Multifocal Electroretinogram in Occult Macular Dystrophy

Chang-Hua Piao, Mineo Kondo, Atsubiro Tanikawa, Hiroko Terasaki, and Yozo Miyake

PURPOSE. Occult macular dystrophy (OMD) is an unusual macular dystrophy presenting with an essentially normal fundus and fluorescein angiography but with progressive central visual loss. The authors studied the function of local retinal areas in the posterior pole of patients with OMD using multifocal electroretinograms (ERGs).

METHODS. Multifocal ERGs were recorded using the Visual Evoked Response Imaging System with 61 hexagonal elements within a visual field of 30° radius from 8 OMD patients and 20 age-matched, normal subjects. The amplitudes and implicit times of the patients and normal control subjects were compared at the various retinal eccentricities.

RESULTS. The amplitudes of the multifocal ERGs in the OMD patients were markedly reduced in the central 7° of the fovea. The difference of the ERG amplitudes between OMD and normal subjects became smaller toward the peripheral retina. Most OMD patients had slightly but significantly delayed implicit times across the whole testing field, and the differences between the OMD and the normal subjects did not change with retinal eccentricity.

CONCLUSIONS. Our results for multifocal ERG amplitudes support the idea that OMD patients have localized retinal dysfunction distal to the ganglion cells in the central retina. The delayed implicit times across the whole test field suggest that the retinal dysfunction has a broader boundary than expected by ERG amplitudes and psychophysical perimetric results. (Invest Ophthalmol Vis Sci. 2000;41:513–517)

Occult macular dystrophy (OMD) is an unusual, inherited macular dystrophy characterized by an essentially normal fundus and fluorescein angiography but progressive decline of visual acuity in both eyes.1,2 These patients have normal full-field electroretinograms (ERGs) but severely reduced focal macular ERGs, which were recorded by conventional techniques using small stimuli under the background illumination.3,4 Thus, it has generally been presumed that patients with OMD have a local retinal dysfunction distal to the ganglion cells in the central retina. It has been emphasized that the main key to differentiate OMD from other diseases, such as optic neuritis, dominant optic atrophy, amblyopia or psychological disorders, was the recording of focal ERGs from the central retina.5–7

The multifocal ERG allows a rapid, simultaneous recording of focal ERGs from multiple retinal locations from the posterior pole of the eye4,8,9 and thus can evaluate local retinal function.6–12 We previously have demonstrated in a preliminary study7 that the multifocal ERG technique can be a valuable tool to diagnose OMD patients. One might expect that it would allow us to explore retinal function topographically in OMD patients. There is some evidence that the implicit times, as well as amplitudes, of the multifocal ERGs can be a potentially useful parameter to determine the locus of the retinal dysfunction in retinal diseases.10,11 In the present study, we therefore examined the multifocal ERGs of OMD patients to assess the amplitudes and implicit times of local retinal cone function in patients with OMD.

METHODS

Subjects

We recruited eight patients diagnosed with OMD from our clinic (Department of Ophthalmology, Nagoya University School of Medicine). The diagnosis of OMD was made by the following findings: bilateral involvement, normal ophthalmoscopic findings, normal fluorescein angiography, decreased visual acuity, normal full-field ERG for both rod and cone components, and decreased focal macular cone ERGs. Some of these characteristics are summarized in Table 1. The eight patients, five men and three women, ranged in age from 43 to 66 years (mean, 52.9 years). Five of eight patients (patients 2, 4, 5, 6, and 8) have been reported previously,2 and these patients correspond to patients 4, 6, 11, 10, and 1, respectively, of the previous paper. Three patients (3, 6, and 7) were considered to be autosomal dominant, and the other five patients were classified as sporadic, because none knew of other family members with a similar visual problem. The corrected visual acuities ranged from 0.1 (20/200) to 0.4 (20/50). Light-adapted perimetry, originally designed by Jacobson et al.,13 showed abnormally elevated cone thresholds within the central 10° in all patients. One randomly selected eye of the patients was tested with multifocal ERG. Twenty age-matched...
(normal subjects, age range from 38 to 69 years (mean, 53.3 years), were selected out of a pool of our normal data. This selection was made only by factor of age, and they were selected before analysis of patients’ data. All normal subjects had normal visual acuity, normal color vision, and normal full-field ERGs.

