

Delayed Regeneration of Foveal Cone Photopigments in Vogt-Koyanagi-Harada Disease at the Convalescent Stage

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PURPOSE. To evaluate the physiological characteristics of the macula in patients with Vogt-Koyanagi-Harada disease during the convalescent stage with specific reference to the kinetics of foveal cone photopigment regeneration.

METHODS. Six eyes of three patients at the convalescent stage of Vogt-Koyanagi-Harada disease were studied. All the eyes had best corrected visual acuity of 1.0 or better and had no recurrence of inflammation for at least 12 months after the last episode. Foveal cone densitometry (FCD), focal macular electroretinograms, color vision tests, two-color perimetry, and optical coherence tomography (OCT) were performed.

RESULTS. No regeneration of cone photopigments was detected within the 7-minute testing time by FCD in all eyes at the first examination after the last episode. However, the other functional tests were normal, and the OCT-determined macular morphology was also normal. The regeneration kinetics of the foveal cone photopigment improved in three of six eyes at 36, 37, and 19 months after the last episode, whereas the other three remained delayed at 18, 18, and 49 months.

CONCLUSIONS. These findings suggest that a disorder of the foveal cone photopigment regeneration, and its recovery, requires a significantly longer time than that of other macular functions in some patients with Vogt-Koyanagi-Harada disease. (*Invest Ophthalmol Vis Sci.* 2004;45:318-322) DOI:10.1167/iov.03-0381

Vogt-Koyanagi-Harada disease is a systemic inflammatory disorder that results from an autoimmune reaction against melanocytes.^{1,2} In most cases of Vogt-Koyanagi-Harada disease, good vision is regained after the inflammation subsides after appropriate treatment, regardless of the severity of the retinal pigment epithelial (RPE) changes.³⁻⁵ Electrophysiological studies have demonstrated that the dysfunction of the outer retinal layer is severe in Vogt-Koyanagi-Harada disease, whereas dysfunction of the inner retinal layer is mild and reversible.⁶⁻⁸

Patients with Vogt-Koyanagi-Harada disease have high retinal detachments involving the macula, resulting in severe visual loss in the acute stage. Unfortunately, there are no studies on the recovery of macular function during the convalescent stage of Vogt-Koyanagi-Harada disease.

Foveal cone densitometry (FCD) is a noninvasive technique for evaluating the kinetics of photopigment regeneration which is related to the function of photoreceptors and retinal pigment epithelium.

The purpose of this study was to evaluate macular function of patients with Vogt-Koyanagi-Harada disease at the convalescent stage. FCD, focal macular electroretinograms (fmERGs), two-color perimetry, and color vision tests were performed on the patients. In addition, optical coherence tomography (OCT) was used to determine the morphology of the macular area.

MATERIALS AND METHODS

Patients

Six eyes of three patients with Vogt-Koyanagi-Harada disease in the convalescent stage were studied. All the eyes had best corrected visual acuity of 1.0 or better and had had no recurrence of inflammation for at least 12 months after the most recent episode. Vogt-Koyanagi-Harada disease had been diagnosed by the clinical findings: anterior segment inflammation, serous retinal detachment, optic disc edema, and the presence of multiple RPE leakage in fluorescein angiography. In addition, human leukocyte antigen (HLA) DR53, DR4, B54, and DQ4 were positive in all cases, and the number of monocytes in the cerebrospinal fluid was increased in patients 2 and 3. The fundus of patients 1 and 3 had the classic sunset glow appearance at the initial visit and at the 3-week follow-up examination. Such a characteristic appearance was not found in patient 2 throughout the follow-up period. Although the revised diagnostic criteria for Vogt-Koyanagi-Harada disease⁹ had not been published at the time patients received diagnosis, a review of the charts of these patients showed that they met the revised diagnostic criteria.

This research was conducted in accordance with the institutional guidelines of Nagoya University and conformed to the tenets of the World Medical Association Declaration of Helsinki. After a complete explanation of the purpose of this study and the procedures to be performed, an informed consent was obtained from each patient.

The pupils were dilated with 0.5% tropicamide and 0.5% phenylephrine before FCD, fmERGs, two-color perimetry, and OCT.

Foveal Cone Densitometry

The apparatus and technique for FCD have been described in detail.^{10,11} In brief, the light from a 500-W xenon lamp was fed into a modified fundus camera through an optic fiber bundle and used as the light source for the bleaching, reference, and measuring beams. The wavelength of the measuring beam was 562 nm and that of the reference beam was 803 nm.

