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INFLAMMATORY DISORDERS

Analysis of choroidal folds in acute Vogt–Koyanagi–Harada disease using high-penetration optical coherence tomography

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Abstract
Purpose To characterize patients with Vogt–Koyanagi–Harada (VKH) disease with choroidal folds (CFs) and determine how the foveal choroidal thickness changes after initial treatment using high-penetration optical coherence tomography (HP-OCT).
Methods In this retrospective observational study, we analyzed 42 eyes of 21 patients with new-onset VKH disease to determine the demographic and clinical differences between patients with and without CFs.
Results Twenty-four eyes (57.1 %) of 13 patients with VKH disease had CFs. The mean age (p=0.0009) of patients with CFs was significantly higher than that of those without CFs (49.1 vs 39.4 years respectively). The frequency of disc swelling (p=0.0001) was significantly higher in eyes with CFs than in those without CFs (95.8 % vs 38.9 %). The choroidal thickness at the first visit (p=0.0011) was significantly greater in eyes with CFs than in those without CFs (794±144 μm vs 649 ±113 μm). The choroid 6 months after the initial treatment (p=0.0118) was significantly thinner in eyes with CFs than in those without CFs (270±92 μm vs 340±80 μm). The frequency of sunset glow fundus at 6 months (p=0.0334) in eyes with CFs was significantly higher than in those without CFs (62.5 % vs 27.8 %).
Conclusion The development of CFs in patients with VKH disease was significantly correlated with age, disc swelling, and choroidal thickness. The eyes with CFs frequently developed a sunset glow fundus. The findings suggested that patients with CFs might have severe and longstanding inflammation of the choroidal tissues.

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Introduction

Acute Vogt–Koyanagi–Harada (VKH) disease is a multisystem autoimmune disorder that primarily affects the pigmented tissues in the ocular, auditory, integumentary, and central nervous systems [1]. Patients with VKH disease usually have bilateral panuveitis, which in the acute uveitic stage is characterized by the presence of an exudative retinal detachment in the posterior pole [2]. The underlying pathologic process of VKH disease in its early stages is the occurrence of diffuse choroiditis.

Choroidal folds (CFs) are undulations or wrinkles in the retinal pigment epithelium (RPE), Bruch's membrane, and inner choroid, and have been reported in eyes with orbital diseases, choroidal tumors, ocular hypotony, scleritis, papilloedema, and choroidal detachment [3, 4]. CFs also have been observed in acute VKH disease, with incidence rates ranging from 52 to 71 % [5–10]. Zhao et al. [7] and Wu et al. [11] reported that CFs radiated from the optic disc to the periphery, were similar to the large retinal vessels in number and shape, and showed hypofluorescent bands on fluorescein angiography (FA). However, the features and the underlying mechanism of CFs in patients with acute VKH disease are not well understood [5, 7, 8, 11].

Advances in optical coherence tomography (OCT) have provided new insights about ocular structure and disease [12, 13]. OCT is useful for observing the retinal architecture; however, the commercial OCT instruments generally use an 840-nm-band wavelength as a light source, and this results in a low signal from the posterior choroid and sclera. Enhanced

depth imaging OCT (EDI-OCT) is a recently standardized technique for imaging the choroid more clearly using spectral-domain OCT (SD-OCT) [14, 15]. EDI-OCT showed that patients with acute VKH disease have a markedly thickened choroid [16]. However, even though EDI-OCT can enhance the sensitivity of the choroid, light-scattering by the RPE and choroid remains problematic [17]. High-penetration OCT (HP-OCT), which uses a long wavelength (1040–1060 nm), allows deeper penetration through the retinal and choroidal layers and better visualization of the posterior tissue [18], which enables observation of choroidal pathologies. We previously used HP-OCT to report that the choroidal thickness in acute VKH disease exceeded 800 μm, and that it decreased after corticosteroid treatment [19].

The purpose of the current study was to characterize patients with VKH disease with and without CFs, and investigate the association between the choroidal thickness and CFs.

