicating the impairment of ONH circulation during the 12-month follow-up period. This study was the first to show the quantitative changes over time in the ONH microcirculation in VKH disease associated with AION.

AION is not a common complication with VKH disease. Nakao et al. [5] reported that in the consecutive series of 52 VKH disease patients, 15 (28.8%) showed optic disc swelling. Among them, 6 (11.5%) were suspected to be accompanied with AION, with the findings of visual field defects, optic disc atrophy, and the decrease of RNFL thickness, while none of the patients without optic disc swelling developed AION [5]. This result indicated that optic disc swelling is a risk factor for AION development in VKH disease patients. Actually, our patient also showed severe bilateral optic disc swelling at the onset.

Usually, AION is diagnosed based on age, disc appearance, and the results of a visual field test and the RNFL thickness [5]. However, these findings did not directly indicate the ischemia of the optic nerve. LSFG is a noninvasive technique to quantitatively measure blood flow velocity, and it can support both the diagnosis and evaluation of the activity in various diseases with choroidal abnormalities, glaucoma, and AION. Maekubo et al. [9] previously reported that in AION, the ONH tissue MBR was 29.5% lower than that of unaffected eyes. In our case, the LSFG also showed a decrease in the ONH tissue MBR, strongly supporting the diagnosis of the development of AION.

The analysis of the retinal layer thickness with the OCT C-scan revealed the appearance of the thinning of the GCC layer in the macular area 2 weeks later and the thinning of the cpRNFL at 5 months, which was thickened at the onset. In AION, it is considered that the demyelination of the optic nerve results in the thinning of cpRNFL. Subsequently, it induces

Fig. 3. The composite color map image of the MBR measured by laser speckle flowgraphy in the left eye. The circles were set at the macula (**a**, **c**, **e**, **g**) and the ONH (**b**, **d**, **f**, **h**). The blue color indicates low MBR, while the red color shows high MBR. The macular MBR increased at 2 weeks, 1 month, and 5 months (**c**, **e**, **g**), compared to that at baseline (**a**). The graph in (**i**) shows the change in the macular MBR in both eyes. The ONH tissue MBR decreased at 2 weeks, 1 month, and 5 months (**d**, **f**, **h**) compared to that at baseline (**b**). The graph in (**j**) shows the change of the ONH tissue MBR in both eyes. MBR, mean blur rate; ONH, optic nerve head. *(For figure see next page.)*

