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Acute uveitic phase of Vogt-Koyanagi-Harada disease: optic nerve head swelling, ocular blood flow and retinal oxygen metabolism

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OBJECTIVES: To investigate the association of optic nerve head (ONH) swelling in the acute uveitic phase of Vogt-Koyanagi-Harada (VKH) disease with blood flow velocity in the choroid and ONH and oxygen saturation and diameter of retinal vessels.

METHODS: In this prospective study, 25 patients (50 eyes) were studied. Thirteen patients (26 eyes) had ONH swelling and 12 patients (24 eyes) had no ONH swelling. Laser speckle flowgraphy (LSFG) and retinal oximetry measurements were performed at presentation.

RESULTS: In the ONH, mean blur rate (MBR)-vessel, representing blood flow velocity in retinal vessels, was significantly lower in the eyes affected by ONH swelling, while choroidal MBR was not significantly different. Eyes with ONH swelling had a significantly lower oxygen saturation in retinal venules, a significantly higher arteriovenous oxygen saturation difference and a significantly smaller calibre of retinal arterioles compared with eyes without ONH swelling. There were significant positive correlations between the MBR-vessel of the ONH and venular oxygen saturation and calibre of retinal arterioles. In addition, MBR-vessel of the ONH had a significant negative correlation with arteriovenous oxygen saturation difference.

CONCLUSIONS: The occurrence of ONH swelling in the acute uveitic phase of VKH disease is associated with lower retinal blood flow velocity and smaller calibre of retinal arterioles as well as lower oxygen saturation in retinal venules and higher arteriovenous difference in oxygen saturation.

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INTRODUCTION

Vogt-Koyanagi-Harada (VKH) disease is a multisystem autoimmune disease directed against antigens associated with melanocytes present in the target organs including uvea, meninges, inner ear, and integumentary system. It was demonstrated that tyrosinase family proteins are important antigens specific to VKH disease [1–3]. Patients with initial-onset acute uveitis present with granulomatous choroiditis with secondary exudative retinal detachment with typical optic nerve head (ONH) hyperaemia. Swelling of the ONH is frequently seen in the acute uveitic phase of VKH disease [4, 5]. Some patients with ONH swelling develop anterior ischaemic optic neuropathy [4]. Accordingly, knowledge on ocular blood flow and retinal oxygen metabolism may elucidate the pathophysiology of VKH disease in the acute uveitic phase.


Laser speckle flowgraphy (LSFG) studies demonstrated inflammation-related impairment of ONH and choroidal blood flow velocity in the acute uveitic phase of VKH disease. Systemic immunosuppressive therapy improved inflammation-related impairment in blood flow velocity [6–8]. LSFG is a noninvasive, convenient, highly reproducible method to quantify velocity of blood flow in the choroid and ONH simultaneously. It is based on laser speckle phenomenon to detect the speckle contrast pattern

produced by the interference of the illuminating laser light that is scattered by the movement of blood cells in the vessels [9]. The mean blur rate (MBR), the measurement parameter of LSFG, can serve as a quantitative index of blood cell velocity [10, 11]. In addition, with the use of the spectrophotometric retinal oximetry [12, 13], we demonstrated the presence of abnormal retinal oxygen metabolism and calibre of retinal vessels in patients with initial-onset acute uveitis associated with VKH disease and that immunosuppressive therapy normalised these changes [14, 15].

The aim of this prospective study was to evaluate the effect of ONH swelling in the acute uveitic phase of VKH disease on blood flow velocity in the ONH and choroid and on retinal vascular oxygen saturation and calibres.