Materials and methods

We retrospectively reviewed 42 eyes of 21 consecutive patients with new-onset VKH disease who visited Osaka University Hospital from December 2009 to March 2013. The research adhered to the tenets of the Declaration of Helsinki. VKH disease was diagnosed according to the revised criteria of the International Committee on VKH Disease [20]. All patients were treated with high-dose corticosteroid therapy followed by slow tapering of the drug over a 5- to 6-month period. The patients were followed for at least 6 months (median follow-up, 16 months; range, 6–40 months). All patients underwent complete ophthalmologic examinations including measurement of the best-corrected visual acuities (BCVAs) and intraocular pressure (IOP) at the 1- and 6-month visits, ophthalmoscopy, FA, indocyanine green angiography (ICGA), SD-OCT using the Cirrus high-definition OCT model 4000 (Carl Zeiss Meditec, Dublin, CA, USA), and Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). The height of the subretinal fluid (SRF) at the fovea was measured from the tip of the RPE layer to the outer border of the detached retina at the fovea using the software in the SD-OCT machine. If there was a hyporeflective layer corresponding to a fibrinous membrane inside the exudative retinal detachment covering the inner face of the RPE or outer face of the retina, it was included in the SRF thickness measurement [21]. CFs were defined as hypofluorescent bands on FA and undulations of the RPE on OCT images (Fig. 1). The CFs radiating from the optic disc were observed easily on the OCT circular scan image around the optic disc (Fig. 2). HP-OCT (Topcon Corporation, Tokyo, Japan) was performed to measure the choroidal thickness at the fovea from the acute stage to the remission of VKH disease in response to treatment. The profile of this machine has been described previously [22]. The macular region was scanned using one 12-mm linear scan centered at the fovea. The choroidal thickness at the fovea was defined as the vertical distance from the RPE line to the hyperreflective line behind the large vessel layers of the choroid, presumed to be the choroidal–scleral interface (Fig. 2) [19]. The choroidal thicknesses were measured manually at the fovea using a software caliper built into the OCT image viewer [23]. When the line was blurred, we defined the choroidal thickness as 800 μm, which was the upper limit stably measured by HP-OCT [19]. The BCVAs measured on decimal charts were converted to the logarithm of the minimum angle of resolution for statistical analysis. The institutional review board of Osaka University Hospital approved the use of HP-OCT.

Statistical analyses of continuous variables were performed using the Student's *t*-test or Wilcoxon rank-sum test as appropriate. The categorical variables were compared using either the chi-square test or Fisher's exact test as appropriate. $P<0.05$ was considered significant. To verify the factors that contribute significantly to development of CFs in patients with VKH disease by excluding possible cross-effects among the variables, multivariate logistic regression analysis was performed with the factors, which showed a significant difference in the univariate analysis as independent variables. Analyses were conducted using JMP statistical software 10.0 (SAS Institute Inc., Cary, NC, USA).

Results

Forty-two eyes of 21 consecutive Japanese patients (eight men, 13 women) with acute VKH disease were included. The median patient age was 45.0 years (range, 31–64 years). FA and OCT examinations detected CFs in 24 (57.1 %) eyes of 13 patients; 11 patients had CFs in both eyes, and two patients had CFs in one eye. The CFs usually radiated from the optic disc to the periphery, and the number and direction differed depending on the case. The demographic and clinical information of the patients with and without CFs are shown in Table 1. The male-to-female ratio, BCVAs, and IOPs at the 1- and 6-month visits; SRF height; and the presence of SRF, pinpoint leakage, septae, and filling patch delay did not differ significantly between eyes with and without CFs ($p>0.05$ for all comparisons). The patients with CFs were significantly ($p=0.0009$) older than those without CFs (49.1±8.6 vs 39.4 ±4.9, respectively). Disc swelling occurred significantly ($p<0.0001$) more often in eyes with CFs than in those without CFs (95.8 % vs 38.9 %). The frequency of a sunset glow fundus at 6 months was significantly ($p=0.0334$) higher in eyes with CFs than in those without CFs (62.5 % vs 27.8 %).

