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Automatic Measurement of Choroidal Thickness with Swept-Source Optical Coherence Tomography for Clinical Follow-Up in Acute Vogt-Koyanagi-Harada Disease

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Abstract

Background: The course of acute Vogt-Koyanagi-Harada is typically assessed qualitatively using indocyanine green angiography. Swept-source optical coherence tomography may provide a safer, non-invasive, more objective approach to follow up. In this study, we assess the clinical value of the automated measurement capabilities of swept-source tomography to measure choroidal thickness.

Design: Prospective, longitudinal case-control study at a tertiary university hospital.

Participants: Nine patients with acute Vogt-Koyanagi-Harada disease (18 eyes) and 17 age-matched controls (34 eyes).

Methods: Choroidal thickness (subfoveal area and ETDRS grid) was automatically measured with swept-source optical coherence tomography. Changes in thickness were compared to changes in visual acuity and indocyanine green angiography findings to check for correlations.

Main outcome measures: Changes in choroidal thickness (micrometers- μm) from baseline. Secondary measures included visual acuity and angiography.

Results: At baseline, patients presented significantly greater mean (SD) subfoveal choroidal thickness (666.9 μm [258.3] *vs.* 302.3 [71.4]) and ETDRS grid choroidal thickness (648.7 μm [260.5] *vs.* 287.5 [69.3]) than controls (p=0.000). Choroidal thinning and improved vision were associated with treatment while increasing thickness and worsening vision were associated with posterior relapse. In 62.5% of recurrences in tomography, no changes in visual acuity were present; however, all recurrences diagnosed with tomography showed signs of inflammation on angiography.

Conclusions: Automatic measurement of choroidal thickness with swept-source optical coherence tomography is a rapid, non-invasive manner of detecting posterior segment recurrences and treatment response in acute Harada patients. Swept-source tomography could reduce the need for angiography to monitor patients with Harada disease.

Keywords: Choroidal thickness; Swept-source optical coherence tomography; Acute Vogt-Koyanagi-Harada.

Introduction

Vogt-Koyanagi-Harada (VKH) syndrome is a bilateral granulomatous uveitis that typically presents with distinct clinical features based on the duration and stage of the disease [1,2]. The acute stage of VKH is characterized by diffuse choroiditis, multifocal areas of subretinal fluid and/or bullous serous retinal detachments, with or without neurologic (headaches, meningismus) or auditory (tinnitus, hypoacusia) symptoms. The convalescent stage of the disease develops 12 weeks after onset and is characterized by resolution of retinal detachments with disappearance of cells from the anterior chamber and the vitreous, with characteristic pigmentary changes in the macula and sunset glow fundus. The chronic/recurrent phase is characterized by clinical signs of disease activity in the anterior segment of the eye with anterior granulomatous uveitis and dermatologic signs (vitiligo, alopecia, poliosis).

Choroidal activity is usually evaluated with indocyanine green angiography (ICGA). Herbort et al. systematized the ICGA findings for follow-up, identifying 4 signs: hypofluorescent dark dots (the most important sign, present in the acute and convalescent stage, indicating stromal granulomas), hyperfluorescent choroidal vessels, fuzzy indistinct large choroidal vessels, and disc hyperfluorescence [3]. An important advantage of ICGA is that it can detect choroidal inflammation even when no clinical signs are present; for this reason, ICGA is recommended to diagnose occult choroidal recurrences [3]. Despite the benefits of ICGA-considered the gold standard for the diagnosis of posterior recurrence-this imaging modality presents several important drawbacks. ICGA is an invasive, time-consuming procedure requiring contrast injection. In addition, the results are qualitative (i.e., subjective) rather than quantitative, and thus it is not

possible to quantify the degree of inflammation. Moreover, the most important sign of inflammation-hypofluorescent spots-are also commonly observed in choroidal atrophy, making it harder to judge the persistence or recurrence of choroidal inflammation.

The relatively recent development of enhanced-depth imaging optical coherence tomography (EDI-OCT), based on spectral-domain OCT, has enabled in vivo evaluation of the choroid, providing high-definition cross-sectional images [4,5]. Numerous studies have used EDI-OCT to assess choroidal thickness in both normal and pathologic eyes [6-10]. However, because EDI-OCT is unable to detect the choroid-scleral interface in many cases (from 4-26% of eyes), choroidal margins must be manually identified-a highly cumbersome and subjective (due to inter-observer differences) process. For all these reasons, automatic segmentation of the choroid layer would be preferable [11-13]. The recent development of swept-source optical coherence tomography (SS-OCT) may offer an alternative approach to segmentation without the drawbacks of manual labeling. SS-OCT uses a 1 μm band light source that allows for deeper penetration into the retinochoroidal structures, providing increased resolution. SS-OCT is able to simultaneously display a focused image of both the retina and choroid, thus providing better visualization of retinal and choroidal changes, especially of the choroid-scleral interface, thus making it a reliable tool for measuring choroidal thickness [14,15].

Due to time and staffing constraints, manual measurements are typically impractical in daily clinical practice [16-21]. For this reason, we use SS-OCT at our centre to automatically measure choroidal thickness. Despite the advantages of automatic segmentation with SS-OCT, to our knowledge, this technique has not been previously used to prospectively monitor the course of disease in patients with acute VKH.

In the present case-control study, we prospectively assessed a series of 9 patients diagnosed with VKH. We used SS-OCT to measure choroidal thickness at baseline and at various time points over the 2-year follow-up. Changes in choroidal thickness were compared to changes in visual acuity (VA), ICGA findings, and clinical symptoms to check for significant associations between these variables.