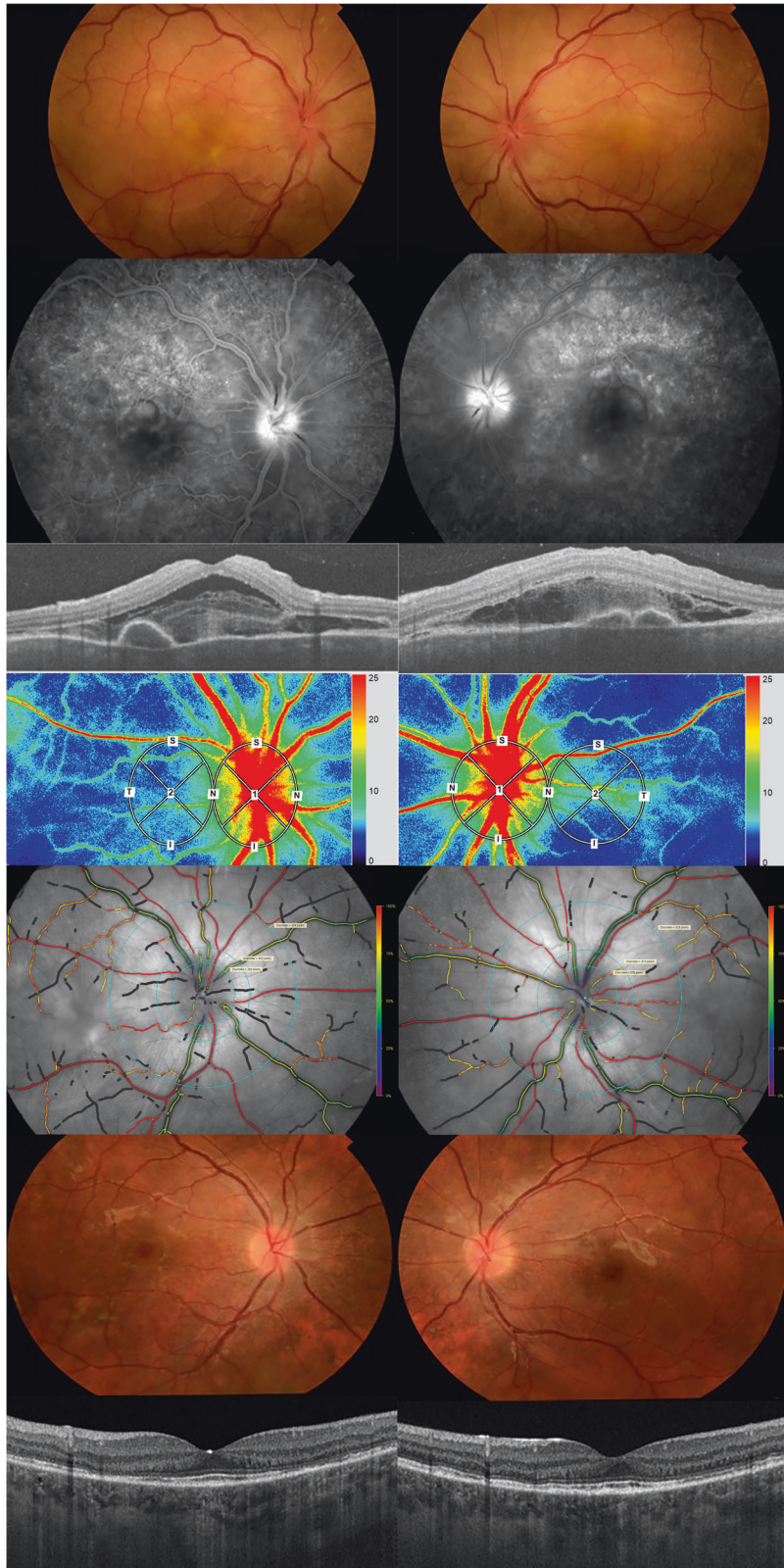
MATERIALS AND METHODS

In this retrospective study, we investigated 25 patients diagnosed with initial-onset acute uveitis associated with VKH disease seen at King Abdulaziz University Hospital, Riyadh, Saudi Arabia [6, 14, 15]. Eleven patients were males and 14 were females, with ages ranging from 16 to 53 years with a mean of 30.5 ± 11.4 years. At presentation, all patients had bilateral exudative retinal detachment at the macula and optic disc hyperaemia with or without ONH swelling. Patients were not included if they present with bullous retinal detachment at the macula. None of the patients had any other relevant

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medical or ocular history, such as systemic or ocular hypertension and ocular surgery or trauma. At presentation, all the patients had a complete ophthalmic examination, including determination of best-corrected Snellen visual acuity (BCVA), Goldmann applanation tonometry, slit-lamp examination of the anterior segment, fundus examination, fluorescein angiography, indocyanine green angiography, optical coherence tomography (Optovue RTVue 100, Fremont, CA, USA), LSFG and retinal oximetry.

