Recovery of macular cone photoreceptors
in Vogt-Koyanagi-Harada disease

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The authors have no financial interest relevant to this manuscript.

Abstract

Purpose: To study changes in macular cone photoreceptors in Vogt-Koyanagi-Harada (VKH) disease patients after high-dose corticosteroid treatment using an adaptive optics (AO) fundus camera.

Methods: We retrospectively analyzed 16 eyes of eight patients with new-onset acute VKH disease were studied retrospectively. After serous retinal detachment (SRD) had resolved, AO images were obtained using the rtx1TM AO fundus camera over a 12-month course. Cone counting was performed in the nasal, temporal, superior and inferior areas of the macula 0.75 mm from the foveal center. A control group of 30 eyes of 30 healthy subjects was established for comparison.

Results: In the eyes with VKH disease, the mean cone densities 0.75 mm from the foveal center were 11,847 at baseline (resolution of SRD), and 15,218, 16,684 and 17,686 cones/mm², at 3, 6, and 12 months later, respectively. The mean cone densities at 3, 6, and 12 months were significantly increased compared to those of baseline ($p=0.007$, $p<0.001$, and $p<0.001$, respectively); however, they were significantly lower than that of the healthy control eyes ($p<0.001$). The mean cone densities at areas with a previous presence of cystoid spaces were significantly lower than those without cystoid spaces at the baseline, and at 3, 6, and 12 months ($p<0.001$, $p=0.007$, $p<0.001$, and $p=0.008$, respectively).

1 **Conclusions:** Cone densities were gradually increased after the resolution of SRD in
2 the eyes of VKH disease patients. The presence of cystoid spaces might be a marker of
3 severe damage to cone photoreceptors.

4

5 **Keywords**

6 adaptive optics, cone density, cystoid space, photoreceptor, serous retinal detachment,
7 Vogt-Koyanagi-Harada disease

1 Introduction

2 Vogt-Koyanagi-Harada (VKH) disease is characterized by bilateral and diffuse
3 choroiditis that usually manifests as serous retinal detachment in the acute stage, with
4 the onset of granulomatous anterior segment inflammation soon thereafter [1]. There are
5 well-known prodromal symptoms involving the central nervous system and the auditory
6 system that aid in the diagnosis of VKH disease at this acute stage. If the disease is left
7 untreated, or is undertreated, the ocular inflammation becomes chronic, with an
8 increased risk of various ocular complications, as well as an increased risk of late
9 integumentary changes such as poliosis, vitiligo, and alopecia [2]. Patients with VKH
10 disease are usually treated with high-dose systemic corticosteroids, either only orally or
11 with an initial intravenous administration followed by oral administration.

12 Several studies have used optical coherence tomography (OCT) to reveal the
13 structural changes in the retina that occur in VKH disease [3]. However, the effects of
14 inflammation and subretinal exudation on cone photoreceptors in the macula of VKH
15 disease remain unexplored. Our group and other researchers have used adaptive optics
16 (AO) imaging clinically to directly visualize cone photoreceptors [4, 5]. Our analyses
17 revealed that the macular cone density values in patients with resolved
18 central serous chorioretinopathy were lower than those in normal eyes, but
19 the values increased gradually in the 12 months [5]. Like central serous
20 chorioretinopathy, VKH disease involves serous retinal detachment (SRD) of
21 the macula; we thus speculated that the macular cone photoreceptors in

VKH eyes were damaged by SRD and recovered with time after the SRD has resolved in VKH eyes. In this study, we retrospectively investigated cone loss and changes in the cone density in patients with VKH during their follow-up period that were identified with an AO fundus camera, and we determined the correlations between cone loss and cone density changes with the forms of SRD.

Patients and Methods

This was a single-center, retrospective study that was conducted in accordance with the Institutional Guidelines of the University of Toyama and was approved by the university's Institutional Review Board. The procedures conformed to the tenets of the World Medical Association's Declaration of Helsinki. All subjects gave their written informed consent before participation in this retrospective study.