Methods

We prospectively recruited nine patients with acute VKH and 17 age-matched healthy controls. Inclusion criteria for the VKH patients included an established diagnosis of VKH at our institution according to the revised diagnostic criteria for VKH disease [16]. Exclusion criteria (both cases and controls) included any history of ocular disease or surgery, myopia or hypermetropia greater than ± 3 diopters [9,17,22,23], or any history of systemic disease (other than VKH) with ocular involvement.

Demographic characteristic were recorded before the clinical ophthalmic examination and OCT image acquisition. A complete ophthalmic examination was performed including best-corrected visual acuity (BCVA) using decimal fractions and Snellen equivalent in feet.

Written informed consent was obtained from all subjects in accordance with our institutional guidelines. This study adhered to the tenets of the Declaration of Helsinki. Institutional Review Board/Ethics Committee approval was obtained from the local Research Ethics Committee (CEIC of University Hospital of Bellvitge), reference number PR204/14.

ICGA was used to check for signs of choroidal inflammation and was performed when signs of anterior or posterior recurrence were present, or when an increase of choroidal thickness was detected on the SS-OCT with a simultaneous decrease in VA, or when the increase was ≥ 50 μm without changes in VA. Based on the standard deviation (SD) of measures of choroidal thickness reported in other studies [18-21], we performed ICGA in all patients who presented an asymptomatic increase of thickness ≥ 50 μm in order to check for signs of inflammation, a finding that would confirm that the increased choroidal thickness was due to relapse.

SS-OCT image acquisition protocol

We scanned the macular area of both the affected and healthy eyes with SS-OCT (Atlantis DRI OCT-1, Topcon, Japan) at a 1,050-nm wavelength and scanning speed of 100,000 A-scans/second using a high-definition set of twelve radial cuts of 12.0 mm each, horizontal scans, and a cube raster scan protocol (12.0 × 9.0 mm). Retinal foveal and choroidal thicknesses were measured automatically. Two choroidal areas were analyzed: the subfoveal choroidal thickness (SFCT) and the area of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid centred on the fovea (Figure 1). The SFCT and the mean of the 9 measures of the choroidal thickness of the grid (mean grid choroidal thickness: MGCT) were used as reference measures. The SS-OCT 3D scan produces a 12 × 9 mm retinal and choroidal thickness map of the macular area after automated segmentation of the retina and the choroid. The retinal and choroidal thickness maps were overlapped with the modified ETDRS grid (6 × 6 mm), thus obtaining automated measures of SFCT and MGCT. These measures were then compared with SFCT and MGCT measures obtained with SS-OCT in healthy age-matched controls both manually and automatically through the same SS-OCT protocols (Table 2).

The number of follow-up consultations in VKH patients was individualized according to need. Based on previous experience [9,17,21,22] with EDI-OCT imaging, which suggests that the choroid could change in high myopia or hypermetropia, and that blood pressure could have diurnal variations, we excluded patients with refractive errors ≥ 3 diopters. In addition, blood pressure was measured at each consultation prior to examination to assure that it was within an acceptable range. Finally, all examinations were performed in the morning to assure consistency.

Definition of relapse

Changes in choroidal thickness were classified as a posterior recurrence when these changes were associated with diminished VA (excluding other causes) and/or with signs of inflammation on ICGA.

Statistical analysis

A descriptive analysis was performed. Measures of the central value (mean and median) and dispersion (SD, interquartile range [IQR]) were determined. For quantitative variables, the Student t test or the Mann-Whitney U test was used, as appropriate, to compare means. All statistical tests were two-tailed, and P values of <0.05 were deemed significant. All analyses were performed using Minitab 17.3.1 software (Minitab, Inc. State College, Pennsylvania, USA).

