Tomographic and Multifocal Electroretinographic Features of Idiopathic Epimacular Membranes

Danjie Li, MD; Masayuki Horiguchi, MD; Shoji Kishi, MD

Objective: To determine the relationship between the tomographic and electrophysiologic characteristics of the retina with an idiopathic epimacular membrane.

Methods: Sixty patients with unilateral idiopathic epimacular membranes underwent optical coherence tomography and multifocal electroretinography (mfERG). The mfERGs were elicited by a pseudorandom m-sequence stimulus with 37 hexagonal elements, and the mfERGs in area 1 (central 4.1°), area 2 (ring from 4.10°-7.15°), and area 3 (ring from 7.15°-13.75°) were compared with the tomographic features of the corresponding area. The data from the normal fellow eyes served as control.

Main Outcome Measures: The retinal thickness, amplitudes, and implicit time of the mfERG.

Results: On optical coherence tomographs, the retina was thickest in area 1, followed by area 2 with low tissue reflectivity of the outer retina, and area 3 was of normal thickness. Electroretinography showed the amplitude ratio (affected vs fellow eyes) of mfERGs from areas 1, 2, and 3 was significantly lower than that of the controls (P<.01), and the implicit times were significantly delayed (P<.01). The amplitude ratio was reduced the most in area 1, and the implicit time was delayed the most in area 3. The foveal thickness was negatively correlated with visual acuity (p = −0.46; P<.001). The mfERG amplitude in area 1 was not significantly correlated with the visual acuity.

Conclusions: It is likely that retinal thickness is correlated with neural dysfunction, but mfERGs demonstrated various physiological changes in the retina.

Arch Ophthalmol. 2004;122:1462-1467

From the Department of Ophthalmology, Gunma University School of Medicine, Maebashi, Gunma, Japan (Drs Li and Kishi); and the Department of Ophthalmology, Fujita-Health University, School of Medicine, Toyoake, Aichi, Japan (Dr Horiguchi). The authors have no relevant financial interest in this article.
Figure 1. Fundus photographs and optical coherence tomographic images from a 64-year-old patient with an idiopathic epimacular membrane in the right eye. The retinal thickness was measured at 5 points (H1, 2 H2 points, and 2 H3 points) in every plane (a, horizontal scan; b, vertical scan). A, The right eye. H1 (the retinal thickness at the fovea or the center of area 1) is 480 µm. The average (H2 is the retinal thickness of area 2) of the 4 H2 points (temporal, 350 µm; nasal, 370 µm; inferior, 395 µm; and superior, 390 µm) is 376 µm. The average (H3 is the retinal thickness of area 3) of the 4 H3 points (temporal, 350 µm, 270 µm, 330 µm, and 325 µm) is 301 µm. B, Normal left eye. H1 is 141 µm. The average of H2 (270 µm, 275 µm, 265 µm, and 260 µm) is 268 µm, and the average of H3 (250 µm, nasal, 370 µm; inferior, 395 µm; and superior, 390 µm) is 376 µm. The average (H3 is the retinal thickness of area 1) is 480 µm. The average (H2 is the retinal thickness of area 2) of the 4 H2 points (temporal, 350 µm; nasal, 370 µm; inferior, 395 µm; and superior, 390 µm) is 376 µm. The average (H3 is the retinal thickness of area 3) of the 4 H3 points (temporal, 350 µm, 270 µm, 330 µm, and 325 µm) is 301 µm. B, Normal left eye. H1 is 141 µm. The average of H2 (270 µm, 275 µm, 265 µm, and 260 µm) is 268 µm, and the average of H3 (250 µm, 240 µm, 265 µm, and 260 µm) is 245 µm.

The patients (35 women and 25 men) ranged in age from 18 to 79 years with a mean age of 62 years. Twenty-seven (45%) of the idiopathic epimacular membranes were in the right eyes and 33 (55%), in the left eyes. All patients had mild distortion, blurred vision, or both and no history of other ophthalmic diseases or relevant systemic diseases. We excluded cases with pseudohole formation and opaque, thick epimacular membranes because white lesions induced stray light effects on the mfERGs.24 The fellow eyes of all patients were normal and served as controls. The degree of senile cataract in eyes with an idiopathic epimacular membrane and in the fellow eyes was similar in all patients. The largest epimacular membrane was about 3 disc diameters. We measured the visual acuities of the affected and normal fellow eyes in all patients.