The ONH of each eye was evaluated to be either swollen or not swollen based on clinical findings and the results of fluorescein angiography at presentation. On fluorescein angiography, the ONHs with hyperfluorescence and leakage were considered to have swelling. The ONHs with hyperfluorescence but no leakage were considered to have no swelling.

All patients were managed and followed-up by one of the authors (AMA). All patients received systemic corticosteroids combined with

Fig. 1 A 23-year-old male patient with initial-onset acute uveitis associated with Vogt-Koyanagi-Harada disease. Visual acuity was counting fingers in both eyes. Note the exudative retinal detachments and optic nerve head (ONH) hyperaemia and swelling in both eyes (first row). Fundus fluorescein angiography shows bilateral multiple pinpoint hyperfluorescence at the level of the retinal pigment epithelium and pooling of dye in the areas of exudative retinal detachment in addition to prominent ONH hyperfluorescence and leakage (second row). Optical coherence tomography shows bilateral exudative retinal detachment (third row). Composite colour maps of the mean blur rate (MBR) as measured by laser speckle flowgraphy. Red colour indicates a high MBR, and blue colour indicates a low MBR. To measure the MBR of the blood flow of the optic nerve head (ONH) and choroid regions, a circle was set around the ONH (rubberband 1) and same-sized circle was set around the temporal side of the ONH to mark the choroid (rubberband 2) (fourth row). Pseudocolour fundus maps automatically generated by the Oxymap T1 oximeter. Colours indicate oxygen saturation in retinal vessels (scale to the right of the image; red is fully saturated, blue and purple is low oxygen saturation (fifth row). The patient received systemic corticosteroids combined with mycophenolate mofetil. Eight months after treatment, best-corrected visual acuity was 20/20 in both eyes. Note the absence of 'sunset glow fundus' and chorioretinal atrophy (sixth row). Optical coherence tomography shows resolution of exudative retinal detachment (seventh row).

mycophenolate mofetil as described previously [6, 14, 15]. The patients were followed-up for at least 6 months. The study followed the tenets of the Declaration of Helsinki for research involving human subjects and all study subjects provided an informed consent. The study was evaluated by the institutional review board of King Abdulaziz University Hospital. Due to the retrospective nature of the study, ethical approval was waived.

Optic nerve head and choroidal blood flow assessment with LSFG

This study used the LSFG-Retflow (Nidek Co., LTD, Camagori, Aichi, Japan) to measure ONH and choroidal blood flow. The principles of LSFG have been described previously [9]. The instrument consists of a fundus camera equipped with an 830-nm diode laser as the light source and an ordinary charge-coupled device as the detector. LSFG measures the motion of the speckle pattern created by illuminating the blood cells in the blood vessels in the ocular fundus with laser light. The main output parameter of LSFG is MBR. MBR measures the relative blood flow and is expressed in arbitrary units (AU). The MBR images of the fundus are acquired at a rate of 30 frames/s over a 4 s period. The software of the instrument is able to track and compensate for the eye movements during the measurement period. To measure blood flow in the ONH, a circular marker was manually set surrounding the ONH. For choroidal assessment, a same-sized circle was set around the temporal side of the ONH to exclude large retinal vessels as described previously [6] (Fig. 1). Within the ONH, the LSFG analyser software separates automatically large vessels from the tissue (capillary) area. Then MBRs are calculated from each area. Thus, three areas of ONH were analysed which are vessel area, tissue area and overall area. MBR-tissue of the ONH has been reported to be a good indicator of blood flow in the deeper regions of the ONH [11, 16]. The MBR-vessel of the ONH can be used to evaluate the blood flow in the retinal vessels excluding the large choroidal blood vessels [17].