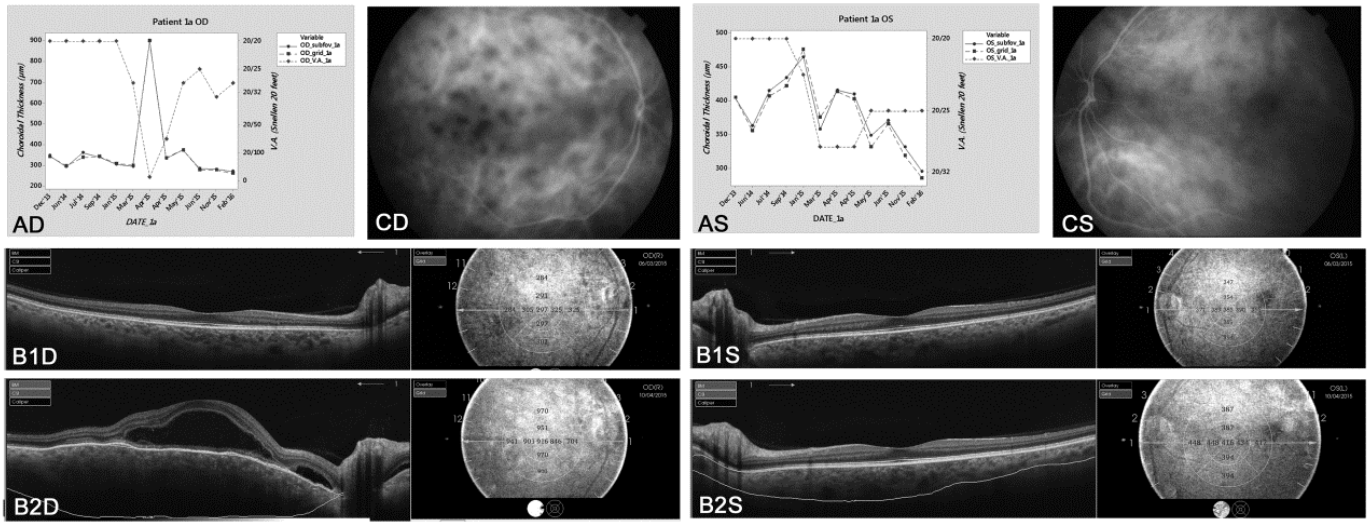

Figure 1: A: Subfoveal choroidal thickness (SFCT) and grid choroidal thickness in micrometers (μm) and Snellen visual acuity (VA) of patient 1 throughout the study (AD right eye, AS left eye) from December 2013 to February 2016. Both eyes had a total of 5 posterior recurrences, 3 of which were asymptomatic without loss of VA. At study completion, a normalization of choroidal thickness was seen (272 μm OD, 296 μm OS). **B:** SS-OCT images with choroidal thickness in μm. B1: SS-OCT in March 2015, B1D right eye and B1S left eye: SFCT, 297 μm in right eye and 385 μm in left eye. B2: SS-OCT in April 2015, B2D right eye and B2S left eye: right eye with increased SFCT (916 μm) and multifocal serous retinal detachments and left eye with increased SFCT (416 μm) but no retinal anomalies. Bilateral relapse diagnosed with SS-OCT images. **C:** Indocyanine green angiography of right eye (CD) and left eye (CS) in April 2015: characteristic hypopigmented spots which confirmed choroidal inflammation in both eyes (more in the right eye, with a greater choroidal thickness on SS-OCT).

	Age	Sex	Clinical presentation		Days until diagnosis	VKH type	Treatment
			Onset	Study end			
1	55	F	Papillitis OU, RDs OS	No fundus changes	14	I	PDN + Sarilumab
2	53	F	Panuveitis, Papillitis, and RDs OU	Macular RPE hyperplasia OU	7	U	PDN + MM
3	15	M	RDs OU, galea capitis hyperesthesia	Macular RPE hyperplasia OU	15	I	PDN + MM
4	37	F	Papilledema and RDs OU	Macular RPE hyperplasia OU, PPA OU	7	I	PDN
5	40	M	Papilledema and RDs OU	Macular RPE hyperplasia OU, Dalen-fuchs OS	21	C	PDN
6	49	M	Panuveitis & RDs OU, Meningism, galea capitis hyperesthesia	Macular RPE hyperplasia and Sunset-glow OU, PPA OD	21	I	PDN
7	21	M	Papilledema and RDs OU	No fundus changes	3	C	PDN
8	39	M	Papilledema and RDs OU Meningism hypoacusia	No fundus changes	1	I	PDN
9	55	M	Panuveitis RDs & Papilledema OU	No fundus changes	3	C	PDN

F: Female; M: Male; OU: Both Eyes; RDs: Multiple Retinal Detachments; OS: Left Eye; RPE: Retinal Pigment Epithelium; PPA: Peripapillary Atrophy; OD: Right Eye; VKH: Vogt-Koyanagi-Harada type: I: Incomplete; U: Uveo-Meningeal; C: Complete; PDN: Prednisone; MM: Mycophenolate Mofetil

Table 1: Demographic and clinical data of studied patients with Vogt-Koyanagi-Harada.

Results

We prospectively recruited 9 patients (3 women and 6 men) with acute VKH (18 eyes) and 17 age-matched healthy controls (34 eyes). All subjects were followed for up to 2 years (range, 6 to 24 months; mean, 12.5 months). Follow up in the patient group was as follows: <1 year (four patients), 1 year (two patients), and two years (three patients).

At baseline, the median decimal VA in the VKH group was 0.75 (IQR, 0.2-0.9) [Snellen equivalent, 20/32 (IQR, 20/100-20/20)] versus 1 (IQR, 0.8-1) [Snellen equivalent 20/20 (IQR20/25-20/20)] at study end (p=0.026).The median VA in the control group was 1 (Snellen equivalent, 20/20) (Table 2). Initial VA was ≥ 0.63 (20/32) in 12 eyes (66.7%), ≤ 0.4 (20/50) in 6 eyes (33.3%), and 1 (20/20) in 3 eyes (see annex).

All VKH patients presented with headaches and blurred vision in addition to other common clinical features of the disease (Table 1). Median age was 40 years (range, 37-53) (Table 1). The control group consisted of 10 women (59%) and 7 men (41%), with a median age of 49 (range, 24-76 years). There were no significant differences between age in the two groups at baseline (p=0.328). Overall analysis of the study variables are shown in Table 2.

At baseline, the median retinal foveal thickness in the control group was 227.1 µm (IQR, 156.1-298.1) versus 290.5µm (IQR, 226.8-475.3) in the VKH group (p=0.000). By study end, the median thickness in the treatment group was 248.5 µm (IQR, 236.8-287.8), a significant change (p=0.038) from baseline (Table 2).