Informed consent was obtained after a full explanation of the procedures. All studies were conducted in accordance with the principles embodied in the Declaration of Helsinki.

Multifocal ERGs

Multifocal ERGs were recorded with the Visual Evoked Response Imaging System (EDI, San Mateo, CA), developed by Sutter et al.4,5 The stimulus matrix consisted of 61 hexagonal elements that were displayed on a CRT color monitor (GDM 2038; Sony, Tokyo, Japan) and driven at a 75-Hz frame rate. The size of the hexagons were scaled with eccentricity to elicit approximately equal amplitude responses at all locations (Fig. 1). At a viewing distance of 27 cm, the radius of the stimulus array subtended approximately 30°. The luminance of each hexagon was independently alternated between black and white according to a pseudorandom binary m-sequence at 75 Hz. The maximum luminance was 138.0 cd/m², and the minimum luminance was 3.5 cd/m², resulting in a mean luminance of approximately 70.8 cd/m². A small red fixation spot was placed at the center of the stimulus matrix.

ERGs were recorded with a Burian–Allen bipolar contact lens electrode (Hansen Ophthalmic Laboratories, Iowa City, IA), and a ground electrode was attached to the earlobe. The subjects’ pupils were fully dilated with a combination of 0.5% tropicamide and 0.5% phenylephrine hydrochloride. The opposite eye was occluded. After the subjects were optically corrected to their best visual acuity for the viewing distance, they were asked to maintain fixation on the red spot. The signal was amplified by 100K, and the bandpass was set at 10 to 300 Hz (Grass, Quincy, MA). An artifact elimination technique was used.4 The total recording took 4 minutes and was divided into eight equal segments. The first-order component and a three-dimensional plot were obtained with VERIS 2.05 software (EDI, San Mateo, CA).

RESULTS

Amplitude of the Multifocal ERGs

Figure 2 shows representative local ERGs from 61 loci (top) and a 3D plot of the amplitudes of the multifocal ERGs (bottom) recorded from the left eye of a normal subject (left) and a patient with OMD (patient 2). The multifocal ERG consists of a negative wave followed by a positive wave, and these negative and positive deflections have been shown to correspond to conventional a- and b-waves, respectively, of the flash cone ERG.14,15 As was expected from our previous study,1,2 the OMD patients had severely depressed responses from the central retina but relatively well-preserved responses in the peripheral retina. The three-dimensional plot did not show the central peak, as was observed in the normal control subject.

To quantify these changes, the responses were grouped by retinal eccentricity as shown in Figure 1, and the amplitude of the positive component was measured (the first trough to the positive peak). The response density (nV/deg · deg) was calculated by dividing the response amplitude (nV) by the retinal area (deg · deg). Figure 3a shows the response densities at five eccentric rings for the eight patients. The gray region represents the calculated 2.5 and 97.5 percentile range for the 20 normal control subjects. It is clear that all eight patients had severely reduced response densities, especially in the central areas (rings 1 and 2). The response of two of the patients fell within the gray region for rings 3 and four of the patients for ring 4. At the most peripheral area (ring 5), six of eight patients

