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Multifocal Electroretinogram in Patients with Central Serous Chorioretinopathy

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Purpose: To assess local retinal function of macula in patients with central serous chorioretinopathy (CSC).

Methods: Multifocal electroretinograms (ERGs) were recorded in 5 patients with unilateral CSC and 20 normal subjects. The waveforms from the central retina within 5° of visual angle were analyzed. The first negative trough was designated as N1, the first positive peak as P1, and the second trough as N2.

Results: The multifocal ERG amplitudes were significantly reduced at the first attack of CSC in all patients compared with the values in the normal controls, for P1–N1 ($P < .01$) and for P1–N2 ($P < .01$). Multifocal ERG latencies of the patients significantly increased compared with normal controls, for P1 ($P < .01$) and N2 ($P < .01$). After the resolution of retinal detachment, although the multifocal ERG amplitudes increased markedly, they did not improve to the normal level during the follow-up period (4–23 months).

Conclusions: Persistent functional impairment of the retina was found by multifocal ERGs in patients with CSC after the resolution of subretinal fluid. A topographical analysis of the multifocal ERG is useful in the clinical observation of CSC. **Jpn J Ophthalmol 2002;46:308–314**

Key Words: Central serous chorioretinopathy, multifocal electroretinogram.

Introduction

Central serous chorioretinopathy (CSC) is an idiopathic syndrome typically seen in young and middle-aged adults.[1] Almost all patients complain of visual disturbances, including metamorphopsia and micropsia. On the other hand, central visual acuity is often less decreased.[1]

Electrophysiological investigations of CSC have included local macular electroretinograms (ERGs). Previous studies using local macular ERG have measured only the amplitudes of the major positive wave (b-wave).[2–4] Miyake and his colleagues measured the first negative wave (a-wave), b-waves, and oscillatory potentials using the averaging technique to improve the signal-to-noise ratio.[5–7] This technique permits the testing of a single local area at a time.[5–7] They suggested that inner retinal functions were affected subclinically.[8,9]

Recently, Sutter and Tran[10] introduced a multifocal ERG system that could stimulate multiple retinal areas simultaneously and detected each response independently by using multi-input system analysis. Using this technique, we investigated the multifocal ERGs from 5 patients with unilateral CSC.

Materials and Methods

We studied 5 patients with CSC. The follow-up periods ranged from 4 to 23 months (median = 15.0 months). The diagnosis of CSC was obtained after fluorescein angiography (FA) (Table 1). The patients had no other ocular diseases. The ages of the patients ranged from 30 to 48 years (median = 41.8 ± 8.0; 4 men and 1 woman). Twenty volunteers who served as normal controls had full visual acuity with appropriate correction; refraction errors ranged from +1 to −4.25

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Table 1. Clinical Characteristics of Patients with Central Serous Chorioretinopathy

Case No.	Age*	Sex	Follow-up Period (Mo)	VA†	Refractive Error	Size‡ (DD)	FA§	VA‖	FT¶ (dB)
1	41	Male	23	20/30	0	2.5	leakage (+)	20/16	35
2	48	Female	6	20/25	−0.5	2	(±)	20/16	33
3	37	Male	22	20/16	0	1	(+)	20/16	34
4	30	Male	20	20/20	−5.0	2	(+)	20/16	36
5	48	Male	4	20/16	1.0	1.5	(+)	20/30	26

*At initial visit.
†Visual activity of Snellen notation at initial visit.
‡Range of subretinal fluid. DD: disc diameter.
§Fluorescein angiography at initial visit.
‖Final visual acuity.
¶Foveal threshold of Humphrey Field analysis at final examination.

diopters (median = −1.4 diopters). They had no history of eye disease and no serious systemic disease. Their ages ranged from 18 to 64 years (median = 34.9 years).

Prior to the experiment, the procedures were explained to the subjects and written informed consent was obtained from each subject. The examination protocol was designed according to the Declaration of Helsinki. Then, we recorded their multifocal ERGs. We also examined their visual acuity and the foveal threshold of static field analysis (Humphrey Field Analyzer [HFA]; Carl Zeiss Instruments, Dublin, CA, USA).

The multifocal ERG recording system that we used has been described by Sutter and Tran[10] The stimulus matrix consisted of 103 hexagonal elements displayed on a black and white monitor (MD-B1700; Chuomusen, Tokyo). The radius of stimulus arrays subtended approximately 40° high and 50° wide. Each hexagon was independently alternated between black (5 cd/m^2) and white (200 cd/m^2) according to a pseudorandom sequence called a binary m-sequence at a frame rate of 75 Hz.[10] A small gray spot or filled cross was placed at the center of the stimulus matrix as a fixation mark. The filled cross was used once at the first onset of case 1.