Variables	Healthy controls (n=34)	VKH (baseline) (n=18)	p-value* (controls *vs.* VKH baseline)	VKH (studyend) (n=18)	p-value* (controls *vs.* VKH study end)
Visual acuity					
Mean (SD)	1.0 (0.0)	0.61 (0.36)	p=0.000	0.88(0.2)	p=0.026
Median (Q1-Q3)	0.9 (0.7 - 1.0)	0.75 (0.2 - 0.9)		1.0 (0.8 - 1.0)	
RFT					
Mean (SD)	225 (71)	427 (314)	p=0.000	260 (36)	p=0.038
Median (Q1-Q3)	227 (156-298)	290 (227 - 475)		248 (237 - 288)	
SFCT					
Mean (SD)	302 (71)	667 (258)	p=0.000	328 (104)	p=0.371
Median(Q1-Q3)	315 (240 - 350)	607 (420- 1000)		317 (254 - 438)	
MGCT					
Mean (SD)	287 (69)	649 (260)	p=0.000	305 (95)	p=0.392
Median(Q1-Q3)	299 (232 - 341)	587 (414- 972)		297 (249 - 386)	

VKH: Vogt-Koyanagi-Harada; MGCT: Mean Grid Choroidal Thickness; SFCT: Subfoveal Choroidal Thickness; RFT: Retinal Foveal Thickness; SD: Standard Deviation; Q1-Q3: Quartile 1 and Quartile 3, *Mann-Whitney's U Test

Table 2: Study variables: Vogt-Koyanagi-Harada patients versus controls: at baseline and study end.

At baseline, the median SFCT in controls was 315.5 µm (IQR, 240.5-350.5) versus 607.5 µm (IQR, 420-1000) in patients (p=0.000). At study completion, the median SFCT in patients was 317.5 µm (IQR, 254-438.3) (p=0.371). Median MGCT in controls was 298.9 µm (IQR 232-341.1) at baseline versus 587 µm (IQR, 414-972.3) (p=0.000) in the patient group. At study end, the median MGCT in patients had decreased to 297.5 µm (IQR, 249-386.5), a non-significant decrease (p=0.392) (Table 2).

There were no statistically significant differences between the MGCT and the SFCT values in the study group (p=0.9114). Given that the SFCT is measured in the area of maximum vision, and that previously-reported studies have used this measure, we elected to use the SFCT as the reference value to monitor choroidal thickness during follow up.

Relapses

A total of 16 recurrences (increased choroidal thickness with or without loss of VA) were observed during the 2-year follow up period. In all cases, choroidal thickness was measured automatically by SS-OCT. All recurrences were confirmed by ICGA (signs of inflammation) (Table 3). In 6 cases (37.5%), the relapse was accompanied by a worsening VA and in 10 eyes presented with an unchanged vision (62.5%); consequently, 62.5% of recurrences were diagnosed based on the SS-OCT findings.

	VA Pre-Relapse	VA at Relapse	Decrease in vision	SFCT (µm) Pre-Relapse	SFCT (µm) at Relapse	Increase in Thickness	Months since diagnosis	Years at study end
P1 1R OD	1	1	no	296	363	67	7	2
P1 2R OS	1	1	no	363	415	52	7	2
P1 3R OS	1	0.9	yes	434	465	31	16	2
P1 4R OD	0.7	0.025	yes	297	900	603	17	2
P1 5R OS	0.7	0.7	no	358	416	58	17	2
P2 6R OS	1	1	no	284	478	192	5	2
P2 7R OD	1	1	no	317	562	245	5	2
P3 8R OD	0.9	0.9	no	505	680	175	4	2
P3 9R OS	0.9	0.9	no	417	478	61	4	2
P5 10R OS	1	0.8	yes	340	1000	660	1	1
P5 11R OD	1	1	no	339	401	62	11	1
P5 12R OS	1	1	no	392	485	91	11	1
P6 13R OS	1	1	no	346	534	188	6	1
P6 14R OD	0.75	0.4	yes	383	438	55	8	1
P6 15R OD	1	0.4	yes	388	468	80	11	1
P6 16R OS	1	0,25	yes	382	438	56	11	1

P: Patient; R: Relapse; OD: Right Eye; OS: Left Eye; VA: Visual Acuity (decimal); SFCT: Subfoveal Choroidal Thickness; µm: Micrometers.

Table 3: Analysis of relapses: best corrected visual acuity and subfoveal choroidal thickness prior to and at relapse. Number of months at relapse since diagnosis of the illness, and years of follow-up at the end of the study.

	Decimal Visual Acuity		Baseline SFCT OD/OS (µm)	Study end SFCT OD/OS (µm)	Normal thickness (220-360 µm)
	Baseline OD/OS	Study end OD/OS			
1	1/1	0.7/0.8	349/405	272/296	Yes OU
2	0.2/0.4	1/1	426/425	239/228	Yes OU
3	0.6/0.8	1/1	≥ 1000 OU	259/284	Yes OU
4	0.6/0.8	1/1	918/790	357/457	Yes OD thicker OS
5	1/0.7	1/1	≥ 1000 OU	339/392	Yes OD Thicker OS
6	0.05/0.05	0.8/1	≥ 1000 OU	448/435	Thicker OU
7	0.2/0.025	0.9/0.7	397/524	276/364	Yes OU
8	0.8/0.9	0.8/0.2	590/605	481/488	Thicker OU
9	0.9/0.9	1/1	610/625	141/170	Thinner OU

OD: Right Eye; OS: Left Eye; SFCT: Subfoveal Choroidal Thickness; µm: Micrometers; OU: Both Eyes

Table 4: Visual acuity and subfoveal choroidal thickness at baseline and study end in acute Vogt-Koyanagi-Harada (VKH) patients. Choroidal thickness of VKH patients at the end of the study compared with controls (normal, thicker or thinner).

The minimum increase in SFCT associated with loss of VA was 31 μm (the maximum was 660 μm). In patients with a recurrence, the mean increase in SFCT was 167.25 μm. Interestingly, loss of VA was not directly correlated with the amount of increase in SFCT: for example, one patient experienced an increase of 660 μm in SFCT but only a 20% decrease in VA (from 1 to 0.8), whereas another patient had an increase of 31 μm that resulted in a 10% decrease in VA (from 1 to 0.9). Relapses occurred as soon as 1 month after disease onset to as late as 17 months after onset. The mean time to relapse was 8.81 months from onset.