Retinal oximetry

The Oxymap T1 retinal oximeter (Oxymap ehf., Reykjavik, Iceland) was used for retinal oximetry measurements. The technical principles of the device have been described previously [12, 13]. It is based on a fundus camera with a 50° view of the fundus (Topcon TRC-50 DX; Topcon, Tokyo, Japan) and specialised software (Oxymap analyzer 2.4, V.6813). The Oxymap Analyzer software acquires two monochromatic images of the fundus simultaneously for calculation of oxygen saturation from optical density measurements at two different wavelengths (570 and 600 nm). A 50° retinal image with the optic disc in the centre was used for analysis. The software created two circles concentric with the optic discs that were 1.5 times and 3 times the optic disc diameter. All measurements were made within the area between these circles as described previously [14, 15] (Fig. 1).

Statistical analysis

Data were collected, stored and managed in a spreadsheet using Microsoft Excel 2010® software. Data were analysed and figures were prepared using SPSS® version 21.0 (IBM Inc., Chicago, Illinois, USA). Snellen visual acuities were converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Tests for normality for the continuous variables were done using Shapiro-Wilk test and Q-Q plots. The data were normally distributed and were reported as mean ± standard deviation (SD) and Range. Consequently, independent *t* test was used to test the differences between the two groups and Pearson correlation coefficients were calculated to test the correlation between the variables. Categorical

variables were presented as frequencies and percentages and Chi-squared test was used for the comparison of proportions between groups. Any output with a *p* below 0.05 was interpreted as an indicator of statistical significance.

RESULTS

Among the 25 patients (50 eyes) with initial-onset acute uveitis associated with VKH disease, 13 patients (26 eyes) were judged as having ONH swelling (Fig. 1) and 12 patients (24 eyes) were judged as having no ONH swelling (Fig. 2). There were no significant differences in the male to female ratio, age and baseline BCVA between eyes with and without ONH swelling (Table 1). At presentation, 5 eyes with ONH swelling had peripapillary haemorrhage, while none of the eye, without ONH swelling had peripapillary haemorrhage. The mean posttreatment BCVA at 6 months was significantly better in eyes affected by swelling of ONH than in eyes unaffected with swelling of the ONH (Table 1).

Mean blur rate in choroid and optic nerve head in eyes with and without swelling of optic nerve head

There was no significant difference in choroidal MBR between eyes with and without swelling of the ONH. In the ONH, the mean MBR-vessel was significantly lower in eyes affected by swelling of ONH than in eyes unaffected with swelling of the ONH. There were no significant differences in the mean ONH MBR-overall and mean ONH MBR-tissue between eyes with and without swelling of the ONH (Table 2).

Oxygen saturation in retinal arterioles and venules, arteriovenous oxygen saturation difference and retinal vessel diameters in eyes with and without swelling of the optic nerve head

Eyes with swelling of ONH had a significantly lower oxygen saturation in retinal venules and a higher arteriovenous oxygen saturation difference compared with eyes without swelling of ONH. There was no significant difference in the oxygen saturation in retinal arterioles between the two groups. The mean diameter of retinal arterioles was significantly smaller in eyes with swelling of ONH compared with eyes unaffected with swelling of ONH. There was no significant difference between eyes with or without swelling of ONH in mean diameter of retinal venules (Table 2).

Correlations between blood flow velocity in the optic nerve head and choroid and oxygen saturation and calibre of retinal vessels

Correlations between values of MBR and oxygen saturation and calibre of retinal vessels in the combined baseline measurements were examined by using Pearson correlation coefficient analyses. The MBR-vessel of the ONH had significant positive correlations with venular oxygen saturation ($r = 0.323, p = 0.028$) and calibre of retinal arterioles ($r = 0.357, p = 0.015$). In addition,