The pupils were fully dilated with a combination of 0.5% tropicamide and 0.5% phenylephrine hydrochloride. The tested eyes of the subjects were fully corrected and the opposite eyes were occluded. The distance between monitor and subject was adjusted according to an implemented nomogram to ensure a similar retinal magnification of the stimulus image regardless of the individual refraction. The ERG responses were recorded with a Burian-Allen bipolar contact lens electrode (Hansen Ophthalmic, Iowa City, IA, USA). The ground electrode was attached to the earlobe. The total recording took 4 minutes and was divided into eight segments. The signal amplification was 100,000 and the bandpass filter was set at 10 Hz–300 Hz (Grass, Model 12; Quincy, MA, USA). Each local ERG was calculated from the raw data by a cross correlation technique, which extracts linear and non-linear components.[10] Figure 1 shows a trace array with all 103 focal ERGs. For further analysis, focal ERGs were grouped into concentric rings and we analyzed the averaged waves in the central area, as shown in Figure 1. The analyzed area was approximately 5° of the central retina.

Peak-to-trough amplitudes were measured from the first (negative) trough (N1) to the first (positive) peak (P1) (P1–N1) and first peak to the second trough (N2) (P1–N2) as shown in Figure 2. The implicit time was measured in each group from the on-

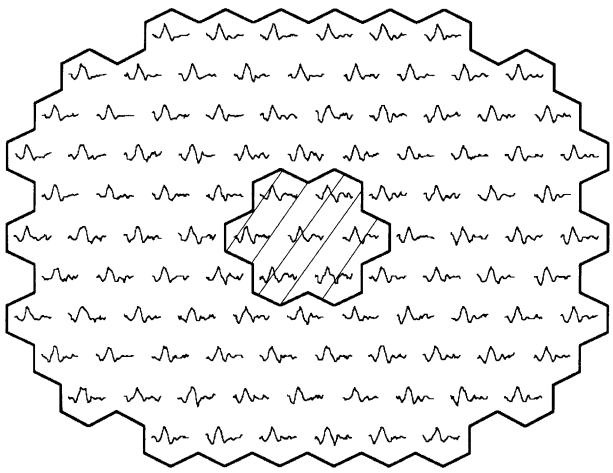

Figure 1. Stimulus array of 103 hexagonal elements. The responses are grouped in six rings. The inner two rings were analyzed; oblique lines show this area.

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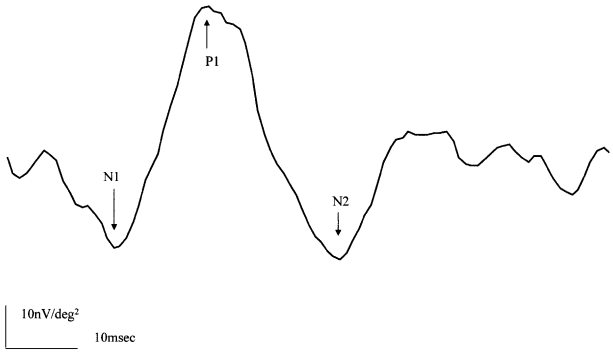

Figure 2. Waveform of multifocal electroretinogram. Positive peak is labeled as P1; negative troughs as N1 and N2.

set of the stimulus to the N1, P1, and N2 of the response. The amplitudes were divided by the area from which each amplitude was evoked, resulting in a measure of response density in nV/deg.[2] We measured the multifocal ERG several times in each case at different phases. In one phase, the subretinal fluid existed. In the other phase, the subretinal fluid was resolved. We divided the multifocal ERG data into two groups: group A (with subretinal fluid) and group B (without subretinal fluid). The number in group A was nine, including the first examination in case 2. The number in group B was 12. We compared the multifocal ERGs from the two groups with those from normal controls by using the unpaired *t* test (Table 2).We also compared the visual acuity (VA) and foveal threshold from the two groups with those from the fellow eyes by using the unpaired *t*-test (Table 3).The foveal threshold was measured by HFA program 30-2.