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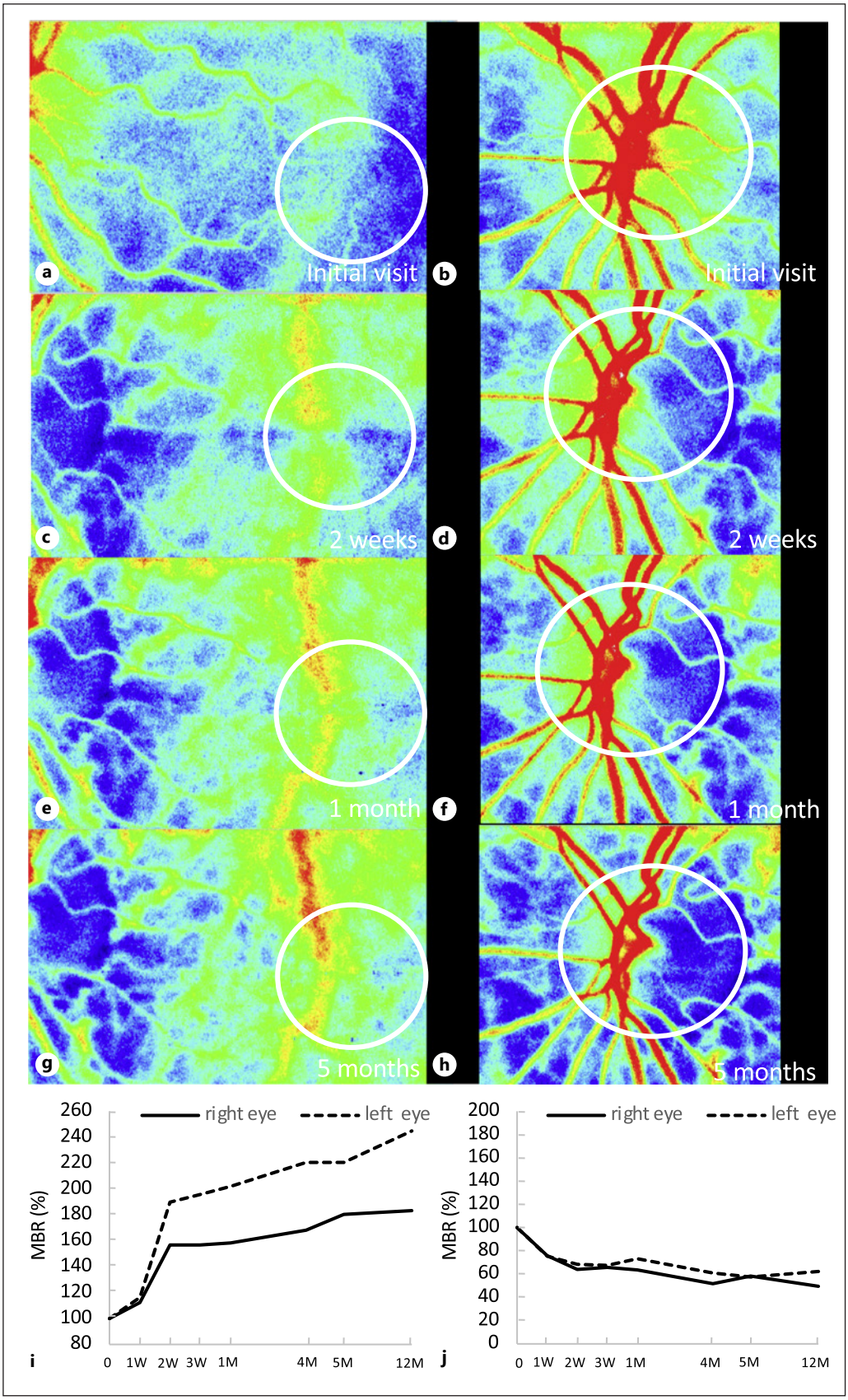

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the apoptosis of retinal ganglion cells, resulting in the thinning of the GCC layer. Indeed, it has already been reported that in AION, the GCC thickness decreased at 1 month from the onset, and the cpRNFL thickness increased at the onset and decreased 6 months later [7]. The results of the retinal layer thickness analysis in our case were consistent with changes reported in AION, ensuring the complication of AION with VKH disease.

The incidence of AION associated with VKH disease has been reported to be 11.5%. However, the diagnosis of AION was made based on the disc appearance and results of the visual field test, both of which were subjective examinations, together with cpRNFL thickness [5]. Further studies with a larger number of cases involving an OCT C-scan and LSFG may reveal the exact incidence of AION in VKH disease.

Conclusion

The analyses of retinal layer thickness with an OCT C-scan and ONH microcirculation with LSFG could support the diagnosis of AION in cases of VKH disease. These examinations would be essential in not only the diagnosis but also the observation of AION complicated with VKH disease.

Acknowledgment

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Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This study protocol was reviewed and the need for approval was waived by the Ethics Committee of Hokkaido University Hospital.

Conflict of Interest Statement

The following authors declare that they have no conflicts of interest: Y.Y., Y.H., K.N., K.M., and S.I.

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Author Contributions

Y.Y. was involved in the design of the study, drafted the manuscript, collected the data, and reviewed the literature. Y.H. collected the data, drafted the manuscript, and revised the manuscript. K.N. was involved in the design of the study, interpretation of the data, drafting of the manuscript, and review of the literature. K.M. participated in collection of the data, and drafting of the manuscript, and interpretation of the data. S.I. drafted the manuscript, interpreted the data, and critically reviewed the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

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