### Table 1. Clinical Characteristics of Examined Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Gender</th>
<th>Test Eye</th>
<th>RE Visual Acuity</th>
<th>LE Visual Acuity</th>
<th>Category</th>
<th>Area of Elevated Cone Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49</td>
<td>M</td>
<td>L</td>
<td>0.3 (20/66)</td>
<td>0.3 (20/66)</td>
<td>Sporadic</td>
<td>Within 10°</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>M</td>
<td>R</td>
<td>0.2 (20/100)</td>
<td>0.3 (20/66)</td>
<td>Sporadic</td>
<td>Within 5°</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>M</td>
<td>L</td>
<td>0.4 (20/50)</td>
<td>0.4 (20/50)</td>
<td>AD</td>
<td>Within 7.5°</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
<td>M</td>
<td>R</td>
<td>0.2 (20/100)</td>
<td>0.1 (20/200)</td>
<td>Sporadic</td>
<td>Within 10°</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>F</td>
<td>L</td>
<td>0.2 (20/100)</td>
<td>0.1 (20/200)</td>
<td>Sporadic</td>
<td>Within 10°</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>F</td>
<td>R</td>
<td>0.3 (20/66)</td>
<td>0.2 (20/100)</td>
<td>AD</td>
<td>Within 5°</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>F</td>
<td>L</td>
<td>0.3 (20/66)</td>
<td>0.4 (20/50)</td>
<td>AD</td>
<td>Within 10°</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>M</td>
<td>R</td>
<td>0.2 (20/100)</td>
<td>0.1 (20/200)</td>
<td>Sporadic</td>
<td>Within 10°</td>
</tr>
</tbody>
</table>
had response densities that fell within the gray zone. However, two patients had abnormally decreased response densities even at the most peripheral ring (20–30°).

Figure 3b shows the means ± SD of the response densities for the five eccentric rings for the OMD patients and normal subjects. The mean response densities of the OMD group were significantly decreased up to the fourth ring (P < 0.05, Mann–Whitney U test; see also Table 2). The difference of the response density between OMD and normal control subjects decreased with increasing eccentricity.

**Implicit Times of the Multifocal ERGs**

The responses were grouped by retinal eccentricity as described above, and the implicit times of the initial positive component at the five eccentric rings were measured. Figure 4a shows the individual implicit times at the five eccentric rings for the eight patients with OMD. The gray region represents the range for the normal control subjects (the 2.5 and 97.5 percentile). Most of the patients had delayed or slightly delayed implicit times at all eccentricities. It should be noted that five of eight patients had abnormally delayed times even at the most peripheral ring, and four patients had implicit times within the normal range for the central ring, where all patients had severely depressed amplitudes.

Figure 4b shows the means ± SDs of the implicit times at the five eccentric rings for the 8 patients and 20 normal subjects. Implicit times of the OMD group were significantly delayed at all concentric rings (P < 0.05, Mann–Whitney U test; see also Table 2). The difference between OMD and normal subjects was maintained with eccentricity.

Figure 5 shows averaged waveforms of multifocal ERGs from the five eccentric rings. Responses for the 8 OMD patients and 20 normal subjects are superimposed. The vertical dotted line indicates an implicit time of 29.4 msec. These findings not only show the depression of the amplitude but also the significant delay of the implicit times at all five rings.

No correlation was found between the amplitude decrease and implicit time delay for the OMD patients. For instance, patients 4 and 6 had normal amplitude at both rings 4 and 5, but had delayed implicit times. On the other hand, the implicit times of patients 1, 3, 5, and 7 were within normal limits at ring 1, but their amplitudes were significantly reduced. We plotted the amplitude decrease relative to the mean of the control subjects against the implicit time delay relative to the mean of the control subjects for the eight patients at each five
There was no significant correlation ($r = -0.17, P = 0.26$, Spearman’s rank correlation test).

**DISCUSSION**

The present study demonstrated that the amplitudes of the multifocal ERGs in OMD patients were markedly depressed in the central retina: all patients had reduced amplitude for rings 1 and 2 (within 7° of the fovea). The differences in the amplitudes for the patients with OMD and the normal control subjects became smaller toward the periphery. These findings are consistent with the proposed interpretation that the disease has localized dysfunction of the retina in the central field. We have previously shown that focal macular ERGs were abnormally decreased, whereas full-field ERGs were within normal range for all OMD patients.\(^1\),\(^2\) In addition, we also have reported that the cone psychophysical perimetric thresholds were abnormally elevated within 10° of the macula but were within the normal range outside the 10° in all OMD patients.\(^2\)

A large variation in the amplitude was observed among the patients. For instance, patients 1 and 4 had reduced amplitude only within 7° (rings 1 and 2) but normal amplitude outside the 7°. On the other hand, patients 2 and 5 had abnormally reduced amplitude across the whole field of study, although the amplitude tended to be closer to normal in the periphery. This large variation in the amplitudes among the OMD patients may