Results

Case 1

A 41-year-old man was examined at the first onset of CSC on 16 June 1997. His chief complaint at the onset was a relative central scotoma. When FA was performed, a smokestack-like dye leakage was found at 500 μm from the fovea in the upper temporal region. Compared with the normal values, amplitudes of P1–N1 and P1–N2 were reduced markedly (22.2, 19.9 nV/deg^2) and the implicit time of N2 was prolonged (52.5 msec). The leak point on the retina was photocoagulated the day after the multifocal ERG was recorded. Before the subretinal fluid was resolved, new dye leakage from another site was found near the papillomacular bundle in August 1997. The subretinal fluid disappeared in December 1997 without further photocoagulation. Seventeen months after the resolution of subretinal fluid (19 May 1999), the amplitudes of P1–N1 and P1–N2 and the N2 latency had improved to within normal levels (44.2, 46.9 nV/deg^2 43.3 msec). The change of waves in this case is shown in Figure 3.

Case 2

A 48-year-old woman was examined at the first onset of CSC on 17 November 1997. Her chief complaint was the same as in case 1. FA showed a number of window defects in the posterior pole, and several were slightly hyperfluorescent at the late stage of FA. The amplitudes of P1–N1 and P1–N2 were reduced compared with those of the normal controls (28.8, 24.8 nV/deg^2). The implicit times were not prolonged significantly in this case. One month later, the subretinal fluid was found to be resolved. Five months after the subretinal fluid had disappeared, the amplitudes improved to almost normal (39.5, 41.7 nV/deg^2). This case showed no recurrence.

Case 3

A 37-year-old man was examined at the first onset of CSC on 19 February 1998. His chief complaint was the same as in case 1. There was a smokestack-like dye leakage near the fovea when FA was performed. Compared with normal values, the ampli-

Table 2. Mean Values and Standard Deviations of the Multifocal Electroretinogram Indices of the Normal Controls and Central Serous Chorioretinopathy Patients at Different Phases*

	SRF(+) (A)	SRF (−) (B)	Normal (N)	N–A	N–B	A–B
Implicit time						
N1	15.9 ± 1.5	14.9 ± 1.1	15.2 ± 1.1	NS	NS	$P = .04$
P1	30.1 ± 1.1	28.9 ± 1.7	28.2 ± 1.3	$P < .01$	NS	NS
N2	46.5 ± 3.2	44.0 ± 2.2	43.8 ± 1.3	$P < .01$	NS	$P = .01$
Amplitude						
P1–N1	25.6 ± 8.1	35.2 ± 5.7	46.0 ± 8.8	$P < .01$	$P < .01$	$P < .01$
P1–N2	24.5 ± 9.9	37.4 ± 11.9	52.1 ± 9.9	$P < .01$	$P < .01$	$P < .01$

*SRF: subretinal fluid, N: normal control, NS: not significant. Unpaired *t*-test.

Table 3. Mean Values of the Best-Corrected Visual Acuity (logMAR) and Foveal Threshold (dB) in the 3 Groups

	SRF(+) (A)	SRF(−) (B)	F	F–A	F–B	A–B
VA	1.0 (0.83–1.23)	1.1 (0.95–1.20)	1.20	$P < .05$	NS	NS
HFA						
Foveal threshold	31.3 ± 4.3	35.0 ± 2.5	35.2 ± 3.7	$P < .05$	NS	$P < .05$

SRF: subretinal fluid, F: normal fellow eye, VA: final visual acuity, HFA: Humphrey field analysis. Unpaired *t*-test.

tudes of P1–N1 and P1–N2 were reduced markedly (24.1, 32.9 nV/deg^2) and the N2 implicit time was prolonged (49.2 msec). The subretinal fluid had disappeared by June 1998. Six months later, CSC recurred: the leakage occurred from the same point as before. Even after recovery (February 1999), the P1–N1 and P1–N2 amplitudes were still markedly reduced (30.7, 32.4 nV/deg^2) and the N2 implicit time was prolonged compared with those of the normal controls (45.8 msec).

Case 4

A 30-year-old man was examined at the first onset of CSC on 19 March 1998. His chief complaint was the same as in case 1. There was a blot-like dye leakage near the papillomacular bundle when FA was performed. Compared with the normal values, the P1–N1 and P1–N2 amplitudes were markedly reduced (20.2, 17.9 nV/deg^2) and the N2 implicit time was prolonged (50.0 msec). The subretinal fluid had disappeared by April 1998. The P1–N1 amplitude and the N2 implicit time were normal in November 1998 (38.2 nV/deg^2 44.2 msec). One year after the subretinal fluid was resolved, it appeared again: the leakage occurred from the same point as before. In October 1999, although the subretinal fluid had disappeared again, both amplitudes had not improved to normal values (29.8, 24.8 nV/deg^2).