The changes in the choroidal thickness are shown in Fig. 3. The choroid at the first visit was significantly ($p=0.0011$)

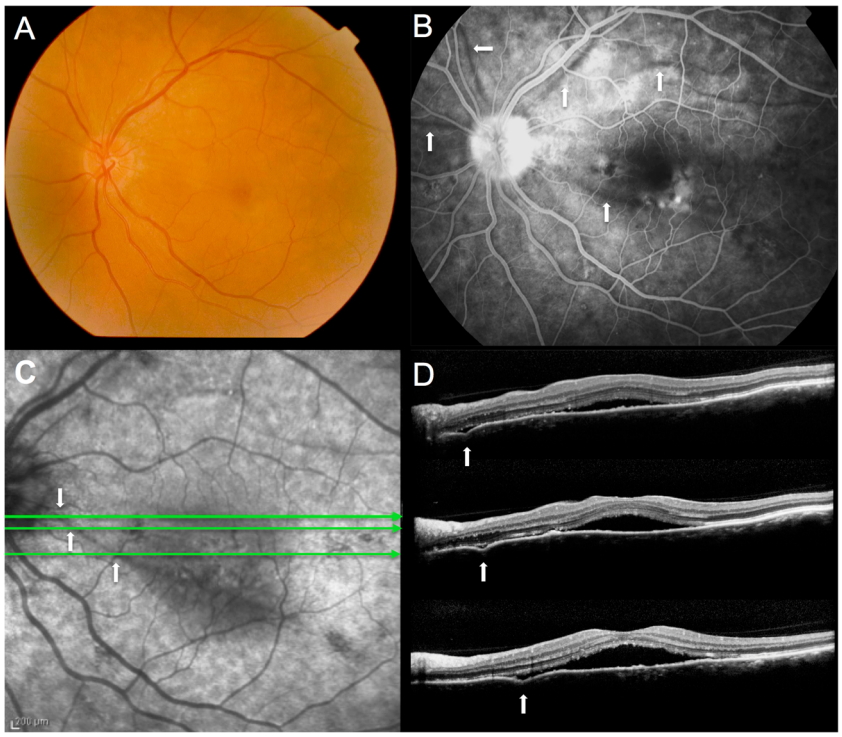

Fig. 1 Choroidal folds (CFs) in patients with Vogt–Koyanagi–Harada disease. **a** A fundus photograph of the left eye shows subretinal fluid and papilloedema. **b** A fundus fluorescein angiogram shows multiple *hypofluorescent lines* radiating from the optic disc to the periphery (*arrows*). **c** A Heidelberg Spectralis optical coherence tomography (Spectralis OCT) image of the fundus shows the placement of the OCT scan lines (*green lines*). The *arrows* indicate points of intersection with the CFs. **d** The three Spectralis OCT images correspond to the *green lines*. The *arrows* show undulations of the retinal pigment epithelium that correspond to the CFs in (**c**)

thicker in eyes with CFs than in those without CFs (794±144 μm vs 649±113 μm). One week after the start of treatment, the choroidal thicknesses did not differ significantly (p=0.7219) between the two groups (424±171 μm vs 445±133 μm), and the CFs resolved in all eyes. The choroidal thicknesses 1 and 3 months after the initial treatment did not differ significantly between the two groups (346±103 μm vs 383±95 μm, p=0.1820, and 342±196 μm vs 344±77 μm, p=0.3215 respectively). However, 6 months after the initial treatment the choroids were significantly (p=0.0118) thinner in eyes with CFs than in those without CFs (270±92 μm vs 340±80 μm).

Multivariate logistic regression analysis was performed with the CFs as the dependent variable, and factors with a $p<0.05$ in a comparison between patients with VKH disease with and without CFs as the independent variables, which included the patient age and disc swelling (Table 2). The analysis showed that age and disc swelling were significant factors (p=0.0028 and p=0.0263 respectively), even after the possible cross-effects among the independent variables were excluded.