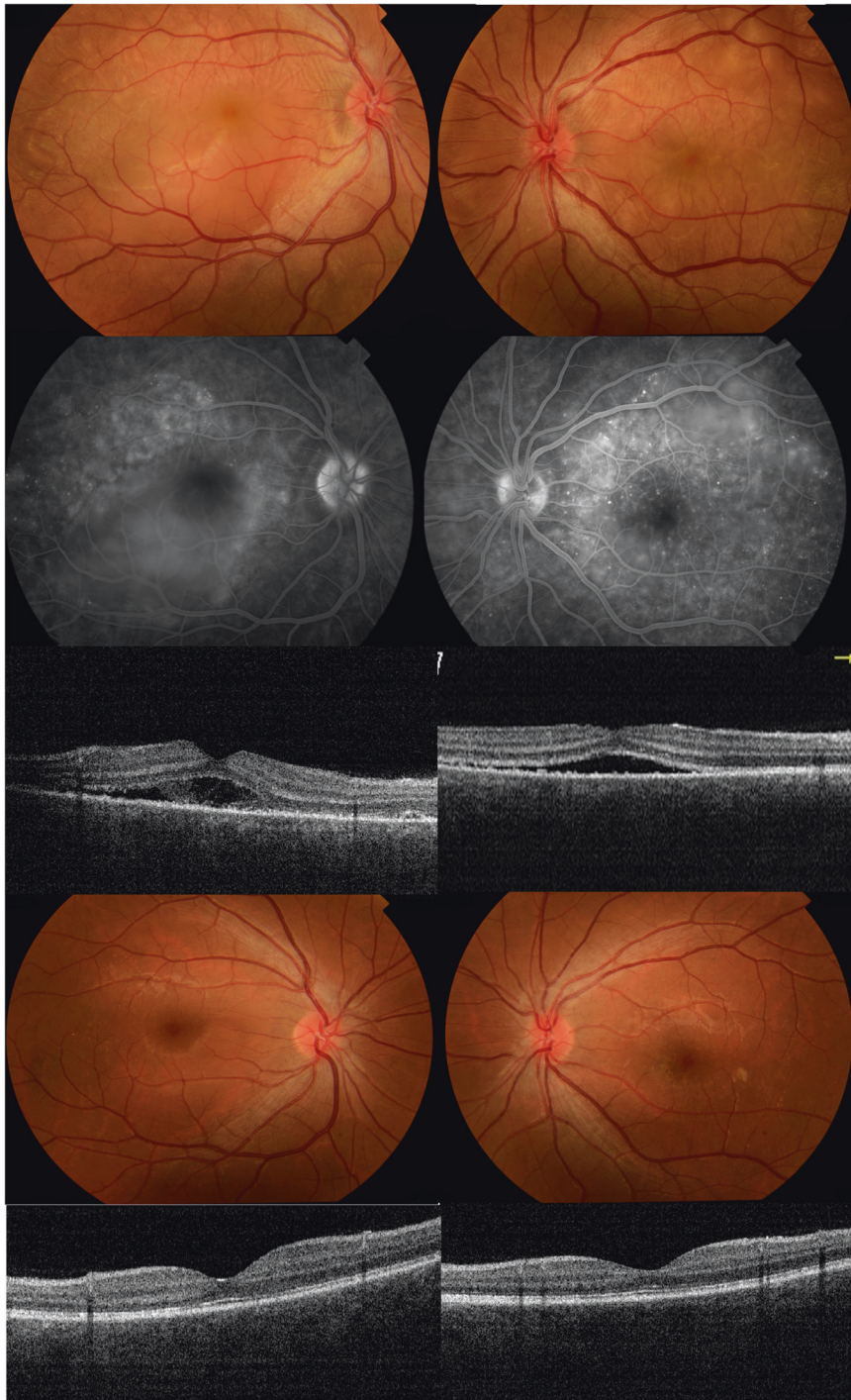


Fig. 2 A 25-year-old male patient with Vogt-Koyanagi-Harada disease in the acute uveitic phase. Visual acuity was counting fingers in the right eye and 20/200 in the left eye. Note the exudative retinal detachments and the hyperaemic optic nerve heads (ONH) (first row). Fundus fluorescein angiography shows bilateral multiple pinpoint hyperfluorescence at the level of the retinal pigment epithelium and pooling of dye in the areas of exudative retinal detachment in addition to mild ONH hyperfluorescence (second arrow). Optical coherence tomography shows bilateral exudative retinal detachment (third row). The patient received systemic corticosteroids combined with mycophenolate mofetil. Thirteen months after treatment, best-corrected visual acuity was 20/20 in both eyes. Note the absence of 'sunset glow fundus' and chorioretinal atrophy (fourth row) and resolution of exudative retinal detachments (fifth row).