At study completion, no recurrences were observed in patients with <1 year from diagnosis. VA and SFCT at baseline and at study completion (Table 4).

Baseline VA was ≥ 0.63 (20/32) in 12 eyes (66.7%), ≤ 0.4 (20/50) in 6 eyes (33.3%); notably, of the 12 eyes with ≥ 0.63 VA, 3 had a baseline VA of 1 (20/20) (Table 4). Thus, 14 eyes experienced an improvement in vision at study completion while vision remained unchanged (maximum vision) in 2 eyes, and 2 eyes experienced a decrease in vision (from VA 1 at baseline to 0.7-0.8) at final follow up.

Using the choroidal thickness of the control group (220-360 μm) as a reference value, 17 eyes in the VKH group presented choroidal thickening at baseline. By study end, 10 eyes had recovered normal choroidal thickness, 6 showed a slight thickening, and 2 showed a notable thinning but without affecting VA (Table 4).

Individualized follow up analysis of each patient (see figure legends and tables): patient 1 (Figure 1), patient 2 (Figure 2), patient 3 (Figure 3), patient 5 (Figure 4), patient 6 (Figure 5), patient 4, 7, 8 and 9 (Table 4).

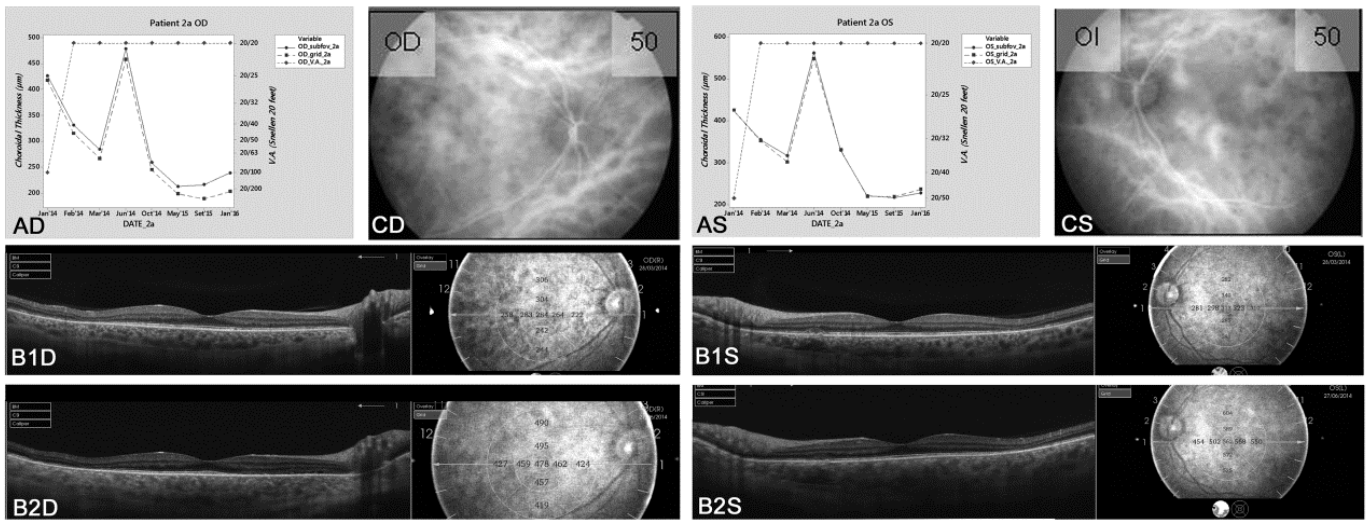

Figure 2: A: Subfoveal choroidal thickness (SFCT) and grid choroidal thickness in micrometers (μm) and Snellen visual acuity (VA) of patient 2 throughout the study (AD right eye, AS left eye) from January 2014 to January 2016. There was an asymptomatic posterior recurrence diagnosed by SS-OCT in March 2014; no other signs of inflammation in the eye were observed but the relapse was confirmed with ICGA. At study completion, choroidal thickness and VA were normal (239 μm right eye, 228 μm left eye). **B:** SS-OCT images with choroidal thickness in μm. Right eye (B1D) and left eye (B1S) in February 2014. Choroidal thickness was normal (<320 μm) in both eyes without retinal anomalies. B2:.SS-OCT March 2014 with increased SFCT: 478 μm in right eye (B2D) and 562 μm in left eye (B2S), no retinal lesions. **C:** Indocyanine green angiography of right eye (CD) and left eye (CS) , March 2014 where inflammation was confirmed (hypopigmented spots and hyperfluorescence of choroidal vessels).

Discussion

Given the drawbacks of ICGA and EDI-OCT, it would be useful to have an alternative approach to assessing the course of VKH disease. In our center, we have been using the automated measurement feature of SS-OCT for the past several years to measure choroidal thickness in patients with VHK. SS-OCT offers a rapid, non- invasive, and objective method of detecting posterior segment recurrences and treatment response. The main aim of our study was to determine the clinical value of measuring choroidal thickness with the automatic segmentation capabilities of SS-OCT. Consistent with previous reports [7,8,18,19,23-26], we found that patients with VKH had significantly thicker SFCT (666.9 μm) than healthy controls (302.3 μm). During follow up, increasing choroidal thickness and worsening VA were associated with posterior relapse. Importantly, in nearly two-thirds (62.5%) of eyes in which relapse was diagnosed by SS-OCT, no changes in VA were present. By contrast, all relapsed eyes showed signs of inflammation on ICGA. These findings suggest that SS-OCT may be a valuable adjunct to ICGA to rapidly, objectively, and non-invasively

detect the likely presence of posterior segment recurrence and to evaluate treatment response in patients with acute VKH.