The size of the retinal area examined for both the measuring and reference beams was 1° in diameter and was centered on the fovea. The area bleached was the central 3°. The retinal luminance of the bleaching beam was 6.0 log photopic trolands, and that of the measuring beam was 950 trolands.

After 5 minutes of bleaching, the density of the cone photopigments was recorded continuously for 7 minutes. The density difference (DD) between the fully bleached and fully dark-adapted condition and the time constant (TC) for photopigment regeneration were deter-

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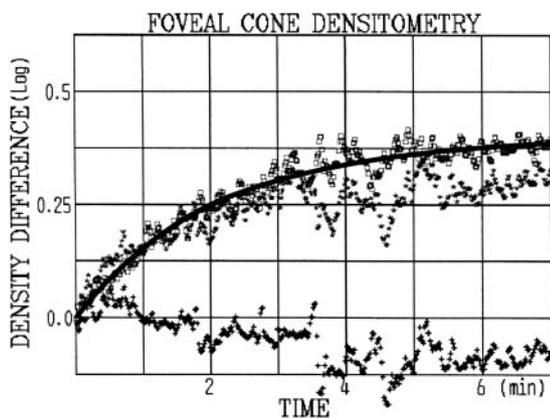


FIGURE 1. Foveal cone densitometry of a normal eye. (\square), (\star), and ($+$) represent the density differences of photopigments, measuring beam, and reference beam, respectively. *Solid line*: best-fit curve.

mined by computer, by determining the best-fit exponential curve (Fig. 1).

Focal Macular Electretinograms

The technique for recording fmERGs has been described in detail.¹²⁻¹⁴ Briefly, an infrared fundus camera, equipped with a stimulus light, background illumination, and fixation target, was used to stimulate and monitor the exact locus of the stimulus on the macula during the recordings. A Burian-Allen bipolar contact lens electrode permitted a clear image of the fundus on the television monitor. Three stimulus spots, 5°, 10°, and 15° in diameter, were used at an intensity of 29.46 cd/m² under a background illumination of 2.84 cd/m². A total of 512 responses were averaged by a signal processor. A time constant of 0.03 second and a 100-Hz high-cut filter were used.

Two-Color Perimetry

Two-color perimetry was performed on a modified Humphrey Field Analyzer model 620 (Carl Zeiss Meditec, Dublin, CA) originally designed by Jacobson et al.¹⁵ and others.^{16,17} Cone sensitivity profiles were determined at 31 test points across the 60° horizontal meridian of the posterior pole under a white background. The stimulus spot was 1.7° in size and 600 nm in wavelength, and the intensity of the background illumination was 31.5 apostilbs. For dark-adapted, two-color perimetry, blue-green (500-nm) and red (650-nm) stimuli were used after 45 minutes of dark adaptation.

Optical Coherence Tomography

OCT (Carl Zeiss Meditec) was performed to assess the morphology of the macula. Patients were asked to fixate the target, and the fovea was scanned horizontally for 4 mm to obtain cross-sectional images of the macula.^{18,19}

Color Vision Tests

Standard pseudoisochromatic plates part 2 for acquired anomaly, Hardy-Rand-Ritter plates, Farnsworth dichotomous panel D-15 test, Farnsworth-Munsell 100-hue test, and Nagel anomaloscopic measurements were used to determine the color vision of the patients.²⁰

RESULTS

Case Reports

Patient 1. A 65-year-old Japanese man reported blurred vision and was referred to the Nagoya University Hospital because of a residual inflammation despite oral and topical steroids. At the initial examination, his visual acuity was 0.5 in

the right eye and 1.0 in the left eye. The anterior segment inflammation was treated with systemic corticosteroids that were tapered over 2 years. His visual acuity improved to 1.0 in both eyes within 2 weeks, and no recurrence was observed. FCD was performed at 24, 36, 42, and 49 months after the last episode.

Patient 2. A 23-year-old Japanese man was referred with blurred vision of 1 week's duration. His visual acuity was 0.3 in both eyes. Treatment with corticosteroid pulse therapy was started approximately 2 weeks after the onset. The serous detachments were resolved within 1 week, and the visual acuity improved to 1.0, approximately 3 weeks later in both eyes. No recurrence was observed. FCD was performed at 4, 15, 19, and 37 months after the last episode (Fig. 2).