OPTICAL COHERENCE TOMOGRAPHY

We prospectively examined both eyes of 60 patients with an idiopathic epimacular membrane by OCT (Humphrey model 2000; Humphrey Instruments, San Leandro, Calif). Because of the difference in reflectivity between the vitreous and retina and between the photoreceptor layer and the retinal pigment epithelium, the retinal thickness was measured using the OCT software.

The scan length was 5.0 mm through the horizontal and vertical planes. The retinal thickness was measured at 5 points in each plane of the cross-sectional image using the OCT software (Figure 1A). Measurements were made at the fovea (H1, center of area 1 of the mfERGs); 1.35 mm temporal, nasal, superior, and inferior to the fovea (H2, corresponding to the mid-point of area 2 of the mfERGs); and at 2.3 mm temporal, nasal, superior, and inferior to the fovea (H3, corresponding to the inner margin of area 3 of the mfERGs). We defined H1 as the retinal thickness of area 1, H2 as the mean thickness of the 4 quadrants and corresponding to area 2, and H3 as the mean thickness of the 4 quadrants and corresponding to the inner margin in area 3. The thickness of the fellow eyes was measured in the same manner (Figure 1B).

MULTIFOCAL ELECTRORETINOGRAMS

The mfERGs were recorded with the VERIS Science 4.1 (Visual evoked response imaging system) (Mayo, Nagoya, Japan). We used a stimulus matrix that consisted of 37 hexagonal elements with a total recording time of 3 minutes 38 seconds that was divided into 8 segments of 27.29 seconds each. The frame rate was 75 Hz, and the luminance of the black-and-white frames was 3.5 candelas (cd) per m² and 200 cd/m², respectively. The contrast was 96.6%.

The amplifier was set at a gain of 100 K, and the bandpass filter was set at 10 Hz to 300 Hz. A Burian-Allen bipolar contact lens electrode was placed on the test eyes after the pupils were fully dilated. The distance from the test eye to the stimulus monitor (32 cm × 24 cm) was 33 cm.

The trace array of mfERGs represents the waveforms extracted from the 37 focal electroretinograms (ERGs) and are displayed topographically. The responses were grouped into 4 rings of approximately equal eccentricities, and the components of the central 3 areas were studied. Their angular sizes were area 1, 0° to 4.10°; area 2, 4.10° to 7.15°; and area 3, 7.15° to 13.75°, and the diameter of each zone was 1.22 mm, 1.51 mm, and 1.96 mm, respectively (Figure 2A and B). The 5-mm OCT scan covered areas 1 and 2 and the beginning of area 3.

The first-order kernels were extracted from the mfERG in areas 1, 2, and 3. The amplitude of the first positive peak was measured from the first negative trough to the peak of the first positive wave. We defined the implicit time as the time from signal onset to the first positive peak. The mfERGs were recorded with a sampling interval of 0.83 milliseconds (Figure 2C).
One iteration of the system's artifact-removal algorithm was used, which effectively eliminated artifacts resulting from blinks and small eye movements. We compared the amplitudes and implicit times of the mfERGs in areas 1, 2, and 3 in the eyes with idiopathic epimacular membranes with the fellow eyes.

STATISTICAL ANALYSIS

The data from the affected eyes were statistically compared with those of the fellow eyes with the paired t test. P < .05 was considered to be statistically significant.

RESULTS

Of the 60 patients, 45 (75%) had a complete posterior vitreous detachment and 15 (25%) had partial or no posterior vitreous detachment. A wrinkling of the internal limiting membrane was observed in 48 eyes (92%) by biomicroscopy. The best-corrected visual acuity in the eyes with an idiopathic epimacular membrane ranged from 20/200 to 20/20, while the visual acuity in the fellow eyes was 20/20 or better.

OCT FEATURES

The retina was thickest in area 1 in all affected eyes with the thickness at the fovea ranging from 230 to 740 μm.
We extracted the first-order kernel of the mfERGs from the affected eyes and the fellow eyes. The mean ± SD of the amplitudes and the implicit times in eyes with an idiopathic epimacular membrane and in the fellow eyes are listed in the Table.

There was a significant reduction in the amplitudes (P<.001) of eyes with idiopathic epimacular membrane compared with those of the control fellow eyes in rings 1, 2, and 3. The reduction of the amplitudes in area 1 was the greatest of the 3 areas (Figure 5) with a mean ratio of 77.4% in area 1, 81.2% in area 2, and 81.3% in area 3.