### Table 2. Statistical Evaluation of Differences Between Patients (OMD) and Normal Subjects

<table>
<thead>
<tr>
<th>Eccentricity Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Density</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of eyes</td>
<td>20</td>
<td>8</td>
<td>20</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>$P$ value</td>
<td>.0001</td>
<td>.0001</td>
<td>.0006</td>
<td>.0076</td>
<td>.0596</td>
</tr>
<tr>
<td>Implicit time</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of eyes</td>
<td>20</td>
<td>8</td>
<td>20</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>$P$ value</td>
<td>.0012</td>
<td>.0002</td>
<td>.0006</td>
<td>.0003</td>
<td>.0019</td>
</tr>
</tbody>
</table>

![Figure 4](image-url)  
**Figure 4.** Implicit times at five eccentric rings in the eight patients with OMD. (a) Individual implicit times at five eccentric rings. The gray region represents the 2.5 and 97.5 percentile range for the 20 normal control subjects. (b) Means ± SD of implicit times at five eccentric rings for the 8 patients and 20 normal subjects. *Significant differences at $P < 0.05$; Mann–Whitney test.

![Figure 5](image-url)  
**Figure 5.** Averaged waveforms of multifocal ERGs for the five eccentric rings. Responses for the 8 OMD patients and 20 normal subjects are superimposed. The vertical dotted line indicates an implicit time of 29.4 msec.
be explained by the stage or severity of the disease, because it is known that OMD is a progressive disorder. We also have previously shown that younger patients tended to have only the macular cone system involved, while some of the older patients had both the macular cone and rod system involved.

Another explanation for the large variation is that our OMD patients may have included different clinical entities with similar appearance but of different genetic basis. To clarify this point, recent genetic techniques should be useful to determine whether patients have same genetic disorder or different genetic changes as in retinitis pigmentosa.

Our finding that most patients had slight but statistically significant delayed implicit times over 60° of the posterior pole is interesting. Five of eight patients had delayed implicit times even at most peripheral ring (20–30°), whereas five patients had normal ERG amplitude, and all patients had normal cone thresholds by psychophysical perimetry (see Table 1). Moreover, timing difference between the OMD patients and the normal subjects did not change with eccentricity, as did the amplitudes. Odel et al. have reported similar results in their two patients with OMD. Although the exact reason for the timing delay at peripheral eccentricities is unknown, there are several possibilities. One plausible hypothesis is that some of the OMD patients may have a subtle but broad dysfunction in the posterior pole than might be expected by the results of psychophysical perimetry and ERG amplitudes. Hood et al. reported that some patients with retinitis pigmentosa had delayed responses in regions, even with near normal sensitivity measured by psychophysical perimetry. They concluded that the implicit time delay in the multifocal ERG can be an early indication of local retinal damage in retinal disease. Thus, the delayed implicit times in the OMD patients in the presence of normal amplitudes may indicate an early sign of retinal dysfunction.

The question then arises is to why conventional full-field ERGs did not detect such implicit time delays in the OMD patients. We suggest that this arises from the same differences in the amplitude, viz., the delayed responses in the multifocal ERGs arise from the cells within a limited area (only the central 60° of the retina, which contains less than one quarter of the total cones), whereas in the full-field ERGs, the implicit time is determined by neurons over the entire retina.

Another factor is the recording conditions in the OMD patients. OMD is a macular disease that predominantly affects the central retina and can lead to some fixation problems. It also is not known how this fixation problem affects the response of the multifocal ERG. Unstable fixation during recording may result in abnormal implicit times in the entire visual field. To clarify this point, it is necessary to study the effect of fixation on the response of multifocal ERGs. The new multifocal ERG system with fundus monitoring may help answer this question.

In conclusion, our results demonstrated that the amplitude of the multifocal ERGs revealed localized retinal dysfunction, predominantly in the central retina. Although the exact reason for the delayed implicit times across large regions of the retina still remains uncertain, our results provide useful topographical information about the pathophysiology of OMD. We also believe that our results can be valuable when one uses this technique for the diagnosis of OMD.

References