Focal Macular Electroretinograms in Eyes with Wet-type Age-Related Macular Degeneration

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PURPOSE. To study the properties of the focal macular electroretinograms (fmERGs) in eyes with untreated wet-type age-related macular degeneration (AMD).

METHODS. fmERGs were recorded from 157 eyes of 157 consecutive patients with untreated wet-type AMD (113 men, 44 women; age, 71.3 ± 8.0 years). The fmERGs were recorded under direct fundus observation using a modified infrared fundus camera and a 15° stimulus spot. Amplitudes and implicit times of the fmERGs recorded from the AMD patients were compared with those from 21 age-similar healthy controls.

RESULTS. The amplitudes of fmERGs in the AMD patients were significantly smaller (P < 0.001) and the implicit times were significantly longer (P < 0.001) than the corresponding values in the control eyes. There was a significant correlation between amplitude and implicit time of the fmERG and visual acuity (logMAR), but the degree of correlation was weak. The correlation between amplitude and implicit time of the fmERGs correlated with the visual acuity (VA) of AMD patients; (3) is the ratio of the amplitudes of the b-wave to the a-wave (b/a ratio) in patients with wet-type AMD different from that of healthy controls?

CONCLUSIONS. The significant reduction in amplitude and the severe delay in implicit times of a- and b-waves of the fmERGs indicated significant functional alterations in the inner and the outer retinal layers of the macular area of eyes with wet-type AMD. (Invest Ophthal Mol Vis Sci. 2008;49:3121–3125) DOI: 10.1167/iovs.08-1835

Age-related macular degeneration (AMD) is the most frequent cause of visual decrease among the elderly in industrialized countries.1 AMD patients present with drusen, hyperplasia of the retinal pigment epithelium (RPE), geographic atrophy, and choroidal neovascularization (CNV).2–4 AMD is conventionally divided into dry type and wet type. Although the dry type is more prevalent, approximately 75% of visual loss in AMD patients is attributed to the wet type.1

Wet-type AMD is characterized by the growth of a CNV under the neurosensory retina and RPE with subsequent subretinal hemorrhage, exudative retinal detachment, retinal edema, fibrous scarring, and retinal atrophy.5–7 Recent medical therapy for AMD has been focused on treating CNV, and various new treatments have been effective, including the suppression of vascular endothelial growth factor (VEGF).5–7

To understand the pathophysiology of wet-type AMD, it is important to evaluate the macular function of wet-type AMD before and after treatment, and various subjective and objective clinical tests have been used. Of these, focal electroretinograms (ERGs)8–11 and multifocal ERGs12–15 have been used to assess the macular function of wet AMD objectively because these techniques can elicit electrical activities directly from the macular area. Our laboratory has also assessed macular function by using focal macular ERG (fmERG) before and after surgery,16 transpupillary thermotherapy,17 and photodynamic therapy.18 However, we have not yet studied in detail the basic properties of the fmERG in eyes with untreated wet-type AMD.

Therefore, the purpose of this study was to investigate the characteristics of fmERGs in 157 consecutive patients with wet-type AMD. We sought to answer three questions: (1) how abnormal are the amplitudes and implicit times of fmERG in wet-type AMD; (2) are the amplitudes and implicit times of the fmERGs correlated with the visual acuity (VA) of AMD patients; and (3) is the ratio of the amplitudes of the b-wave to the a-wave (b/a ratio) in patients with wet-type AMD different from that of healthy controls?

PATIENTS AND METHODS

Patients

We retrospectively reviewed the fmERGs recorded from 157 eyes of 157 consecutive patients with wet-type AMD (113 men, 44 women; age, 71.3 ± 8.0 years [mean ± SD]), who were examined at Nagoya University Hospital from February 2000 through December 2006. Patients with subfoveal CNV caused by AMD and those with polypoidal choroidal vasculopathy (PCV) were studied. Patients with CNV lesions caused by other retinal diseases were excluded. Of the 157 patients, 82 (52%) had AMD and 75 (48%) had PCV. Patients were excluded if they had been treated by laser photocoagulation, radiation, transpupillary thermotherapy, surgery, or photodynamic therapy. For controls, fmERGs were recorded from 21 eyes of 21 age-similar healthy controls (7 men, 14 women; age, 69.1 ± 2.7 years).

This research was conducted in accordance with the institutional guidelines of Nagoya University, and the procedures used conformed to the tenets of the World Medical Association’s Declaration of Helsinki. Informed consent had been obtained from each of the patients after sufficient information was provided on the procedures to be used.

Visual Acuity

The standard Japanese VA chart was used to measure VA, and the results were converted to Snellen VA and to the logarithm of minimal angle of resolution (logMAR units) for statistical analyses. VA in our 157 patients ranged from counting fingers to 0.8. The VA of counting fingers was set to 0.004, though there are still discussions on this estimation.24–26 Mean best-corrected VA in logMAR units was −0.80 ± 0.42 (mean ± SD; 20/123, Snellen equivalent).