MBR-vessel of the ONH had a significant negative correlation with the arteriovenous saturation difference ($r = -0.418$, $p = 0.004$) (Fig. 3). The correlations between choroidal MBR and oxygen saturation and calibre of retinal vessels were not significant.

DISCUSSION

The present study is the first to demonstrate the association between swelling of ONH in the acute uveitic phase of VKH disease with blood flow velocity in the choroid and ONH and oxygen saturation and calibre of retinal vessels. We simultaneously

Table 1. Demographics and clinical characteristics in 25 patients with initial-onset acute uveitis associated with Vogt-Koyanagi-Harada disease with ($n = 13$) and without ($n = 12$) swelling of optic nerve head (ONH).

	All ($n = 50$ eyes)	ONH Swelling ($n = 26$ eyes)	No ONH swelling ($n = 24$ eyes)	<i>p</i> value
Gender, male/female	11/14	6/7	5/7	0.821
Age, years	30.5 ± 11.4	30.2 ± 12.2	30.9 ± 10.9	0.871
Visual acuity at presentation				0.761
logMAR	0.66 ± 0.58	0.69 ± 0.57	0.64 ± 0.60	
Snellen equivalent	20/92	20/98	20/88	
Peripapillary haemorrhage (%)	5 (10)	5 (19.5)	0 (0.0)	<0.001 ^a
Visual acuity at 6-month follow-up				0.015 ^a
logMAR	0.04 ± 0.1	0.01 ± 0.03	0.07 ± 0.13	
Snellen equivalent	20/22	20/20.5	20/23.5	

^aStatistically significant at 5% level of significance.

Table 2. Mean blur rate (MBR) in choroid and optic nerve head (ONH) and retinal oximetry results in eyes with and without swelling of ONH.

Parameter	ONH Swelling ($n = 26$ eyes)	No ONH swelling ($n = 24$ eyes)	<i>p</i> value
Choroidal MBR (AU)	6.6 ± 2.5	6.6 ± 3.3	0.981
ONH MBR (overall) (AU)	25.6 ± 6.6	27.9 ± 6.5	0.212
ONH MBR (vessel) (AU)	39.9 ± 7.6	47 ± 8.5	0.003 ^a
ONH MBR (tissue) (AU)	16.3 ± 3.8	15.6 ± 3.4	0.537
Mean arteriolar oxygen saturation (%)	105.5 ± 9.1	102.3 ± 4.7	0.158
Mean venular oxygen saturation (%)	59.7 ± 9.8	65.0 ± 7.5	0.041 ^a
Mean arteriovenous difference (%)	45.8 ± 9.5	37.2 ± 6.4	0.001 ^a
Mean arteriolar diameter (pixels)	11.5 ± 0.9	12.6 ± 1.4	0.005 ^a
Mean venular diameter (pixels)	16.8 ± 1.8	16.6 ± 1.7	0.737
Image quality	7.4 ± 0.8	7.7 ± 0.8	0.215

AU arbitrary unit.

^aStatistically significant at 5% level of significance.

used LSGF and spectrophotometric retinal oximetry in patients with initial-onset acute uveitis associated with VKH disease at presentation. We demonstrated the following findings:

1. Eyes with swelling of ONH had significantly lower ONH MBR-vessel, representing blood flow in retinal vessels, than in the eyes unaffected with swelling of ONH, while MBR-tissue of the ONH, representing blood flow in the deeper regions of the ONH, was not significantly different.
2. Choroidal MBR did not differ significantly between eyes affected with swelling of the ONH and eyes without swelling of ONH.
3. Eyes with swelling of ONH had a significantly lower oxygen saturation in retinal venules and a significantly higher arteriovenous difference in oxygen saturation than eyes without swelling of ONH, but there was no significant difference in oxygen saturation in retinal arterioles between the two groups.
4. The presence of swelling of the ONH was associated with a significant decrease in the calibre of retinal arterioles, while the calibre of retinal venules was unaffected.
5. MBR-vessel of the ONH had significant positive correlations with calibre of retinal arterioles and venular oxygen saturation and a significant negative correlation with the arteriovenous oxygen saturation difference.