Patients

We examined the 16 eyes of eight consecutive patients with new-onset acute VKH disease who visited Toyama University Hospital between January 2013 and July 2015. The diagnosis of VKH was based on established international criteria [2]. Only patients with SRD involving the foveal center before steroid treatment were included in this study. All patients underwent comprehensive eye examinations at the initial visit before treatment, including the measurement of decimal best-corrected visual acuity (BCVA), a fundus examination, standard spectral domain (SD) OCT, enhanced depth

imaging-optical coherence tomography (EDI-OCT) (RS-3000 Advance, Nidek, Aichi, Japan), fluorescein angiography, and indocyanine green angiography. The standard OCT and EDI-OCT were performed at the initial visit before treatment, every 2 to 3 days over the first 2 weeks, every 2 weeks until the SRD resolved, and then every month thereafter. All patients received an intravenous administration of methylprednisolone (1000 mg/day) for 3 days followed by tapering oral doses of prednisolone. One patient received oral prednisolone and cyclosporine concomitantly. To establish a healthy control group for comparison to the patients with VKH disease, we also included 30 eyes from 30 healthy volunteer subjects.

Adaptive optics imaging and the measurement of cone density

After the patient's SRD was resolved by high-dose corticosteroid treatment, AO images were obtained at the macula. AO images were taken in the nasal, temporal, superior and inferior areas at 0.75 mm from the foveal center in each eye with an rtx1TM AO fundus camera (Imagine Eyes, Orsay, France). The images were processed with software tools supplied by the manufacturer (CK V.1.3 and AOdetect V.0.1). These images were registered using a cross-correlation method and averaged to produce a final image with an enhanced signal-to-noise ratio [6]. Montage images were created using image editing software (Photoshop Elements 11; Adobe, Mountain View, CA).

Cone counting was performed in the nasal, temporal, superior, and inferior areas at 0.75 mm from the foveal center (Fig. 1). The size of the counting areas was set as $100\ \mu\text{m} \times 100\ \mu\text{m}$ square. Scales of the macular images were calculated using Littmann's method [7]. Cone density was counted automatically using AOdetect software (Imagine Eyes).

We defined each patient's baseline as the first time that the resolution of the SRD was confirmed by the vertical and horizontal OCT images was set as the baseline. Measurements of cone density using AO images were performed at the baseline, and at 3, 6, and 12 months after the baseline at the same locations in each eye.

We used the mean value of the cone density of each of the four locations (the nasal, temporal, superior, and inferior areas) to compare the mean cone density of the healthy control eyes and to analyze the correlations between the choroidal thickness and the mean areas of subretinal fluid (SRF), cystoid space, and the SRF + cystoid space.

To further investigate the relationship between the presence or absence of SRF or cystoid space and the cone density, we analyzed the forms of SRD in OCT at 0.75 mm from the foveal center at each patient's initial visit before treatment, corresponding to the cone density measurement site. The cone densities of the nasal, temporal, superior, and inferior areas at 0.75 mm from the foveal center were separated into the areas with the previous presence of SRF and/or cystoid space and the areas without previous SRF or cystoid space. Changes in the mean cone densities were evaluated in these groups of areas.

1 *Measurement of the areas of subretinal fluid and cystoid space*

2 We used horizontal and vertical slices of OCT crossing the foveal center taken at each
3 patient's initial visit before treatment to identify the locations of SRF and cystoid spaces
4 and then measure the areas (Fig. 2). As reported, serous retinal detachment in VKH
5 disease shows both intra-retinal fluid (cystoid space) and SRF [3]. Each area was
6 manually measured using ImageJ software (U.S. National Institutes of Health, Bethesda,
7 MD).

8
9 *Measurement of the subfoveal choroidal thickness.*

10 The subfoveal choroidal thickness was measured using EDI-OCT images. Choroidal
11 thickness was determined between the outer border of the retinal pigment epithelium
12 and the outer border of the choroid under the foveal center. The subfoveal choroidal
13 thickness measurements were performed at the resolution of SRD (i.e., the baseline),
14 and at 3, 6, and 12 months after the baseline measurement. The mean value of the
15 vertical and horizontal thickness was used for analysis.