In the acute phase of VKH disease, bilateral granulomatous panuveitis is present with diffuse choroiditis and multifocal exudative retinal detachments. While EDI-OCT allows for visualization and measurement of the choroidal thickness, it may be difficult to delineate the outer edge of the choroid with this technique. For this reason, the thickness must be measured manually-a time-consuming task that makes this approach prohibitive in many case [18,23,24,27,28]. The benefit of these studies is that they have confirmed the presence of choroidal thickening-which may be related not only to inflammatory infiltration but also increased exudation-in acute VKH. Importantly, however, those studies did not evaluate choroidal thickness over time as a follow-up measure [18].

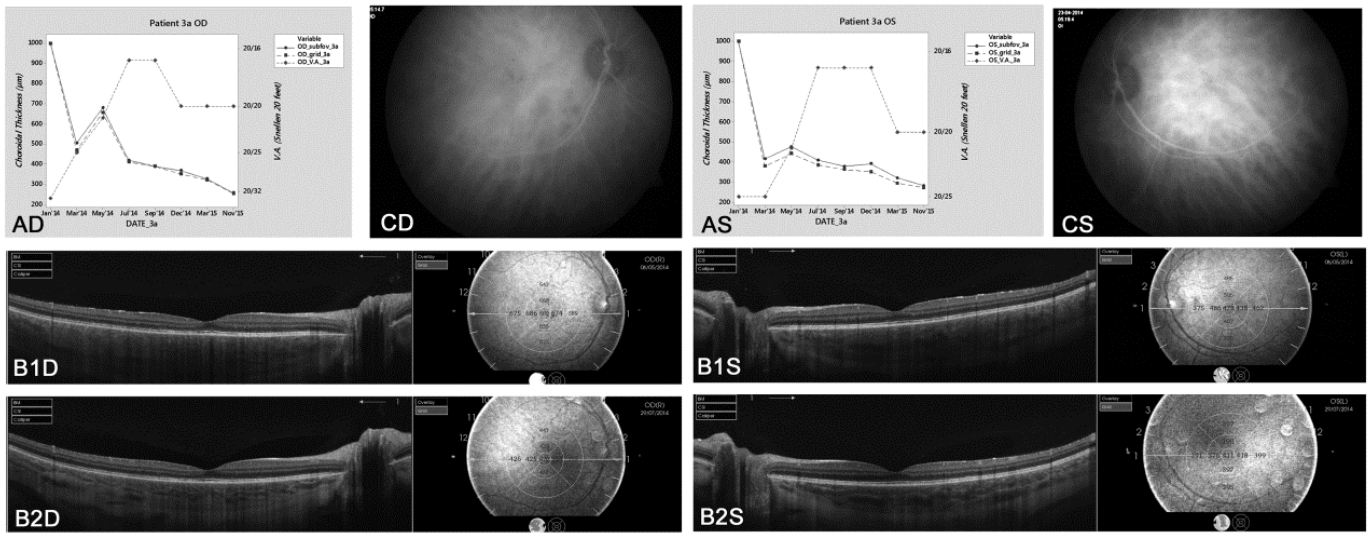

Figure 3: A: Subfoveal choroidal thickness (SFCT) and grid choroidal thickness in micrometers (μm) and Snellen visual acuity (VA) of patient 3 throughout the study (AD right eye, AS left eye) from January 2014 to November 2015. During follow up (May 2014) an asymptomatic posterior recurrence was diagnosed by choroidal thickness (SS-OCT). At study end the choroidal thickness and VA were normal (259 μm right eye and 284 μm left eye, VA 20/20 both eyes). **B:** SS-OCT images with choroidal thickness in μm. Right eye (B1D) and left eye (B1S) in May 2014 with an increased SFCT in both eyes (680 and 478 μm). B2: SS-OCT in July 2014 of right eye (B2D) and left eye (B2S) with a decrease in SFCT (420 vs. 411 μm). **C:** Indocyanine green angiography of right eye (CD) and left eye (CS) in July 2014 with subtle signs of inflammation.

Although the manual approach to measuring choroidal thickness provide valuable data-particularly with regards to the association between choroidal thickness and acute VKH-it is not practical for clinical use due to the time required to perform the measurements. The discovery of the presence of choroidal thickening in acute VKH opens up the possibility of alternative approaches to diagnosing and monitoring the course of VKH. The emergence of SS-OCT-with its automatic measurement capabilities-provides clinicians with a new tool to quickly evaluate choroidal thickness to monitor the clinical course of VKH. In this study, we hypothesized that we could use SS-OCT to measure changes in the thickness of the choroid to both assess treatment response and to detect posterior relapse. Our results appear to confirm this hypothesis. We found that, after treatment, patients with acute VKH experienced a significant decrease in choroidal thickness and a gain in VA, a finding that seems to support the use of automatic measurement of choroidal thickness to evaluate treatment response. In addition, in symptomatic patients, we found that an increased choroidal thickness was associated with partial vision loss. By contrast, in asymptomatic patients with recurrent disease, the first sign of relapse was an increase in choroidal thickness (detected by SS-OCT) without loss of VA (all relapses were confirmed with ICGA). Thus, although ICGA is necessary to confirm the relapse, SS-OCT offers the possibility of detecting recurrent disease without the need for such an invasive, time-consuming procedure. Moreover, although ICGA gives a qualitative diagnosis of choroidal inflammation, SS-OCT provides an objective, quantitative diagnosis of that inflammation (evidence by the increase in choroidal thickness). Notably, personalized follow-up with SS-OCT scanning allowed us to diagnose pathologic increases in choroidal thickness in all eyes with posterior recurrences; it was also useful for the diagnosis of 10 posterior recurrences without loss of VA that were later confirmed with ICGA.