In the current study, we demonstrated that in eyes with swelling of ONH, decreased ONH MBR-vessel, representing retinal

blood flow, is associated with a significant decrease in oxygen saturation in retinal venules, a significant increase in arteriovenous oxygen saturation difference and a significant decrease in calibre of retinal arterioles. Our results are in agreement with previous colour Doppler imaging studies that demonstrated significant reduction in central retinal artery blood flow velocity in patients with optic disc oedema [18, 19]. Our analysis demonstrated that ONH MBR-vessel had significant positive correlations with oxygen saturation in the venules and diameter of retinal arterioles and an inverse correlation with arteriovenous difference in oxygen saturation. Similarly, previous studies demonstrated the inverse correlation between retinal blood flow and arteriovenous difference in oxygen saturation [20–22]. The retinal arteriovenous difference in oxygen saturation is an indicator of retinal oxygen consumption [23]. Increased arteriovenous difference in oxygen saturation reflects increased oxygen delivery to retinal tissue [24]. The increased arteriovenous oxygen saturation difference in eyes with swelling of ONH might indicate an attempt by the retina to maintain oxygen delivery in the face of reduced retinal blood flow.

The retinal venous oxygen saturation reflects the amount of oxygen remaining after passage through the retinal microcirculation. Increased retinal oxygen consumption in eyes with swelling of ONH can explain the lower oxygen saturation in retinal venules [25, 26]. Similarly, a previous study reported reduced oxygen saturation in retinal venules and increased arteriovenous difference in eyes with central retinal vein occlusion [25]. We speculate that in eyes with swelling of ONH, the decreased retinal blood flow decreases oxygen delivery to the retinal tissue. The hypoxic tissue

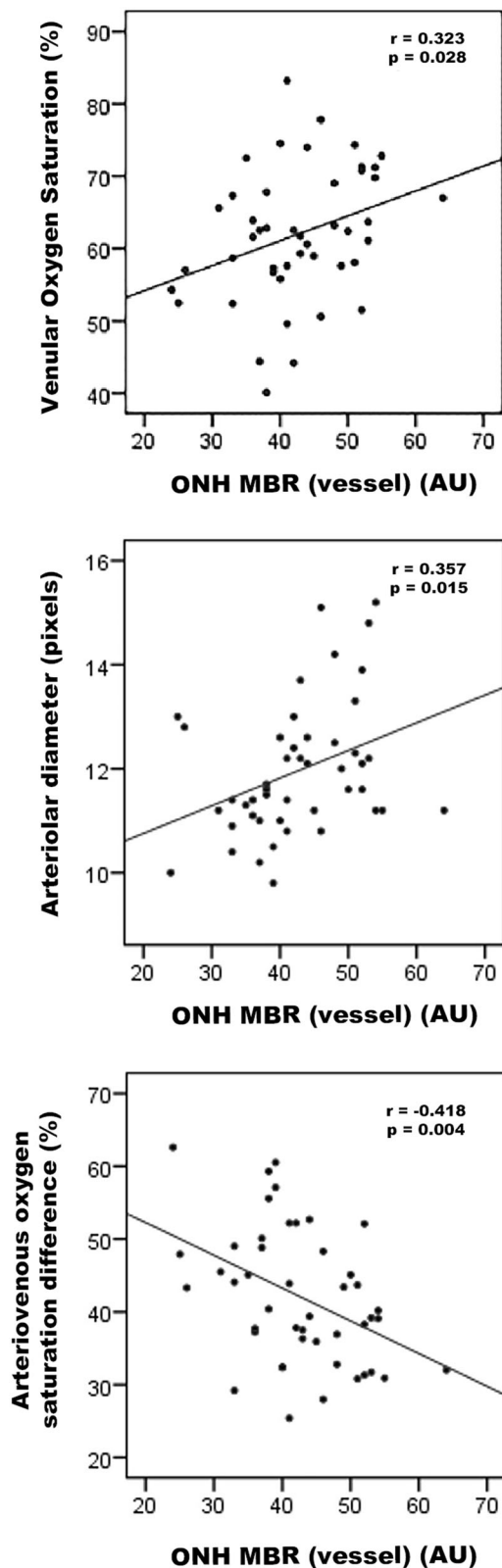


Fig. 3 Correlations between optic nerve head (ONH) mean blur rate (MBR)-vessel and retinal oximetry measurements. AU arbitrary unit.