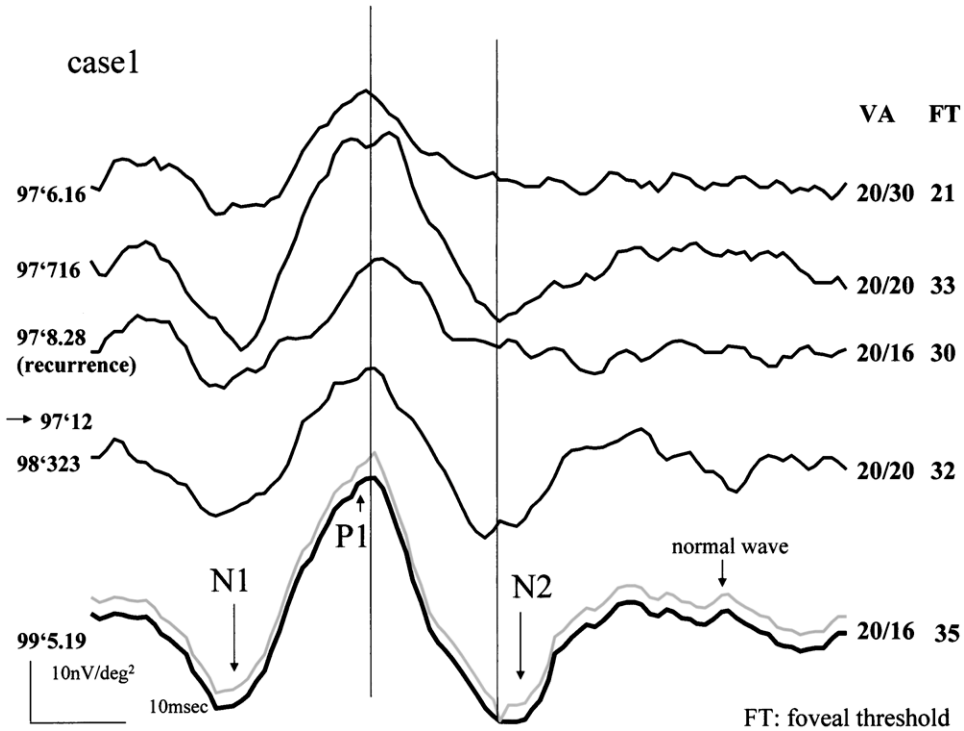

Figure 3. The wave change in case 1.

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Case 5

A 48-year-old man was examined at the first onset of CSC on 19 January 1998. His chief complaint was the same as in case 1. There was a blot-like dye leakage near the papillomacular bundle when FA was performed. The amplitudes of P1–N1 and P1–N2 were markedly reduced compared with those of the normal controls (21, 16 nV/deg^2). The subretinal fluid was still present at the last examination in May 1998.

Statistical Difference in Multifocal ERG Amplitudes and Implicit Times

Table 2 shows the mean and SD of the multifocal ERG indices of all 5 patients. Statistical differences were found among groups A and B and the normal subjects. Patients in group A had subretinal fluid, but patients in group B had no subretinal fluid in the macular region.

The mean values of P1–N1 and P1–N2 were the smallest (25.6 and 24.5 nV/deg^2) in group A. Although the mean amplitudes in group B were 9.6–14.9 nV/deg^2 higher than those in group A, the values did not improve to the normal level. Significant differences ($P < .01$) in the amplitudes were found among these 3 groups.

The mean N2 in group A was significantly ($P \leqq .01$) greater than in the other groups. It meant that N2 decreased sensitively to normal level after resolution of the subretinal fluid. On the other hand, there were no significant differences between groups A and B for P1 implicit time. Thus, N2 changed more than P1 after resolution of the subretinal fluid. Compared with the early component of N1, the P1 and N2 latencies were more prolonged ($P < .01$) in group A.

The mean ratio and SD of (P1–N2)/(P1–N1) were 0.91 ± 0.16 in group A and 1.07 ± 0.21 in group B. Thus, P1–N2 was decreased more than P1–N1 in the acute phase of CSC.

We recorded the multifocal ERG from the fellow eye several times in each case. In two cases, P1–N2 amplitude decreased compared with values in the normal controls. Mean value of the P1–N2 was 39.8 nV/deg^2 in case 2 and 32.0 nV/deg^2 in case 4.