Patient 3. A 45-year-old Japanese woman was referred who reported blurred vision and had visual acuity of 0.03 in both eyes. She was started on corticosteroid pulse therapy 20 days after the onset. The serous detachments were resolved promptly, and her visual acuity improved to 1.0 within 3 weeks in both eyes. An anterior segment inflammation was detected 2 and 10 months later. Each time, she was treated with systemic

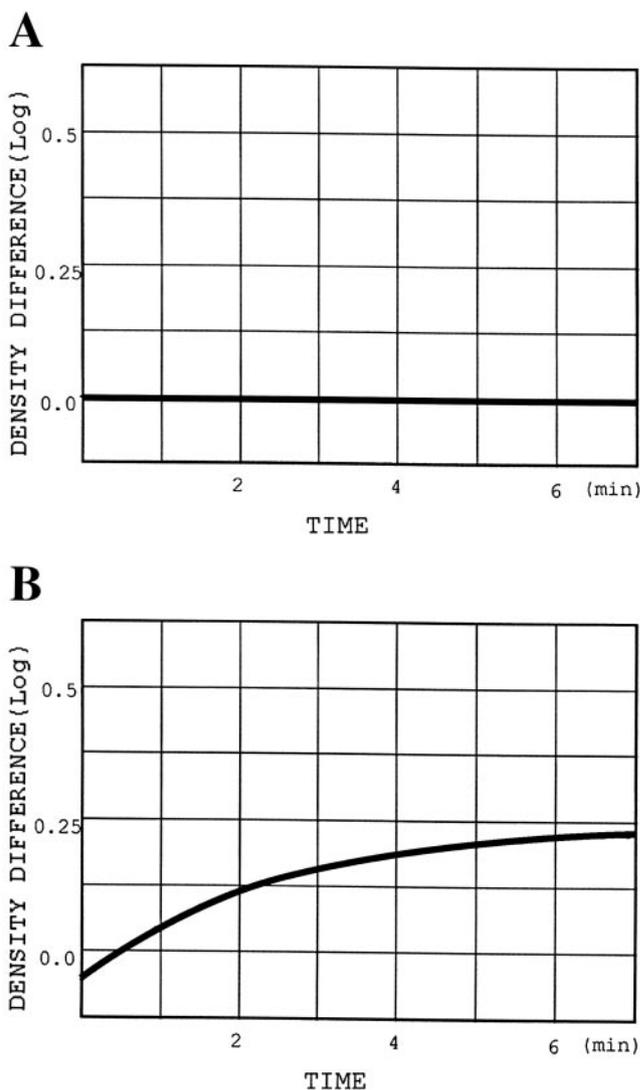


FIGURE 2. Foveal cone densitometry of the left eye of patient 2. *Solid line*: best-fit curve. (A) Regeneration of cone photopigments was not detected in the data obtained 15 months after the last episode. (B) The cone photopigment kinetics improved and attained normal levels 19 months after the last episode.

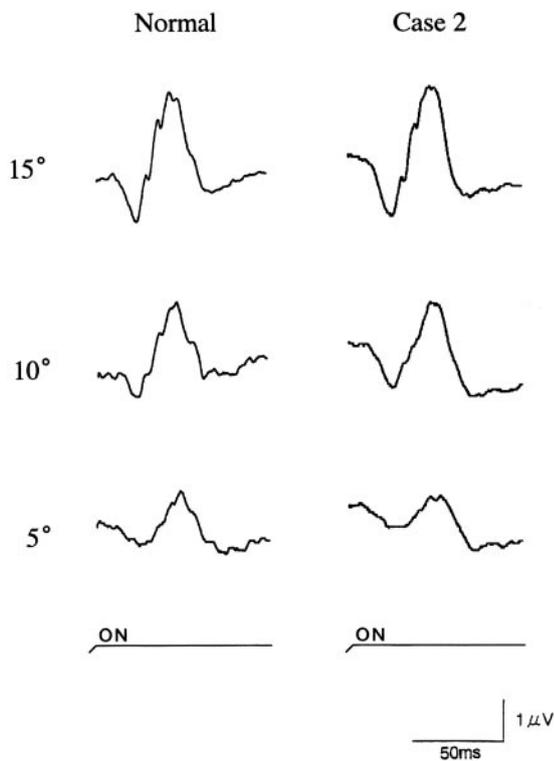


FIGURE 3. Focal macular electroretinograms from the left eye of patient 2. At the first examination after the last episode, focal macular ERGs were within normal limits.

steroids, and the inflammation subsided. FCD was performed 7 and 18 months after the last episode.

Macular Function

At the first examination after the last episode when the visual acuity had recovered to 1.0 or better (mean interval of 19.3 months), the fmERGs (Fig. 3) and two-color perimetry (Fig. 4) were normal in all eyes. The OCT-determined macular configuration was also normal in all eyes (Fig. 5). Color vision tests were normal except for one eye which showed slightly abnormal anomaloscopic values (Table 1).

In contrast to these normal findings, no regeneration of cone photopigments was detected during the 7-minute testing time by FCD in all eyes at the first examination. The kinetics of the cone photopigments improved and attained normal levels in three of six eyes at 36 months in the right eye of patient 1 (DD: 0.21 log, TC: 169.9 seconds) and at 37 months in the right eye (DD: 0.41 log, TC: 161.5 seconds) and at 19 months in the left eye (DD: 0.29 log, TC: 145.5 seconds) of patient 2 after the last episode. For reference, the DD of healthy subjects, ranging in age from 20 to 47 years, was 0.36 ± 0.09 log, and the TC was 124.0 ± 28.7 seconds¹¹ (Table 2).

DISCUSSION

The fmERGs, color vision, and two-color perimetry improved to the normal range in patients with Vogt-Koyanagi-Harada disease after the inflammation subsided. However, our findings demonstrated that the recovery of the photopigment regeneration kinetics takes much longer than the recovery of other macular functions. Thus, the photopigment regeneration kinetics were impaired even when the static functions of the visual pathway, obtained by color vision tests and two-color perimetry, had recovered. These discrepancies in visual functions in

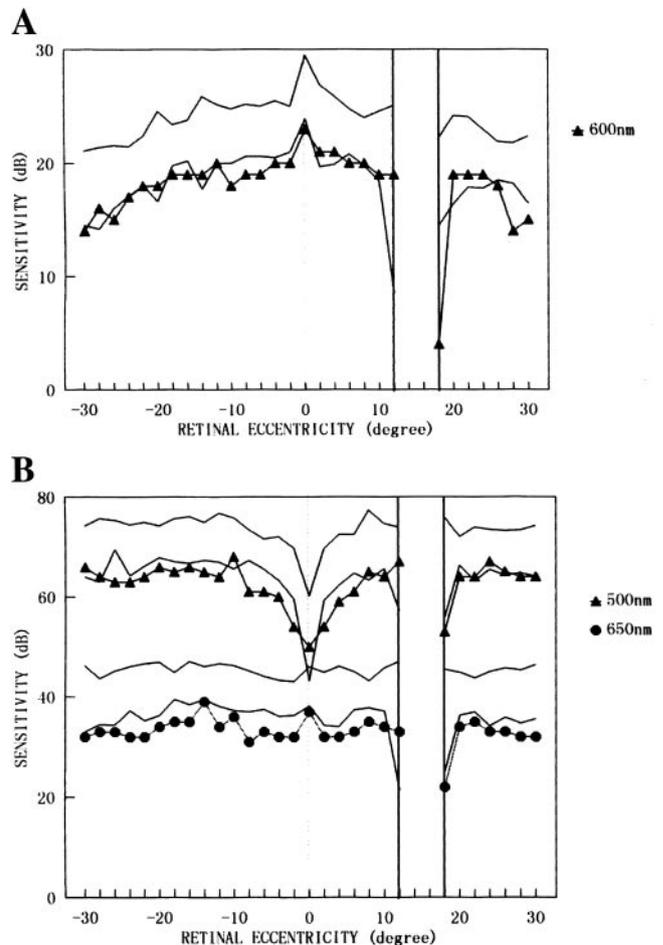


FIGURE 4. Profile plots of (A) light and (B) dark-adapted two-color perimetry in patient 2. The region between the two lines in each panel indicates the normal range (mean \pm 2 SD) in 30 normal subjects. At the first examination after the last episode, the macular cone sensitivity was almost normal and the macular rod sensitivity was normal.

the macula in eyes with Vogt-Koyanagi-Harada disease at the convalescent stage have not been reported.

Vogt-Koyanagi-Harada disease is characterized by extensive retinal detachment and inflammation involving the retina and choroid. The question arises whether the regeneration kinetics abnormality simply reflects the aftereffects of the severity of the retinal detachment caused by Vogt-Koyanagi-Harada dis-

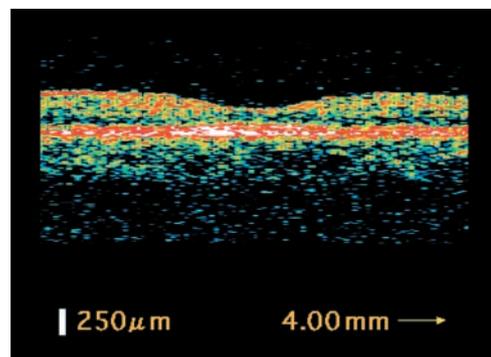


FIGURE 5. OCT of the left eye of patient 2. At the first examination after the last episode, OCT showed normal macula configuration, and serous retinal detachment and macular edema were not present.

TABLE 1. Results of Color Vision Test at the First Examination after the Last Episode

Patient/Age (y)	Eye	Anomaloscope Red-Green Scale (Yellow Scale)	100-Hue Test Error Score	SPP 2
1/65	R	33-40 (15)	152	BY1 fail
	L	35-40 (15)	108	BY1 fail
2/23	R	39 (16)	72	Pass
	L	38 (16)	80	Pass
3/45	R	37-40 (15, 16)	76	Pass
	L	35-40 (15) (17)	80	Pass

SPP 2: Standard pseudoisochromatic plate part 2.

ease. Liem et al.²¹ reported that there was a gradual recovery of the density of foveal cone photopigments in nine eyes of nine patients within 14 months after rhegmatogenous retinal detachment surgery by foveal cone densitometry. In our cases, the kinetics of foveal cone photopigments improved in only three of six eyes, and the recovery did not begin until at least 15 months after the resolution of the retinal detachment, despite good visual acuity. In addition, OCT showed no retinal detachment or macular edema in our cases. Our data indicate that the delayed recovery of the foveal cone photopigment kinetics in Vogt-Koyanagi-Harada disease was not only due to the former retinal detachment but also to the inflammatory impairment in the retina and RPE.

It has been reported that the hyperosmolarity response of the ocular standing potential is suppressed at the convalescent stage of Vogt-Koyanagi-Harada disease.⁷ Pathologically, abnormalities of choroid and RPE, including marked loss of choroidal melanocytes, scattered infiltration of lymphocytes in the choroid, and destruction or hyperplasia of RPE have been reported in eyes with Vogt-Koyanagi-Harada disease.²²⁻²⁴ In addition, abnormalities of the choroid and RPE have been detected by indocyanine green video angiography in eyes with Vogt-Koyanagi-Harada disease in the convalescent stage.^{25,26} Therefore, pathologic and functional disorders of the RPE may contribute to the longstanding abnormality in the visual photopigment kinetics. In addition, the recovery of cone dark adaptation was reported to be slow in severely affected patients at the convalescent stage,²⁷ which supports the abnormal function of cone system in our patients.

In patient 2, a recovery of cone photopigment kinetics was observed earlier than in the other two cases. His visual acuity before treatment was better, and he was much younger than the others. In addition, his fundus did not show the sunset glow appearance. These factors may have led to the relatively

rapid recovery of his outer retinal function. The recovery of cone function in Vogt-Koyanagi-Harada disease has been reported to be different and dependent on the severity of the inflammation.²⁷

We are observing these patients and will collect similar data from any new patients with Vogt-Koyanagi-Harada disease as they become available. Data from more cases of different severity and longer follow-up periods will be helpful in determining the convalescent course of patients with Vogt-Koyanagi-Harada disease.

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TABLE 2. Foveal Cone Densitometry in Eyes after the Last Episode

Patient/Eye	Period after the Last Episode (mo)	Foveal Cone Densitometry	
		Density Difference (log)	Time Constant (s)
1/right	24	0.00	NM
	36	0.21	169.9
	49	0.28	158.3
2/right	15	0.00	NM
	19	0.00	NM
	37	0.41	161.5
2/left	15	0.00	NM
	19	0.29	145.5
	37	0.40	108.9

Mean \pm SD of density difference in normal subjects is 0.36 ± 0.09 log, and the time constant is 124.0 ± 28.7 seconds.¹¹ NM, not measurable.

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