16
17 *Statistical analysis*

18 Statistical analyses were performed with JMP[®] 11 (SAS Institute, Cary, NC, USA). The
19 decimal visual acuity was converted to the logarithm of the minimal angle of resolution

(logMAR) unit for statistical analysis. The paired t-test or Mann-Whitney U-test was used, and two-tail p-values <0.05 were considered significant. We used the Spearman rank correlation was calculated to assess the correlation among the data.

Results

The mean age of the VKH patient group (mean $\pm$ standard deviation) was 39.5 ± 12.0 years (range, 25–54 years), and that of the healthy control group was 34.5 ± 9.4 years old (range, 22–50 years) ($p=0.12$). The mean BCVA of all 16 VKH eyes was 0.14 ± 0.30 logMAR units (range, -0.18 to 0.82 logMAR units) before steroid treatment, -0.06 ± 0.15 logMAR units (range, -0.18 to 0.40 logMAR units) at baseline (serous retinal detachment resolution), and -0.11 ± 0.08 logMAR units (range, -0.18 to 0.15 logMAR units) at 3 months, -0.12 ± 0.08 logMAR units (range, -0.18 to 0.10 logMAR units) at 6 months, and -0.13 ± 0.09 logMAR units (range, -0.18 to 0.15 logMAR units) at 12 months after baseline. The mean BCVA was significantly improved at baseline and 3, 6, and 12 months compared to that before steroid treatment ($p=0.005$, $p=0.003$, $p=0.001$, $p=0.001$, respectively). Compared to the baseline value, the mean BCVA at 6 and 12 months was significantly improved ($p=0.04$, $p=0.005$, respectively). When the patients' SRD had resolved (baseline), 12 of the 16 eyes had improved to -0.08 logMAR units (1.2 on decimal visual acuity) or more. Three months after the baseline, 15 of the 16 eyes had improved to -0.08 logMAR units or more and maintained that acuity until the study's end. There was no significant correlation between the mean area

of SRF or cystoid space and the logMAR BCVA values at the before-treatment point, the baseline, or at 3, 6, or 12 months. The mean area of SRF + cystoid space was significantly correlated with logMAR BCVA at before-treatment ($\rho=0.84$, $p<0.001$). There was no significant correlation between the mean area of SRF + cystoid space and logMAR BCVA at the baseline, or at 3, 6, or 12 months.

As shown in Figure 3, the mean cone densities at 0.75 mm from the foveal center of all 16 VKH eyes at baseline and at 3, 6, and 12 months were $11,847\pm6243$, $15,218\pm6839$, $16,684\pm5033$, and $17,686\pm4183$ cones/mm², respectively. The mean cone densities at 3, 6, and 12 months were significantly increased compared to those at baseline ($p=0.007$, $p<0.001$, and $p<0.001$, respectively). In the healthy eyes, the mean cone density at 0.75 mm from the foveal center was $24,496\pm3220$ cones/mm². Throughout the 12-month observation period, the mean cone densities measured in the eyes of the patients with VKH were significantly lower than those in the healthy control eyes ($p<0.001$) (Fig. 4).

The correlations between the mean cone densities and the mean area of SRF, cystoid space, and SRF + cystoid space in each eye are shown in Figure 5 and Table 1. The mean SRF area was not correlated with the mean cone densities until 12 months after baseline. However, the mean area of the cystoid space was significantly correlated with the mean cone density at the baseline ($\rho=-0.64$; $p=0.004$). The area of SRF + cystoid space was associated with the mean cone densities at baseline and at 3 and 6 months ($\rho=-0.62$, $p=0.005$; $\rho=-0.57$, $p=0.01$; and $\rho=-0.47$, $p=0.04$, respectively).

We also examined the changes in cone densities were also examined in relation to the previous presence or absence of SRF and/or cystoid space. The previous presence or absence of SRF did not significantly affect the recovery of the mean cone density at any observation point (Fig. 6a). However, the mean cone densities with the previous presence of cystoid space were significantly lower than those without cystoid space at baseline, 3, 6, and 12 months ($p<0.001$, $p=0.007$, $p<0.001$, and $p=0.008$, respectively)(Fig. 6b). Typical changes of cone density are shown in Figure 7.