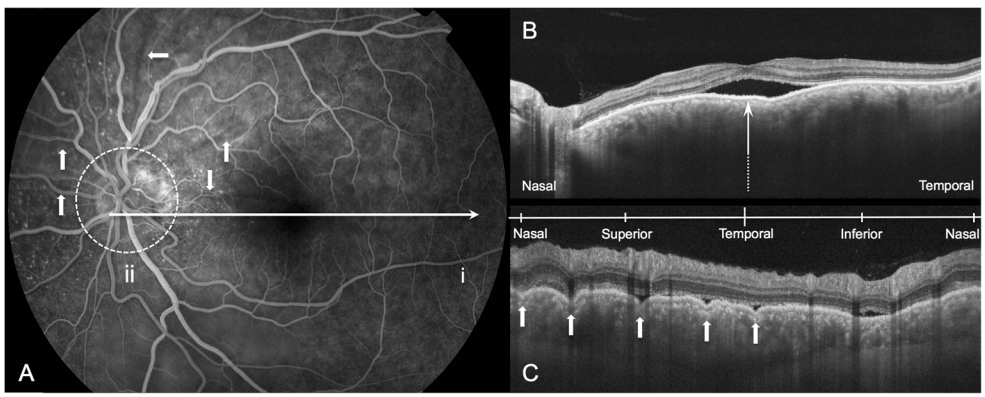

Fig. 2 Analysis of choroidal thickness and choroidal folds (CFs). **a** The location of the scans used. The macular scan (*solid line marked i*) is 12 mm long and centered on the fovea. The peripapillary scan (*dotted circle marked ii*) is performed along a circle 3.4 mm in diameter centered on the optic disc. The *arrows* indicate hypofluorescent bands radiating from the optic disc. **b** A high-penetration optical coherence tomography scan of the macula. The choroidal thickness at the fovea is defined as the *vertical* distance from the retinal pigment *epithelium line* to the *hyperreflective line* behind the large vessel layers of the choroid, presumed to be the choroidal-scleral interface at the fovea (*arrow*). The retinal and choroidal thicknesses are measured manually at the fovea using the scale included in the software. **c** A scan of the peripapillary region scan in which the circular area is arrayed linearly, with the horizontal meridian at the *dotted line* and superior to the *left* and inferior to the *right*. The *arrows* indicate CFs

Table 1 Demographics and ocular findings of patients with Vogt–Koyanagi–Harada disease with and without choroidal folds

Characteristic	VKH with CFs (n=24)	VKH without CFs (n=18)	P value
Age (years)	49.1±8.6	39.4±4.9	0.0009
Men/women	10/14	6/12	0.7501
Initial visual acuity (logMAR)	0.24±0.36	0.23±0.36	0.8579
Initial IOP (mmHg)	15.2±3.9	15.3±3.4	0.7110
Disc swelling	23 (95.8 %)	7 (38.9 %)	<0.0001
Subretinal fluid	22 (91.6 %)	14 (77.8 %)	0.3752
Subretinal fluid height (μm)	402±444	527±534	0.5747
Pinpoint leakage	19 (79.2 %)	14 (77.8 %)	1.0000
Septae	10 (41.7 %)	10 (55.6 %)	0.5335
Filling patch delay	20 (83.3 %)	15 (83.3 %)	1.0000
6-month visual acuity (logMAR)	−0.10±0.09	−0.13±0.07	0.1443
6 months IOP (mmHg)	16.3±0.66	14.8±2.26	0.1641
Sunset glow fundus at 6 months	15 (62.5 %)	5 (27.8 %)	0.0334

Data are expressed as the means ± standard deviation for continuous variables and as the number (%) for categorical variables. *VKH* Vogt–Koyanagi–Harada disease, *IOP* intraocular pressure, *logMAR* logarithm of the minimum angle of resolution, *CFs* choroidal folds

Discussion

In the current study, CFs were detected at baseline in more than half of eyes with VKH disease. Detailed analyses indicated that CFs occurred more frequently in older patients with VKH disease and disc swelling. Eyes with CFs had a thicker choroid at baseline, which became thinner after treatment compared with those without CFs. The results may indicate that CFs occur in eyes with severe and longstanding inflammation of the choroidal tissues.

The CFs probably developed as a result of compression of Bruch's membrane and RPE when the choroidal thickness increased to a certain degree, which results in CFs developing much more frequently in eyes with a thicker choroid. However, we observed that the choroidal tissue was thinner at 6 months in eyes with CFs than in those without CFs. In addition, the frequency of a sunset glow fundus at the 6-month evaluation was significantly higher in eyes with CFs than in those without CFs. These results agreed with previous studies that have reported that the choroidal tissue thinned in eyes with a sunset glow fundus [19, 24]; and a sunset glow fundus develops primarily in patients with longstanding uveitis [24, 25]. Patients with VKH disease with CFs may have a longer disease duration than those without CFs, which is similar to a study that reported that patients with CFs had a longer disease duration at the first visit than those without CFs [7].