extracts more oxygen from the decreased amount of blood flow through the vessels, leaving a lower level of oxygen in the retinal venules. Decreased retinal arteriolar calibre in eyes with swelling of ONH might be an autoregulatory response to decreased retinal

blood flow to keep blood flow constant. These findings are in agreement with previous studies that demonstrated reduced retinal arteriolar diameter and concomitant decreased retinal blood velocity and flow in response to hyperoxic provocation [27].

In a previous Japanese report of 58 patients (116 eyes) with new VKH disease, 27.6% of the eyes had disc swelling. The mean age of these patients was 46.2 years, and the mean age of the patients with disc swelling was higher than that of those without disc swelling (58.9 vs. 41.4 years). Moreover, patients with disc swelling had significantly more underlying systemic vascular disease, such as diabetes mellitus [4]. Interestingly, some of the eyes with disc swelling developed anterior ischaemic optic neuropathy with subsequent optic disc pallor [4]. A previous LSFG study demonstrated decreased MBR-tissue of the ONH, representing blood flow in the deeper regions of the ONH, in eyes with nonarteritic ischaemic optic neuropathy [28]. In the present study, the mean MBR-tissue of the ONH did not differ significantly between eyes affected with swelling of ONH and eyes without swelling of the ONH. These findings suggest that swelling of the ONH in our patients was not associated with ischaemic optic neuropathy. These differences can be attributed to the differences in age and systemic disease association between our patients and Japanese patients. It was suggested that the occurrence of disc swelling is associated with the severity of choroidal inflammation [4]. However, in the present study, choroidal blood flow, reflecting severity of choroidal inflammation [6], did not differ significantly between the two groups.

In conclusion, eyes with swelling of ONH in the acute uveitic phase of VKH disease had a significantly lower retinal blood flow velocity associated with lower oxygen saturation in retinal venules, higher arteriovenous difference in oxygen saturation and narrower calibre of retinal arterioles compared with eyes unaffected with swelling of ONH. Our findings demonstrate changes in retinal vascular physiology and retinal oxygen metabolism that help to explain the pathophysiology of VKH disease.

SUMMARY

What was known before

- Patients with initial-onset acute uveitis associated with VKH disease present with granulomatous choroiditis with secondary exudative retinal detachment with typical ONH hyperaemia.
- Swelling of the ONH is frequently seen in the acute uveitic phase of VKH disease.
- Some patients with ONH swelling develop anterior ischaemic optic neuropathy.

What this study adds

- The occurrence of ONH swelling in the acute uveitic phase of VKH disease is associated with lower retinal blood flow velocity correlating with lower oxygen saturation in retinal venules, higher arteriovenous difference in oxygen saturation and smaller calibre of retinal arterioles.

DATA AVAILABILITY

Data are available from authors upon request.

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AUTHOR CONTRIBUTIONS

AMA was responsible for conceptualisation, designing of methodology, validation of outputs, investigation, providing resources, data curation, writing, review and editing, supervision, project administration and funding. ES was responsible for conceptualisation, designing of methodology, review and editing. AFB was responsible for conceptualisation, designing of methodology, investigation, and data curation. PWG was responsible for designing of methodology, statistical analysis, investigation, data curation and review and editing. AA was responsible for designing of methodology, investigation and review and editing.

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COMPETING INTERESTS

AMA, None; AFA, None; PWG, None; AA, None; ES, Oxymap ehf. (I, S). has financial interests in the retinal oximeter used in the study.

ADDITIONAL INFORMATION

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