The mean choroidal thicknesses as measured by EDI-OCT of all 16 VKH eyes at baseline (i.e., the resolution of SRD) and at 3, 6, and 12 months after the baseline were $335\pm89\text{ }\mu\text{m}$, $333\pm83\text{ }\mu\text{m}$, $313\pm79\text{ }\mu\text{m}$, and $303\pm82\text{ }\mu\text{m}$, respectively. The mean choroidal thickness was significantly decreased at 6 and 12 months compared to the baseline ($p=0.01$ and $p=0.01$, respectively). There were no significant correlations between the mean choroidal thickness at baseline and the mean areas of SRF, cystoid space, and SRF + cystoid space ($\rho=-0.16$, $p=0.53$; $\rho=0.35$, $p=0.17$; and $\rho=0.23$, $p=0.38$, respectively). The correlations between the mean cone density and the mean subretinal choroidal thickness at baseline and at 3, 6 and 12 months after the baseline are provided in Table 2. There were significant correlations between the mean cone density and the mean subretinal choroidal thickness at 3 months and 6 months after baseline ($\rho=-0.51$, $p=0.02$; and $\rho=-0.50$, $p=0.04$, respectively).

Discussion

1 We observed cone densities in the eyes of patients with VKH disease for a 12-month
2 period after the resolution of their serous retinal detachment (SRD). The mean cone
3 density gradually increased throughout the follow-up period. According to previous
4 studies, the cone mosaic is corresponds to the outer segments (OS) of the
5 photoreceptors [8-10]. Zhang et al. studied the correlation between AO images and
6 SD-OCT images by using a high-speed adaptive optics SD-OCT camera and found that
7 the regular distribution of bright spots observed within the C-scans at the inner segment/
8 outer segment junctions (referred to as the ellipsoid zone) and those at the posterior tips
9 of the OS were highly correlated with one another, as well as with the expected cone
10 spacing [8]. The results of our present study's AO imaging provided direct evidence
11 indicating that the OS was damaged in the eyes of VKH patients.

12 It has been demonstrated that there are two main causes of OS damage in eyes
13 with VKH. The first cause of the OS damage is damage due to inflammation. Yamaki et
14 al. observed shortening and degenerative changes of the OS in a tyrosinase-protein-1-
15 and -2- induced experimental autoimmune uveitis rat model [9]. In another animal
16 model of VKH, Hayakawa et al. reported that the photoreceptor OS, outer nuclear layer,
17 and outer plexiform layer were partly destroyed when the severe inflammation extended
18 into the retinal layer [10]. These animal models of VKH strongly suggest that
19 inflammation induces OS damage. The second cause of the OS damage is damage due
20 to SRD. In an experimental retinal detachment model, Sakai et al. reported that the OS
21 length measurements of short and middle-wavelength-sensitive cones demonstrated the

1 shortening of the OS by retinal detachment [11]. We and others have used AO imaging
2 in a clinical setting to visualize the cone densities of eyes with central serous
3 chorioretinopathy or rhegmatogenous retinal detachment [4, 5, 12].

4 Bae et al. evaluated the photoreceptor outer segment (PROS) volume in VKH
5 patients using spectral domain OCT, and they reported that the PROS volume decreased
6 after the total resolution of macular SRF; however, the PROS volume increased at the
7 final follow-up visit [17]. They hypothesized that the PROS shortening occurred in
8 response to inflammation, and that once the inflammatory stimulus had been removed,
9 the OS enlarged and recovered. Sakai et al. reported that the OS was shortened after
10 retinal detachment, but progressively recovered after reattachment and continued for 96
11 days after reattachment [11].

12 In contrast to these OCT studies, our results showed that the mean cone density
13 in the VKH eyes did not recover to the healthy control levels, even at 12 months after
14 the resolution of serous retinal detachment. This indicates that compared to OCT,
15 observations with an AO fundus camera might reveal more detailed changes of
16 photoreceptors.