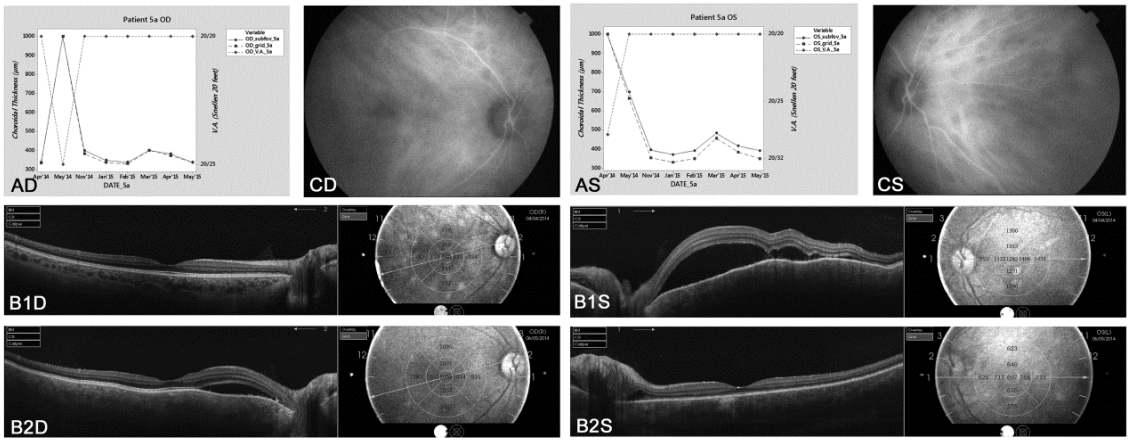

Figure 4: A: Subfoveal choroidal thickness (SFCT) and grid choroidal thickness in micrometers (μm) and Snellen visual acuity (VA) of patient 5 throughout the study (AD right eye, AS left eye) from April 2014 to May 2015. Baseline with increased SFCT in left eye (1283 μm) and blurred vision. Relapse in right eye 1 month later (SFCT 1068 μm). Asymptomatic SFCT increase in both eyes in March 2015. At study end, the choroidal thickness was 339 μm and 392 μm, in the right and left eyes, respectively, with VA 20/20 in both eyes. **B:** SS-OCT images with choroidal thickness in μm. Right eye (B1D) and left eye (B1S) in April 2014: standard SFCT in right eye (340 μm) and increased SFCT in left eye (1283 μm) with multifocal serous retinal detachments, typically seen in the acute phase of the disease. The limit between choroid and sclera was not visible due to choroidal thickness > 1000 μm. B2: SS-OCT in May 2014: B2D right eye with 1068 μm of SFCT with juxtapapillary serous retinal detachment; B2S, right eye with less thickness after corticoid treatment (697 μm). **C:** Indocyanine green angiography of right eye (CD) and left eye (CS) of Mars 2015 confirmed the existence of inflammation with hypopigmented spots in both eyes.

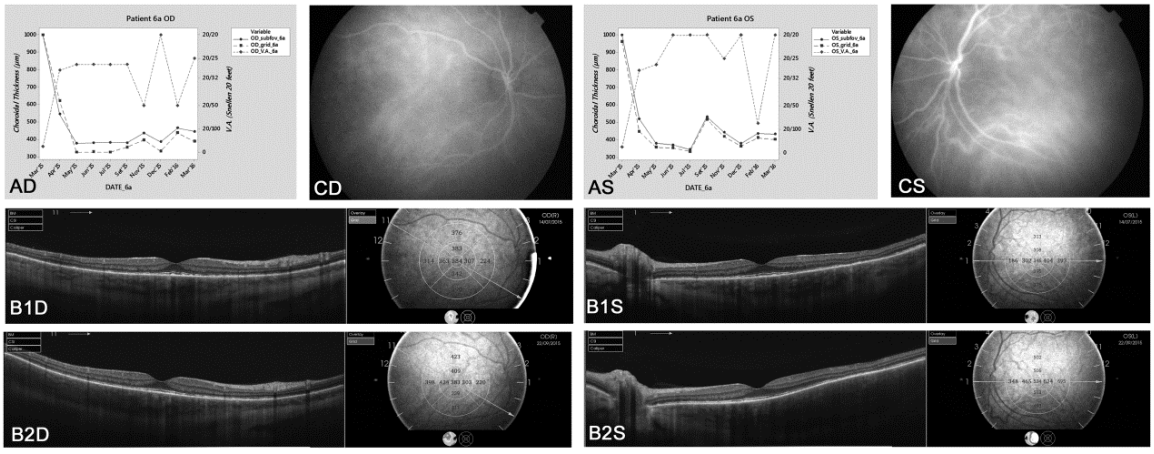

Figure 5: A: Subfoveal choroidal thickness (SFCT) and grid choroidal thickness in micrometers (μm) and Snellen visual acuity (VA) of patient 6 throughout the study (AD right eye, AS left eye) from March 2015 to March 2016. Baseline SFCT >1000 μm in both eyes. Two recurrences were detected in the right eye, with increased choroidal thickness and diminished VA. In the left eye an increase in choroidal thickness was detected before diagnosis of symptomatic blurred vision and posterior recurrence (534 μm) without diminished VA. **B:** SS-OCT images with choroidal thickness in μm. Right eye (B1D) and left eye (B1S) in July 2015: SFCT almost normal (384 y 346 μm) in both eyes. B2: SS-OCT of right eye (B2D) and left eye (B2S) in September 2015: SFCT of right eye remained normal (383 μm), while there was an increase in the left eye (534 μm). **C:** Indocyanine green angiography of right eye (CD) and left eye (CS) of September 2015 confirmed the inflammation in left eye with choroidal vasculitis.