Focal Macular ERGs

Our system for eliciting and recording fmERGs has been described in detail.20–22 Briefly, an infrared fundus camera, equipped with a stimu-
lus light, background illumination, and fixation target, was used. The image from the fundus camera was fed to a television monitor, and the examiner used the image on the monitor to maintain the stimulus on the macula.

The stimulus spot was 15° in diameter and was centered on the fovea. Background light was delivered to the eye from the fundus camera at a visual angle of 45°. Additional background illumination outside the central 45° produced a homogeneous background illumination for nearly the entire visual field. The luminance of the white stimulus light and background light was 29.46 cd/m² and 2.89 cd/m², respectively.

A Burian-Allen bipolar contact lens electrode (Hansen Ophthalmic Development Laboratories, Iowa City, IA) was used to pick up the fmERG. This contact lens electrode system allowed not only low electrical noise but also permitted a clear view of the fundus by the camera during the recordings. After the patients’ pupils were fully dilated with 0.5% tropicamide and 0.5% phenylephrine hydrochloride, fmERGs were elicited by 5 Hz rectangular stimuli (100-ms light on and 100-ms light off). A total of 512 responses were averaged by a signal processor. The time constant of the amplifier was set at 0.03 seconds with a 100-Hz high-cut filter to record the a- and b-waves.

The amplitude of the a-wave was measured from the baseline to the first negative trough, and the amplitude of b-wave was measured from the trough of the a-wave to the positive peak of the b-wave. For very low amplitude waveforms, implicit times were measured after the waveforms were magnified in the vertical direction. fmERG was considered absent when the amplitude was less than the noise level (<0.1 μV).

**Statistical Analyses**

The significance of the differences between patients and healthy controls was determined by the nonparametric Mann-Whitney U test. Correlations between VA and fmERG amplitudes were analyzed using Spearman rank correlation. Differences were considered significant when \( P < 0.05 \).

**Results**

**fmERGs in Wet-type AMD**

fmERGs recorded from a representative healthy control and four AMD patients with different VAs are shown in Figure 1. The amplitudes of fmERGs in the AMD patients were clearly smaller than those in healthy controls, and the degree of reduction was more severe in AMD patients with greater reductions of VA. The vertical dotted line was drawn at 42.3 ms, corresponding to the median value of the b-wave implicit time for healthy controls. Implicit time was delayed for AMD patients, and the degree of delay appeared to be more severe in AMD patients with greater reductions of VA.

We next compared the amplitudes of the a- and b-waves of the fmERG recorded from our 157 AMD patients with those recorded from the 21 age-similar healthy controls. The amplitudes of a- and b-waves in the AMD patients were significantly smaller than those in healthy controls (\( P < 0.001 \) for a- and b-waves; Fig. 2A). Median amplitudes of a- and b-waves in AMD patients were only 29% and 35%, respectively, of the corresponding waves in the healthy controls.

Implicit times were delayed in the AMD patients. The implicit times for a- and b-waves in AMD patients were significantly longer than those in healthy controls (\( P < 0.001 \) for a- and b-waves; Fig. 2B). Median implicit times of the a- and b-waves in the AMD patients were 3.8 ms and 10.2 ms longer, respectively, than in the controls.

**Correlation between fmERG and Visual Acuity**

We next investigated whether there was any significant correlation between amplitude and implicit time of the fmERG and the VA. Amplitudes of the a- and b-waves in the 157 AMD patients are plotted against the logMAR VA in Figure 3A. The gray area shows the range of the fmERG amplitude for age-similar healthy controls (\( n = 21 \)), and the dotted line shows the median value of healthy controls. There was a weak but significant correlation between amplitude of a- and b-waves of the fmERGs and VA \( (P < 0.05) \). The coefficient of correlation \( (\rho) \) was 0.202 for the a-wave and 0.262 for the b-wave.

Implicit times of the a- and b-waves of the fmERGs in the 157 AMD patients are plotted against the logMAR VA in Figure 3B. The gray area shows the range of age-similar healthy controls (\( n = 21 \)), and the dotted line indicates the median value of healthy controls. There was a significant correlation between the implicit time of a- and b-waves of the fmERG and VA \( (P < 0.05) \), but again, the degree of correlation was weak \( (\rho = 0.181 \) for the a-wave; \( \rho = 0.202 \) for the b-wave).

**b/a Amplitude Ratio of fmERG**

Finally, we studied whether there was a significant change in the ratio of the amplitude of the b-wave to the a-wave, the b/a amplitude ratio in our patients with wet-type AMD. Box plots of the b/a amplitude ratio for the healthy controls and the patients with wet-type AMD are shown in Figure 4A. The difference in the b/a amplitude ratio between the AMD patients and healthy controls was not significant \( (P = 0.672) \).