17 We also observed that the mean area of cystoid space was correlated with the
18 mean cone density at baseline and that the mean cone densities at areas with cystoid
19 space were significantly lower than those of areas without cystoid space. In the acute
20 phase of VKH disease, SRD involving the septa occurs, forming a cystoid space. It is
21 hypothesized that this septa and membrane structure is a part of the retinal structure and

1 is composed of inflammatory products such as fibrin [3, 13, 14]. Ishihara et al. analyzed
2 serous retinal detachment in VKH disease using SD-OCT and found that the
3 membranous structure was continuous with the IS/OS junction of the attached area [15].
4 These results suggested that the membranous structure and cystoid spaces resulted from
5 an extension or break of the outer limiting membrane and the formation of
6 inflammatory products such as fibrin.

7 Lee et al. speculated that cystoid spaces caused the outer segments to separate
8 from the inner segments [16]. Because SRF causes the outer segments to detach from
9 the retinal pigment epithelium, the formation of cystoid space may cause more damage
10 to the photoreceptors than the formation of SRF. This appears to be supported by the
11 findings reported by Bae et al., which showed that the PROS volumes were decreased in
12 VKH cases with a high fibrinous index after serous retinal detachment resolution [17].

13 Although the mean cone density of our present VKH group at 12 months after
14 the baseline was lower than that of the healthy control group, the visual acuity was –
15 0.08 logMAR units or more at 12 months after the baseline in 15 of the 16 VKH eyes.
16 Similarly, we and others reported that even though the cone density was decreased,
17 the visual acuity was well maintained in resolved central serous retinopathy and
18 rhegmatogenous retinal detachment eyes [5,12]. It has been speculated that the
19 redundancy of cone photoreceptors to retinal ganglion cells may exist to preserve the
20 visual acuity [18].

1 Patients with VKH disease showed an increase in choroidal thickness, and this
2 was decreased by steroid treatment [19, 20]. Nakayama et al. noted that the choroidal
3 thickness at 1 week after treatment was correlated with the occurrence of peripapillary
4 atrophy after 12 months, and they suggested that the choroidal thickness may serve as a
5 marker of choroidal inflammation in acute VKH disease [20]. In the present study, we
6 observed a negative correlation between the subfoveal choroidal thickness and the mean
7 cone density at 3 months and 6 months. Considering that the choroidal thickness is
8 related to the choroidal inflammation in VKH disease, the recovery of the cone
9 photoreceptors may be delayed in patients with persistent inflammation after several
10 months of treatment.

11 There are some limitations to our study; the small number of cases, the
12 relatively short (1-year) follow-up, and the retrospective nature of the study. Moreover,
13 current AO imaging is not able to show individual cone photoreceptors in the foveal
14 center. However, we, for the first time, visualized longitudinal changes during the
15 recovery of cone photoreceptors in the eyes of VKH patients. Still, even at 12 months
16 after the resolution of serous retinal detachment, the mean cone density the VKH eyes
17 was lower than that of the healthy controls. Cystoid spaces in the OCT image might
18 induce more damage to the cone photoreceptors than subretinal fluid. Further studies
19 with longer follow-ups are needed to clarify the recovery of macular cone density in
20 VKH disease.

Funding: No funding was received for this reserch.

Conflicts of Interest: All authors have no financial interest in the subject matter or materials disucussed in this manuscript.

Ethical approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study, formal consent is not required.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Table 1

Correlation between the mean cone density (the mean value of cone densities of four locations; nasal, temporal, superior and inferior from the foveal center) and the mean area of subretinal fluid, cystoid space, and SRF + cystoid space.

	Baseline	3 mos.	6 mos.	12 mos.
SRF	$\rho = -0.11$ $p = 0.65$	$\rho = -0.05$ $p = 0.82$	$\rho = 0.10$ $p = 0.68$	$\rho = 0.18$ $p = 0.46$
Cystoid space	$\rho = -0.64$ $p = 0.004^{**}$	$\rho = -0.33$ $p = 0.19$	$\rho = -0.38$ $p = 0.11$	$\rho = -0.28$ $p = 0.25$
SRF+ Cystoid space	$\rho = -0.62$ $p = 0.005^{**}$	$\rho = -0.57$ $p = 0.01^{*}$	$\rho = -0.47$ $p = 0.04^{*}$	$\rho = -0.30$ $p = 0.21$

* $p < 0.05$, ** $p < 0.01$; ρ , Spearman's correlation coefficient; SRF, subretinal fluid.