Comparison of Psychophysical Data Among Groups A and B and Fellow Eyes (F)

There was a significant difference ($P < .05$) in visual acuity between groups A and F. There were no significant differences between groups F and B or between A and B.

The foveal threshold of static perimetry in group A was significantly reduced ($P < .05$) compared with group B or group F. There was no significant difference between F and B.

Discussion

The usefulness of multifocal ERG in the evaluation of central retinal dysfunction is widely accepted.[11–17] CSC is one of the retinal diseases of the central retinal area. Several authors have reported wave changes in patients with CSC.[15–17] The amplitudes of multifocal ERG can be decreased a long time after subretinal fluid has disappeared.[16,17] On the other hand, Aoyagi[15] reported that the P1–N1 amplitude of affected eyes was significantly reduced and the implicit time of P1 was significantly prolonged; one month after the subretinal fluid had resolved, the multifocal ERG returned to normal. However, Chappelow and Marmor[16] and Kretschmann et al[17] reported delayed recovery of multifocal ERG amplitudes after the resolution of subretinal fluid. Our results also indicate the delayed recovery of multifocal ERG amplitudes after the resolution of subretinal fluid.

Miyake et al reported local macular ERG in CSC.[8,9] They found a reduction of amplitudes and prolongation of implicit times while subretinal fluid existed. They also reported the delayed recovery of oscillatory potentials after the resolution of subretinal fluid. The amplitudes of oscillatory potentials were the most significantly decreased, followed by those of the b-wave. Two to five months after the macular detachment resolved, recordings showed a remarkable recovery of a- and b-waves and shortened implicit times. However, oscillatory potentials showed only a small recovery in amplitude. On the basis of these results, Miyake et al suggested that inner retinal functions were affected as well as outer retinal function.

It is difficult to compare directly the results of multifocal ERGs with those of other ERG studies.[8,9] There are many methodological differences in ERG techniques, and the origin of the N2 component is still obscure. Kondo et al[18] reported that high-luminance, rapid, random stimuli produced first-order kernel responses with short implicit times similar to those of flash cone ERG responses. Hood and his colleagues[19] reported that the first negative wave of the multifocal ERG comprised the same components as the a-wave of the full-field ERG, and that the positive wave of the multifocal ERG was some combination of the positive components of the full

field ERG. From those reports[18,19] the positive wave in multifocal ERG should include oscillatory potentials. In our study, the P1–N2 amplitudes were decreased more than the P1–N1 in the acute phase of CSC. Thus, our results are in good agreement with previous results.[8,9] and suggest that the inner retina as well as the photoreceptors are affected in patients with CSC.

Retinal ganglion cells are lost in glaucoma as optic nerve damage progresses.[20] It is also known that the inner two-thirds of the retina is damaged in patients with branch retinal artery occlusion (BRAO).[21] There have been few reports of the quantitative relationship between the multifocal ERG and sensitivity loss measured behaviorally by perimetry in patients with glaucoma. Hasegawa et al[22] reported a relationship between the waveform changes of the multifocal ERG and perimetric field loss. The changes in the peak latencies of P1 and N2 in a group with primary open angle glaucoma were small but significant compared with those in the normal group. Hasegawa et al[23] reported that the later components (P1, N2) of the multifocal ERG in patients with BRAO were changed more than the earlier ones (N1) by artery occlusion. They concluded that these later components may contain more information regarding the inner retina than the earlier ones.[22,23] On the other hand, ophthalmoscopic examination of patients with CSC revealed an accumulation of serous fluid in the subretinal space, which suggests a functional disturbance of the outer retina in the macula.[24] In our study, the later component of N2 was more prolonged in CSC patients while subretinal fluid existed. Thus, we hypothesize that changes in the later components of multifocal ERGs might indicate a dysfunction of the postreceptoral components in CSC.

Compared with the normal controls, we found a significant decrease in the multifocal ERG amplitudes in group B patients whose subretinal fluid resolved. On the other hand, there were no significant differences in the visual acuity or in the foveal threshold between the normal fellow eyes and the group B patients. Thus, the multifocal ERG indices could detect abnormal retinal function more sensitively than psychophysiological tests of visual acuity or perimetric threshold.

Our results revealed persistent abnormality of the multifocal ERG after the resolution of subretinal fluid in patients with CSC. Moreover, more significant changes were found in the later components of the multifocal ERG. These results suggest that the inner retina is also involved in patients with CSC. In conclusion, multifocal ERGs were useful to show topographic and layer-by-layer information on the retina in patients with CSC.

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