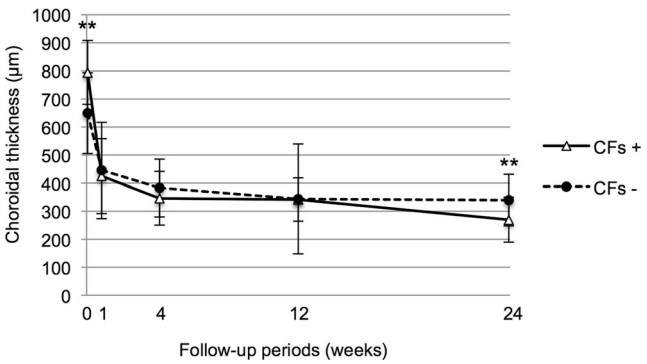

Fig. 3 Changes in mean choroidal thickness measured by high-penetration optical coherence tomography in patients with Vogt–Koyanagi–Harada disease with and without choroidal folds (CFs) during the follow-up period. The *cpr* indicate the standard deviations. The *double asterisks* indicate that the choroidal thickness in eyes with CFs differ significantly (p<0.05) from those without CFs

The patients with CFs were significantly older than those without CFs, and had disc swelling more often than those without CFs. Previous studies have also reported that disc swelling developed frequently in older patients with VKH disease, and hypothesized that the disc swelling may result from mechanical compression of the choroidal tissue and optic nerve [26, 27]. Choroidal thickening also caused CFs by mechanical compression as mentioned previously, so these patients may have disc swelling. Considering previous studies and the current results, older patients with VKH disease had a thicker choroid at the first visit compared with younger patients with VKH disease. As a result, CFs and disc swelling were observed frequently in older patients with VKH disease; however, the reason why they tended to have a thickening choroid at the first visit is unknown.

Bilateral SRF is a typical ocular finding in patients with acute VKH disease [2, 20]. In contrast, VKH disease rarely presents with optic disc swelling or CFs without SRF. We hypothesized that these episodes may occur because patients without visual loss do not present to a hospital. Shinoda et al. [8] reported that the CFs appear before SRF appears, and Nazari and Rao [21] found that the heights of SRF were correlated with VA. Considering these factors, we speculated that most patients with CFs do not visit a hospital until SRF develops; therefore, the disease duration at the first visit was longer in patients with CFs, and patients with VKH disease with CFs without SRF are rare.

Table 2 Multivariate analysis for the presence of choroidal folds

	No CFs vs CFs		
	OR	95 % CI	*P* value
Age	1.55	1.17–2.67	0.0028
Disc swelling	60.16	6.15–1706.01	0.0263

CFs choroidal folds, *OR* odds ratio, *CI* confidence interval

The current results shed some light on the mechanisms and features of CFs in acute VKH disease. Kato et al. [9] reported that detection of CFs is an effective method for diagnosing acute VKH disease. The current findings indicated that CFs result from choroidal thickening, which is a hallmark of acute VKH disease. Therefore, detecting CFs is helpful for diagnosing VKH disease, especially in patients with VKH disease without SRF. In addition, patients with VKH disease with CFs may have a longer disease duration and frequently a sunset glow fundus, so that these patients require more cautious observation and treatment.

Recently, OCT has proven to be an effective tool for evaluating choroidal thickness and choroidal changes in pathological states in VKH disease. However, ICGA also has proven to be useful to investigate choroidal disorders. Herbort et al. reported residual hypofluorescent dark dots on ICGA even after SRF resolved, and considered that there might be silent inflammatory activity in a high percentage of patients with VKH disease despite use of high-dose immunosuppressive agents [28]. Therefore, several studies have reported that using ICGA to evaluate inflammatory activity helps to detect subclinical choroiditis in VKH disease, and may avoid sunset glow fundus by allowing precise adjustment of therapy [28, 29]. In contrast, Knecht et al. reported that in some cases hypofluorescent dark dots on ICGA do not represent active lesions but presumed intrastromal scarring [30]. Considering these factors, choroidal inflammatory activity is difficult to evaluate by ICGA only. As a result, we believe that multimodal imaging including HP-OCT is important in the modern management of VKH disease.

The limitations of the current study were its retrospective nature and the limited number of patients. In addition, the reason why older patients with VKH disease frequently have CFs is unknown. Further prospective studies with more patients are needed to validate the current observations.

In conclusion, CFs indicate a thickened choroid, and patients with CFs may have longstanding inflammation. These findings may provide additional knowledge to guide the diagnosis and treatment of patients with acute VKH disease.

Conflict of interest None.

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