Table 2

Correlation between the mean cone density (the mean value of cone densities of four locations; nasal, temporal, superior and inferior area from the foveal center) and the mean subfoveal choroidal thickness.

Correlation between choroidal thickness and cone density		
Baseline (resolution of SRD)	$\rho = -0.37$	$p = 0.15$
3 mos. after baseline	$\rho = -0.51$	$p = 0.02^{*}$
6 mos. after baseline	$\rho = -0.50$	$p = 0.04^{*}$
12 mos. after baseline	$\rho = -0.34$	$p = 0.19$

* $p < 0.05$; ρ , Spearman's correlation coefficient; SRD, serous retinal detachment.

Figure legends

Fig. 1. Panoramic adaptive optics images of the right eye of a 51-year-old woman with Vogt-Koyanagi-Harada disease after high-dose systemic corticosteroid treatment. The nasal, temporal, superior, and inferior areas at 0.75 mm from the foveal center were measured. Asterisk: foveal center, Bar: 200 μ m.

Fig. 2. a: Horizontal SD-OCT images of the fovea of the left eye of a 44-year-old woman with Vogt-Koyanagi-Harada disease before steroid treatment. **b:** SD-OCT image cropped in the range of 0.75 mm on both sides from the foveal center. **c:** The compartment that had detached leaving only the retinal pigment epithelium was defined as subretinal fluid (SRF), and the fluid inside the retina was defined as a cystoid space. Areas of SRF and cystoid space were manually measured.

Fig. 3. Mean cone densities (the mean value of cone densities of the nasal, temporal, superior, and inferior areas from the foveal center) of patients with Vogt-Koyanagi-Harada disease from the time of the resolution of serous retinal detachment until 12 months later. Error bars indicate standard deviations.

Fig. 4. Box plots of the mean cone densities (the mean value of cone densities of the nasal, temporal, superior, and inferior areas from the foveal center) at 12 months in eyes with Vogt-Koyanagi-Harada disease and in healthy control eyes. Centerlines show the medians; box limits indicate the 25th and 75th percentiles; whiskers extend to 1.5 times the interquartile range from the 25th and 75th percentiles; outliers are represented by dots. $n = 16, 30$ sample points.

Fig. 5. Correlations between the mean cone densities (the mean value of cone densities of the nasal, temporal, superior, and inferior areas from the foveal center) at 12 months and the mean areas of subretinal fluid (SRF) (**a**) ($\rho = -0.11$, $p = 0.65$), cystoid space (**b**) ($\rho = -0.64$, $p = 0.004$), and SRF + cystoid space (**c**) ($\rho = -0.62$, $p = 0.005$) in the eight Vogt-Koyanagi-Harada patients.

Fig. 6. Correlation between the cone density of each of the four locations (the nasal, temporal, superior and inferior areas) and the previous presence or absence of subretinal fluid (SRF) (**a**) or cystoid space (**b**) in the OCT slice. Error bars indicate standard deviations.

Fig. 7. Horizontal SD-OCT images of the fovea of the right eye of a 51-year-old woman with Vogt-Koyanagi-Harada (VKH) disease before steroid treatment. Subretinal fluid

1 (SRF) was observed at the temporal area 0.75mm from the foveal center. There was no
2 SRF or cystoid space at the nasal area 0.75mm from the foveal center (**a**). AO images of
3 nasal (**b**) and temporal area (**c**) 0.75mm from the foveal center at baseline and 3, 6, and
4 12 months. Horizontal SD-OCT images of the fovea of the left eye of a 31-year-old
5 woman with VKH disease before steroid treatment. A massive cystoid space (*asterisk*)
6 was observed (**d**). AO images of the temporal area (**e**) 0.75mm from the foveal center at
7 baseline and 3, 6, and 12 months. AO images are $100\ \mu\text{m} \times 100\ \mu\text{m}$ square. Bar: $20\mu\text{m}$.

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