We also examined whether there was any correlation between the b/a amplitude ratio and the VA in our 157 patients with wet-type AMD and found that there was no significant correlation between these two factors \( (P = 0.174; \rho = 0.106; \text{Fig. 4B}) \).

**Discussion**

Our results showed that the amplitudes of the a- and b-waves of the fmERG in the AMD patients were significantly reduced and that the median values were only 29% for the a-wave and 35% for the b-wave of the corresponding waves of healthy controls. Similarly, implicit times in the AMD patients were severely delayed, and the median value in AMD patients were 3.8 ms...
longer for the a-waves and 10.2 ms longer for the b-waves than in age-similar healthy controls. These results are similar to those of past electrophysiological studies on wet-type AMD\textsuperscript{13–23} and suggest that the macular function of these patients is severely impaired.

fmERG-determined macular function was weakly but significantly correlated with VA in patients with wet-type AMD; the amplitude decreased and the implicit time increased as the VA decreased. A similar significant correlation between the amplitude of the focal ERG and VA was reported by Fish and Birch\textsuperscript{8} in patients with different kinds of macular disease.

Although there was a significant correlation between the fmERG and VA, the degree of correlation was weak in our AMD patients. The coefficient of correlation was 0.20 to 0.26 for the amplitude and 0.18 to 0.20 for the implicit time. The reason for the weak correlation was probably the basic methodological difference between the two tests; the fmERG is the sum electrical response from a 15° area of the macula, whereas the VA is determined by a small retinal area with the highest resolving power.

Although the neural origin of each component of fmERG has not been completely determined, the best evidence, based on recent experiments in primates, is that the initial negative a-wave originates mainly from cone photoreceptors and the cone off-bipolar cells.\textsuperscript{27,28} The photopic b-wave is determined by the combined activities of the cone on- and off-bipolar cells.\textsuperscript{29–31} We have previously shown that there was reduction in the b/a amplitude ratio of the fmERG in eyes with different macular diseases, especially when the postreceptoral retinal neurons were selectively impaired, as in congenital retinoschisis,\textsuperscript{32} aphakic cystoid macular edema,\textsuperscript{33} and epiretinal membrane.\textsuperscript{34,35} In contrast, the b/a amplitude ratio of the fmERG tended to be larger in patients with retinitis pigmentosa, who have a predominantly outer retinal dysfunction.\textsuperscript{36} Thus, we wanted to know which retinal layer was more impaired in wet-type AMD by assessing the b/a amplitude ratio of the fmERG. Our results demonstrated that the b/a amplitude ratio of the fmERG in AMD patients was not significantly different from that of age-similar healthy controls (Fig. 4). These results, combined with the severe delay in the implicit times in a- and b-waves, suggested that there are considerable functional alterations in outer and inner retinal layers of the macula in wet-type AMD. These findings are consistent with recent anatomic studies using optical coherence tomography in wet-type AMD.\textsuperscript{37}
One major limitation of this study was that we used a relatively large spot size (15° diameter) for the stimulus. A smaller stimulus spot size might be more desirable for studying the functional change in the central retina and the correlation between fmERG and VA. We actually tried to use smaller stimulus spot sizes at the preliminary stage of the study, but they elicited reduced fmERGs, which made it difficult to measure precisely the amplitudes and implicit times in our patients with wet-type AMD.

In conclusion, the significant reduction in amplitude and the severe delay in implicit time of a- and b-waves of the

FIGURE 3. Relationship between the amplitude of the fmERGs and VA. (A) Relationship between the amplitudes and implicit times of the a-wave (left) and b-wave (right) of the fmERG and logMAR VA in 157 eyes with wet-type AMD. There is a weak but significant correlation between the amplitudes of fmERGs and VA (P < 0.05). (B) Relationship between the implicit times of the a-wave (left) and b-wave (right) of the fmERG and logMAR VA in 157 eyes with wet-type AMD. There is a weak, but significant, correlation between the implicit times of fmERGs and VA (P < 0.05). Gray area: range of age-similar healthy controls. Dotted line: median of age-similar healthy controls.

FIGURE 4. Relationship between the b- and a-wave ratios in patients with wet-type AMD. (A) Box plots of the ratio of the amplitudes of the b-wave to the a-wave of the fmERGs in 157 patients with wet-type AMD patients and 21 age-similar healthy controls. There was no significant difference in the b/a amplitude ratio between two groups (P = 0.67). The line within the box represents the median, the height of the boxes represents the 25th and 75th percentiles, and the ends of the error bars represent the 10th and 90th percentiles. (B) Relationship between the b/a amplitude ratio of the fmERG and VA (logMAR). There is no significant correlation between these two factors (P = 0.174). Gray area: range of age-similar healthy controls. Dotted line: median of age-similar healthy controls.
fMERGs indicate considerable functional alterations in the inner and outer retinal layers of the macular area in eyes with wet-type AMD.

References