The implicit times were prolonged compared with those of the fellow eyes (P <.001) for all areas. The implicit times were prolonged by 1.55 milliseconds in area 1, 1.49 milliseconds in area 2, and 1.81 milliseconds in area 3. The difference between areas 1 and 2 was not significantly different, but there was a significant difference between areas 3 and 2 (P =.02) (Figure 6).

The correlation between the amplitude of the mfERGs in area 1 and the best-corrected visual acuity was not significant. The amplitudes of the mfERGs were also not significantly correlated with the increased fovea thickness in area 1 (Spearman rank correlation) (Figure 3B and C).

**REPORT OF A CASE**

A 64-year-old man complained of blurred and distorted vision of 10 months’ duration in his right eye. He noted a recent worsening of his symptoms, and his visual acuity was 20/40 OD and 20/20 OS. Fundus examination by biomicroscopy revealed a transparent epimacular membrane about 1.5 disc diameters. Optical coherence tomography demonstrated a thickening of the retina with...
the outer retina having low reflectivity in the macular area (Figure 1A). The thickness was 480 µm at the fovea (H1), 376 µm at H2 (temporal = 350 µm, nasal = 370 µm, inferior = 395 µm, and superior = 390 µm), and 301 µm at H3 (temporal = 280 µm, nasal = 270 µm, inferior = 330 µm, and superior = 325 µm). Compared with the normal left eye (Figure 1B), the overall retinal thickness was increased with the biggest increase in area 1.

In the normal left eye, H1 was 141 µm, H2 was 268 µm (average of 270 µm, 275 µm, 265 µm, and 260 µm), and H3 was 245 µm (average of 250 µm, 240 µm, 265 µm, and 260 µm).

The mfERGs were smaller than those of the normal left eye with a ratio of 75.1% (34.8/46.3 nV/deg²) in area 1, 79.5% (23.6/29.7 nV/deg²) in area 2, and 85.3% (17.4/20.4 nV/deg²) in area 3. The implicit times were prolonged in each area (Figure 7).

**COMMENT**

Our results showed that in the 60 eyes with an idiopathic epimacular membrane, the retina was thickest at the fovea (457±121 µm) and was thinner at area 2 but the thickness was still thicker than that in the normal fellow eyes. At the beginning of area 3, the mean±SD retinal thickness (246±30 µm) was not significantly different from the fellow eyes. In areas 1 and 2, the outer retina was swollen with low reflectivity, but the inner retina maintained normal reflectivity and normal thickness.

The visual acuity was negatively correlated with the retinal thickness at the fovea (area 1), which is consistent with a previous report. Area 1 was 1.2 mm in diameter and included the foveal pit, which was 0.5 mm in diameter with only photoreceptors, and the foveal slope where bipolar cells and the ganglion cells are present. The swelling of the outer retinal layer with low reflectivity on OCT images indicates that the photoreceptors were edematous, which was most likely the cause of the visual disturbance in these eyes.

The amplitudes of the mfERGs were reduced to 77.4% in area 1, 81.2% in area 2, and 81.3% in area 3 compared with the control fellow eyes. The implicit times were delayed by a mean±SD of 1.55±1.71 milliseconds in area 1.

These abnormalities in the mfERG in area 1 were not correlated with the visual acuity (Figures 3B) or with the retinal thickness (Figure 3C). In addition, abnormalities in the mfERGs in area 3 were found but the retinal thickness was not altered (Figures 4, 5, and 6).

Hood et al and Horiguchi et al investigated the retinal origins of the different components of the mfERGs in animals using various pharmacological agents that had selective blocking activity of specific cells. From their findings and from data on the origin of conventional ERGs, they suggested that the light-evoked increase of extracellular potassium caused by the activity of on-bipolar and off-bipolar cells leads to an influx of potassium into Mueller cells. The mfERGs are then generated by a potassium current sink in Mueller cells and by current source at the inner limiting membrane (ILM), the basement membrane of Mueller cells. Histological examination of idiopathic epimacular membranes has shown that the ILM is firmly attached to the idiopathic epimacular membrane with numerous attachment plaques. A recent study reported that removal of the ILM prolonged the
implicit times of focal macular ERGs. These observations may explain the discrepancies between the mfERGs and retinal thickness in area 3 (ie, normal retinal thickness and abnormal mfERG results). We suggest that idioptic epimacular membranes damage the ILM, and the alteration of its normal function as a current source can lead to abnormal mfERG results. