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Fast and Slow Oscillation Electrooculography in Harada Disease

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We assessed clinical utility of fast and slow oscillations (FO and SO) of the electrooculogram (EOG) in Harada disease. In 12 eyes of 4 female and 2 male subject patients aged 18 to 77 years (average: 41.8 years), FO and SO were recorded using an automated electrooculograph, the Nidek EOG-2, in the acute period before treatment and in the remission period under corticosteroid therapy. FO parameters, namely the Rf_{FO} [the average ratio in percentage of the maximum amplitude in the dark period (AD)/the minimum amplitude in the light period (AL) during FO measurement] and the df_{FO} (the average difference in μV between AD and AL) were evaluated. The L/D_{SO} (the light peak/dark trough ratio of the SO) was calculated as an SO parameter. The Rf_{FO}, df_{FO} and L/D_{SO} showed low values in 7 (58.3%), 10 (83.3%) and 8 (66.7%) out of all 12 eyes in the acute period, respectively. In the remission period, values in the normal range were obtained in 12 (100%), 11 (91.7%) and 8 (66.7%) out of 12 eyes in the Rf_{FO}, df_{FO} and L/D_{SO}, respectively. In mutual relation to each Rf_{FO}, df_{FO} and L/D_{SO} in the acute and remission periods, all 12 eyes showed recovery values both in the Rf_{FO} and df_{FO} in the remission stage after systemic administration of corticosteroids, but 4 out of 12 eyes (33.3%) showed no recovery in the L/D_{SO}. The FO may therefore well reflect the affected or ameliorated conditions in the outer layers of the retina and the choroid in Harada disease, in contrast to the SO. However, further observations are requested in more Harada disease patients.

Key words: acute and remission periods; electrooculogram; fast oscillation; Harada disease; slow oscillation

Harada disease is a posterior uveitic disease manifesting exudative retinal detachment that is classified as the posterior uveitis type of Vogt-Koyanagi-Harada (VKH) syndrome. Indocyanine green (ICG) fluorescence angiography has revealed severe disturbance of choroidal circulation derived from compression due to the high-grade infiltration of inflammatory cells into the choroid in

Abbreviations: AD, maximum amplitude in the dark period; AL, minimum amplitude in the light period during FO measurement; CRVO, Central retinal vein occlusion; df_{FO}, average difference in μV between AD and AL during the FO measurement; EOG, electrooculogram; FO, fast oscillation; ICG, indocynine green; L/D_{SO}, light/dark trough ratio of the SO; Rf_{FO}, average ratio in percentage of AD/AL; SO, slow oscillation; VKH, Vogt-Koyanagi-Harada

Harada disease; in the early to late stage, leakage from the choroid into the subretinal space is seen in ICG angiography at the same leak points seen in fluorescein fundus angiography, and in the late phase, filling delay of the choroidal circulation and indistinct choroidal vessels correlate with the severity of the disease (Matsunaga et al., 1994).

VKH syndrome is considered to be an autoimmune syndrome against melanocytes (Moorthy et al., 1995). The mechanism and immunological reactions against melanocytes are not well understood (Hayakawa et al., 2004), but clinically VKH syndrome can be treated relatively easily by systemic corticosteroids, although the inflammation may be prolonged and result in reduced visual acuity in some cases.

Choroidal circulation supplies the outer portion of the retina, including the photoreceptor cells and retinal pigment epithelium. Thus, it is natural that choroidal circulation disturbance should influence fast and slow oscillations (FO and SO) of the electrooculogram (EOG) originating from the outer portion of the retina, mainly the retinal pigment epithelium under the influence of choroidal circulation (Nakao et al., 1995; Tamai et al., 1997; Inoue et al., 2003), but little attention has been paid to the behavior of both potentials, especially the FO in various types of choroidal diseases including Harada disease (Tamai et al., 1997; Tamai, 2003). In the present study, we assessed clinical utility of the FO and SO of the EOG in Harada disease.

Patients and Methods

Patient selection

Six patients (2 males, 4 females; age range 18–77 years, average 41.8 years) with Harada disease in the acute period before treatment were randomly chosen for EOG recording over the past 4 years (August 1996 to September 2000) at the Department of Ophthalmology, Tottori University Hospital (Table 1). Both eyes showed typically affected diffuse or focal chorioretinal lesions, ophthalmoscopically and fluorescein fundus angiographically at the initial clinical examination in each patient. All patients were treated by systemic corticosteroids with intravenous injection of methylpredonisolone 1,000 mg for 3 days

Table 1. Clinical data of 12 eyes of 6 patients with Harada disease

Patient number	Age (year)	Sex	Affected eye	Corrected visual acuity		Type of RD
				Acute period	Remission period	
1	47	Female	Right	0.03	1.2	Diffuse
			Left	0.04	0.8	Diffuse
2	77	Female	Right	0.5	0.9	Diffuse
			Left	0.2	0.9	Diffuse
3	21	Female	Right	0.03	1.2	Diffuse
			Left	0.02	1.2	Diffuse
4	18	Female	Right	0.7	1.0	Focal†
			Left	0.7	0.8	Focal
5	33	Male	Right	0.5	1.2	Diffuse
			Left	0.05	1.2	Diffuse
6	55	Male	Right	0.8	1.0	Focal
			Left	0.7	0.9	Focal
Average	41.8			0.23	0.87	

RD, exudative retinal detachment in the acute period.
† Limited in the arcade.

Table 2. Results of the Rf_{FO} of the EOG in 12 eyes of 6 patients with Harada disease

Patient number	Affected eye	Acute period		Remission period		
		Rf_{FO} (%)	<114.7%*	Rf_{FO} (%)	≥114.7%†	Recovery value§
1	Right	108	●	119	●	●
	Left	109	●	121	●	●
2	Right	124		139	●	●
	Left	110	●	124	●	●
3	Right	138		147	●	●
	Left	127		133	●	●
4	Right	114	●	155	●	●
	Left	113	●	150	●	●
5	Right	108	●	135	●	●
	Left	108	●	142	●	●
6	Right	130		135	●	●
	Left	128		138	●	●
Ratio			7/12 (58.3%)		12/12 (100%)	12/12 (100%)

* Data under 114.7% indicate low values of the Rf_{FO} in the present study.
† Data over 114.7% indicate values in the normal range.
§ Increased Rf_{FO} obtained in the remission period, compared with the Rf_{FO} in the acute period.
Pertinent data in each column are marked by a solid circle (●).

followed by gradually decreased administration of predonisolone from 60 mg to 5 mg every week until the remission stage.

Their corrected visual acuities from 0.02 to 0.7 averaging 0.23 in the acute period showed remarkably recovered visions from 0.8 to 1.2 averaging 0.87 in the remission period under corticosteroid therapy (Table 1).

Patients were excluded from this study if they had an opaque media and a bilateral refraction error difference of more than 3 diopters.

FO and SO recordings

By a newly devised automated electrooculograph, the Nidek EOG-2 (Nidek, Gamagori, Japan) (Nakao et al., 1995; Inoue et al., 2003), the FO and SO were recorded in the acute period before treatment and in the remission period under corticosteroid therapy in each patient. The EOG-2 consists of a dome, a personal computer, an index controller, an amplifier, a printer and an EOG pen recorder. Inside the dome is a hemispheric screen with a radius of 300 nm. Four tungsten lamps (115 V, 50 W) produce a background luminance of 1,270 lx, when measured at the location of the patient's eyes.

For every patient, cup-shaped silver-silver chloride conductive electrodes, 8 mm in diameter, were placed beside both canthi of each eye on the orbital margin, and a grounding electrode, with the same cup shape, was placed on the left earlobe, as routinely used. Before setting these electrodes, the skin was cleaned with 90% alcohol, and then electrodes were applied with a conductive paste. Electrode resistance was below 10 kΩ.

Before FO recording, a 10-min adaptation period at a background luminance level of 1,270 lx was given to the patients. Then the patients were instructed to fixate alternately on a pair of targets on the screen inside the dome. The 2 targets subtended 40° to the eye, and were presented alternately with a frequency of 0.5 Hz.

On the FO recording, the dome was periodically illuminated for 1 min followed by 1 min of darkness. The measurements were started 40 s after each dark or light period began. There were 10 measurements in each dark or light period. Six out of 10 EOG amplitudes were automatically

Table 3. Results of the df_{FO} of the EOG in 12 eyes of 6 patients with Harada disease

Patient number	Affected eye	Acute period df_{FO} (μV)	Acute period <108.4 μV*	Remission period df_{FO} (μV)	Remission period ≥108.4 μV†	Recovery value§
1	Right	55	●	109	●	●
	Left	45	●	124	●	●
2	Right	83	●	181	●	●
	Left	47	●	125	●	●
3	Right	80	●	113	●	●
	Left	78	●	104		●
4	Right	124		191	●	●
	Left	114		144	●	●
5	Right	23	●	210	●	●
	Left	18	●	110	●	●
6	Right	92	●	138	●	●
	Left	101	●	127	●	●
Ratio			10/12 (83.3%)		11/12 (91.7%)	12/12 (100%)

* Data under 108.4 μV indicate low values of the df_{FO} in the present study.
† Data over 108.4 μV indicate values in the normal range.
§ Increased df_{FO} obtained in the remission period, compared with the df_{FO} in the acute period.
Pertinent data in each column are marked by a solid circle (●).

averaged and recorded at the end of each dark or light period through the EOG artifact rejection system on the Nidek EOG-2 (Inoue et al., 2003).

In 10 pairs of FO measurements (dark-light period of 1 min each), FO parameters, namely the Rf_{FO} [the average ratio in percentage of the maximum amplitude in the dark period (AD)/the minimum amplitude in the light period (AL)] and the df_{FO} (the average difference in μV between AD and AL during the FO measurement) were calculated, referring to the report by De Rouck and Kayembe (1981), only if at least 3 successive steps

Table 4. Results of the L/D_{SO} of the EOG in 12 eyes of 6 patients with Harada disease

Patient number	Affected eye	Acute period L/D_{SO}	Acute period <1.6*	Remission period L/D_{SO}	Remission period ≥1.6†	Recovery value§
1	Right	1.37	●	2.14	●	●
	Left	1.29	●	2.14	●	●
2	Right	2.45		1.96	●	
	Left	1.76		1.47		
3	Right	1.40	●	3.37	●	●
	Left	1.34	●	3.59	●	●
4	Right	1.43	●	1.85	●	●
	Left	1.44	●	1.91	●	●
5	Right	1.00	●	1.06		●
	Left	1.30	●	1.48		●
6	Right	2.37		1.51		
	Left	2.27		1.68	●	
Ratio			8/12 (66.7%)		8/12 (66.7%)	8/12 (66.7%)

* Data under 1.6 indicate low values of the L/D_{SO} in the present study.
† Data over 1.6 indicate values in the normal range.
§ Increased L/DSO obtained in the remission period, compared with the L/D_{SO} in the acute period.
Pertinent data in each column are marked by a solid circle (●).

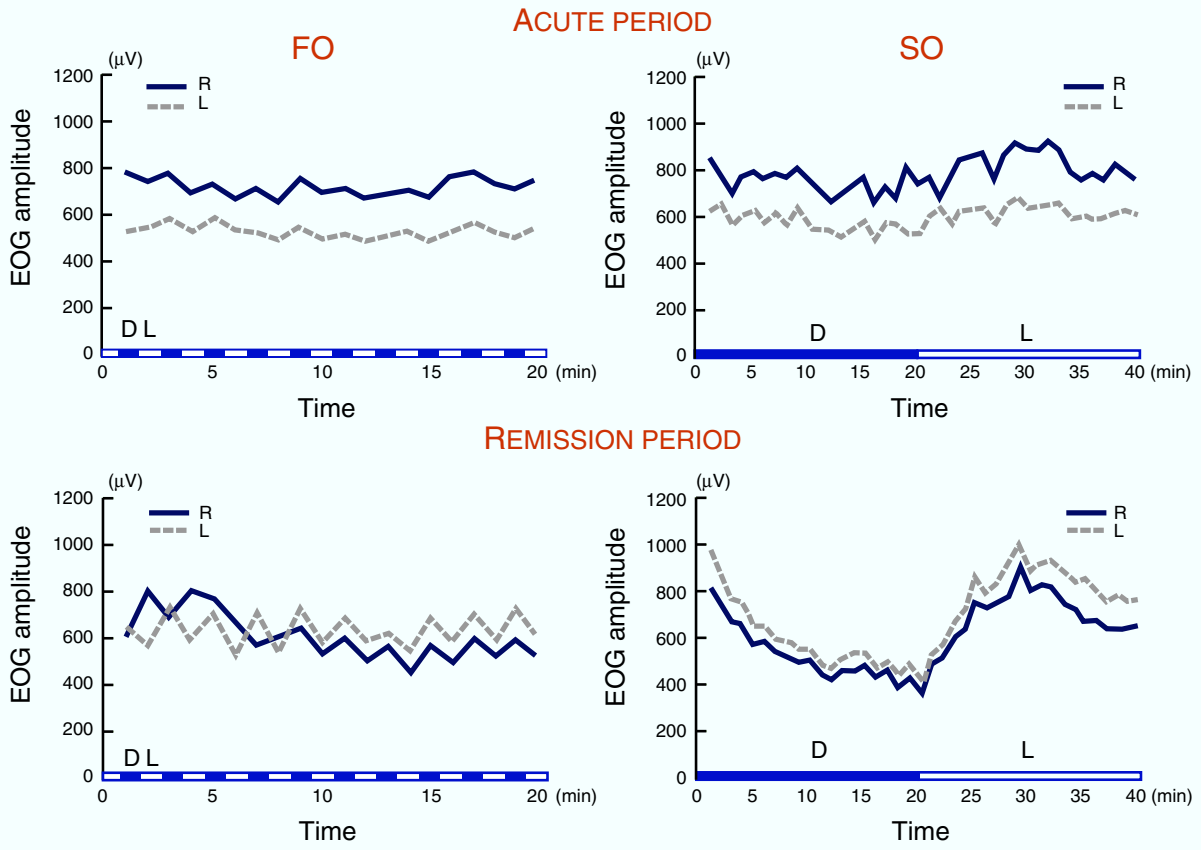


Fig. 1. EOG fast oscillation (FO) and slow oscillation (SO) patterns in the acute and remission periods in both eyes of Patient 1 with Harada disease (47-year-old female). R, right eye; L, left eye. D, dark period; L, light period (horizontal axis).

showed some identical amplitude change. Dated and occasional large amplitude changes were not taken into account (Inoue et al., 2003).

Then the SO was recorded in all patients. Before the SO recording, the patients were subjected to a 10-min pre-light adaptation in the same manner as in the FO recording. On the recording, where 20 min of darkness was followed by 20 min of illumination, EOG measurements were started 40 s before the end of each 1-min period during the dark and light adaptations. Six out of 10 EOG amplitudes were automatically averaged and recorded every 1 min during the SO measurement as in the FO recording.

The SO shows a trough in the dark adaptation (dark trough) and a peak in the light adaptation (light peak) in response to dark and light periods of approximately 12.5 min each. The L/D_{SO} (the light peak/dark trough ratio of the SO) developed by Arden and others (1962) was automatically calculated as an SO parameter in the present survey.

In this study, the calibration sensitivity for the pen recorder was 200 μV/division on the printer. The time constant of the amplifier was set at 3 s, and a high frequency cutoff of -3 dB was set at 20 Hz for both FO and SO recordings.

Pupillary dilation provides better control of retinal illumination levels, but prolongs the time for the EOG examination and may make the examination somewhat more uncomfortable for some patients. Therefore, the FO and SO recordings were performed with pupils undilated.

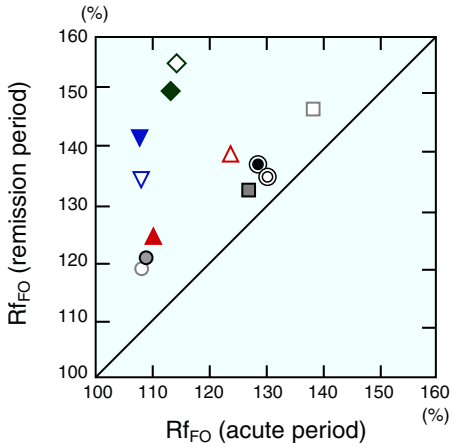


Fig. 2. Mutual relation to the Rf_{FO} of the EOG in the acute and remission periods in 12 eyes of 6 patients with Harada disease.

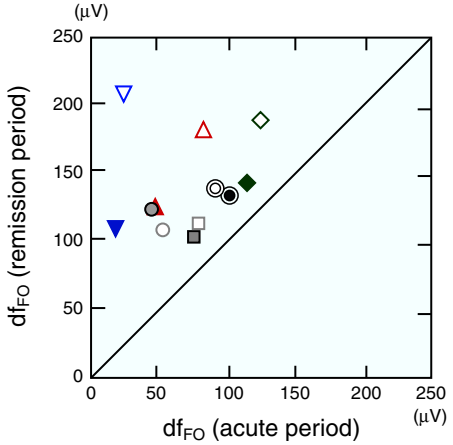


Fig. 3. Mutual relation to the df_{FO} of the EOG in the acute and remission periods in 12 eyes of 6 patients with Harada disease.

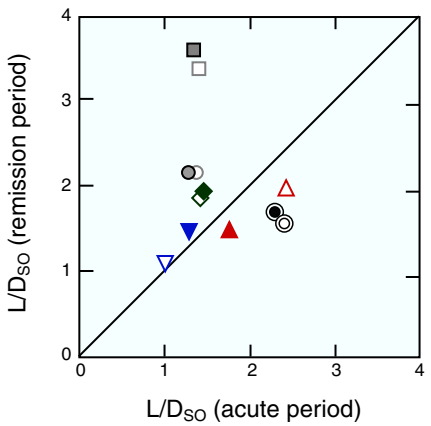
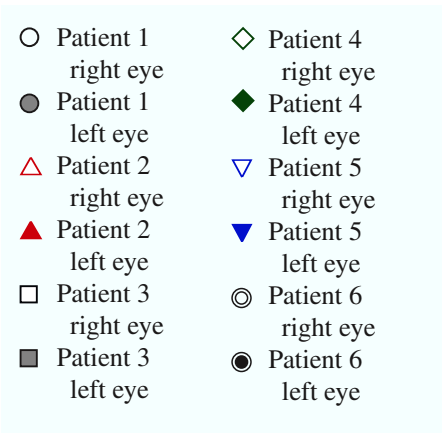


Fig. 4. Mutual relation to the L/D_{SO} of the EOG in the acute and remission periods in 12 eyes of 6 patients with Harada disease.

Marks indicating each eye of each patient in Figs. 2 to 4:



Normal control eyes

Twenty-one fellow intact eyes of 21 patients with unilateral, ischemic central retinal vein occlusion (CRVO) previously reported by Inoue and others (2003) served as normal control eyes in the present survey. Mean ± SD of the Rf_{FO}, df_{FO} and L/D_{SO} were 125.9 ± 11.2% [n = 21], 168.9 ± 60.5 μV [n = 21] and 1.93 ± 0.33 [n = 20], respectively in their FO and SO measurements (Inoue et al., 2003). Therefore, values over 114.7%, 108.4 μV and 1.6 in the Rf_{FO}, df_{FO} and L/D_{SO}, respectively were tentatively regarded as those in the normal range in the present analysis.

Results

The FO and SO results obtained in the present study are summarized in Tables 2 to 4.

Practical EOG FO and SO patterns in both eyes of Patient 1 (47-year-old female) are demonstrated in Fig. 1. In this patient, reduced or deteriorated FO and SO patterns were observed in both eyes in

the acute period manifesting diffuse chorioretinal lesions before treatment. Normal FO and SO patterns, however, were detected in both eyes in the remission period after systemic administration of corticosteroids reflecting ameliorated conditions in her fundi.

Compared with normal control eyes, the Rf_{FO}, df_{FO} and L/D_{SO} showed low values in 7 (58.3%), 10 (83.3%) and 8 (66.7%) out of all 12 examined eyes of the 6 patients in the acute period, respectively (Tables 2 to 4). In the remission period, values in the normal range were obtained in 12 (100%), 11 (91.7%) and 8 (66.7%) out of 12 eyes of the patients in the Rf_{FO}, df_{FO} and L/D_{SO}, respectively (Tables 2 to 4).

In mutual relation to the Rf_{FO} in the acute and remission periods in the 6 patients (12 eyes), all 12 eyes showed recovery values in the remission stage under corticosteroid therapy (Table 2, Fig. 2).

In mutual relation to the df_{FO} in the acute and remission periods in the 6 patients (12 eyes), all 12 eyes also showed recovery values in the remission period (Table 3, Fig. 3).

However, in mutual relation to the L/D_{SO} in the acute and remission periods in the 6 patients (12 eyes), 4 out of 12 eyes (33.3%) showed no recovery in their values in the remission stage under the therapy (Table 4, Fig. 4).

Discussion

Concerning the origin and occurrence of the FO and SO potentials in which the outer layers of the retina, mainly the retinal pigment epithelium in its basal membrane are almost equally involved under the influence of choroidal disorders (Arden et al., 1962; Steinberg et al., 1983; Joseph and Miller, 1991), our FO-dominated pattern changes in the present study are not necessarily explainable, but it is of note that in 2 patients (2 eyes) with acute posterior multifocal placoid pigment epitheliopathy, one of the other chorioretinal diseases, almost the same tendency of recovery of their reduced FO patterns before treatment was observed after systemic administration of corticosteroids with amelioration of their ocular findings, although their highly fluctuated, irregular SO patterns before treatment showed no remarkable recovery in their patterns after the treatment by systemic corticosteroids (Tamai et al., 1997; Tamai, 2003).

The FO may therefore be well reflected even in Harada disease, in contrast to the SO, although further observation is required using more Harada disease patients.

Some physiological factors, such as age and sex, may influence the FO potential (Nakao et al., 1995; Tamai et al., 1997). Thus we need more prudent, long-term observations on the FO patterns in these chorioretinal diseases including Harada disease, considering these factors.

In the present study, the visual outcome after the treatment by systemic corticosteroids was all well in the 12 eyes of the 6 patients. This time, statistical analysis was not undertaken on the correlation between each parameter in the FO and SO recordings and corrected visual acuity in each patient's eye both in the acute and remission period due to a small number of samples. As for the visual prognosis, utility of a cone-dominated activity on the FO was pointed out in patients with unilateral, ischemic CRVO (Inoue et al., 2003). Accordingly, although the background of macular functional disturbance in Harada disease is different from that in CRVO in etiology, such FO-dominated pattern changes in the present survey might be helpful for detecting the severity of macular functional disturbance and predicting the visual outcome for this entity. Further work is required to investigate these aspects in more Harada disease patients.

Anyway, the results obtained in the present study may indicate that the FO is an effective examination method to detect the affected or ameliorated conditions in the outer layers of the retina and the choroid in Harada disease, in contrast to the SO. However, further observations are requested in more Harada disease patients, as described above.

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