The findings in our study are consistent with previous reports describing a significant increase in choroidal thickness in patients with acute VKH [18,19,23,26-30]. To verify the representativeness of the SFCT values measured automatically with SS-OCT in our control group, we compared these with the manual measurements (also obtained with SS-OCT) in 276 healthy volunteers in another study

[14]. Those authors reported a mean SFCT of 301.89 μm (SD=80), a finding that was similar to our control group (mean, 302.3 μm). We performed a t-test to check for differences between these two groups, finding a mean difference of only 11.89 μm (95% CI, 14.27-38.05), which was not statistically significant (p=0.3718). This comparison confirmed the representativeness of our control group. Perhaps more importantly, our SFCT data was obtained using the automated measurement feature of SS-OCT. This is an enormous advantage because it does not require a trained professional to make the measurements and it can be done much faster and easier, making it an excellent method for use in daily clinical practice.

Nakayama et al. evaluated 8 patients recently diagnosed with VKH. In that study, the authors measured choroidal thickness manually with EDI-OCT, defining a recurrence as an increase in choroidal thickness >100 μm from measurement [24]. In our study, we defined the relapse as the minimum increase in thickness required to induce a decrease in VA (not otherwise attributable to other causes) and with the presence of inflammatory signs on ICGA, or without loss of vision but with an increase of ≥ 50 μm in thickness combined with the presence of inflammatory signs on ICGA. The 50 μm cut off was selected because this was the mean SD among published studies [7,8,19,21]. As in our study, Nakayama et al. found that VKH patients had an increased SFCT at baseline (mean, 578 μm). Likewise, those authors found, as we did, that choroidal thickness decreased with treatment. However, they also found a rebound in choroidal thickening in 3 patients (5 eyes) during corticosteroid tapering but without evidence of increased inflammation (1 year follow-up and manual measurements). By comparison, in our study, 5 patients (10 eyes) presented asymptomatic relapses. We suspect that the higher relapse rate observed in our study versus Nakayama et al. is due to our longer follow-up (12 months *vs.* 24 months).

In VKH, the reported relapse rate ranges from 25% to 54% with anterior recurrences accounting for 50% of all recurrences [3,25,31]. Posterior recurrences are usually associated with poor VA at diagnosis or with a rapid tapering of the corticosteroid dose [25]. In our study, recurrent inflammation was found in 5 out of 9 patients (56%), all of which were posterior recurrences. In general, baseline VA was not particularly low (two-thirds of patients had a VA>0.63 and 3 of the 18 eyes had a decimal VA of 1. In addition, corticosteroids were tapered slowly in all cases (minimum of 1 year of treatment with prednisone). Consequently, given that VA in our sample was relatively acceptable and that corticosteroids were tapered slowly, the high relapse rate must be due to other factors. Based on our data, which showed that recurrences were associated with the duration of follow-up from diagnosis (all cases of recurrence were observed only in patients with ≥ 1 year from diagnosis), it appears that the likelihood of recurrence depends on the duration of the disease.

It is well known that the presence of a hypopigmented fundus (sunset glow) could be attributable to unidentified (and thus, untreated) posterior recurrences. For this reason, the routine use of ICGA during follow up is recommended in VKH patients [3]. However, given the aforementioned drawbacks of ICGA, the use of this modality should be minimized to the extent possible. In this sense, monitoring SFCT with SS-OCT may offer a valuable complement to ICGA. We used ICGA to confirm the presence of inflammation in all relapses but we found that SS-OCT was quicker, easier and safer than angiography. We observed sunset glow fundus in only 1 patient (both eyes), but this finding was not unexpected given that this patient experienced three asymptomatic relapses and it seems likely that there is an association between asymptomatic relapse and sunset glow fundus.

Study strengths and limitations

To our knowledge, the present study is the first to use the automated measurement features of SS-OCT to measure choroidal thickness in patients with acute VKH. Moreover, our prospective study includes the largest sample to Caucasian, Western European patients with VKH. We are aware of other studies that measured choroidal thickness in acute VKH; however, those studies were conducted in Japanese patients using EDI-OCT or SS-OCT with manual measurement [18,19,24]. Ours is the first study to present data on automated-and therefore objective-measurement of choroidal thickness obtained during the course of this disease.

This study has several limitations, primarily the small sample size and the fact that-despite the recurrent nature of this disease-we did not perform standardized monthly follow-up appointments for all patients. Rather, examinations were scheduled according to need depending on the severity of each individual case. Another limitation is that the decision to use a cut-off value of ≥ 50 μm before performing the ICGA, as this may have led to an under diagnosis of recurrences; however, this was a conscious decision to limit ICGA choroidal assessments to avoid performing unnecessary angiographies.

Conclusions

The results of this study suggest that the automatic measurement of choroidal thickness using SS-OCT can be a valuable tool to both evaluate treatment response and to help diagnose posterior recurrences. If confirmed, the findings presented here may reduce the need to use ICGA for routine follow-up, as angiography may only be necessary in asymptomatic patients who develop an increase in choroidal thickness. However, this finding must be first confirmed in prospective studies with larger patient samples.

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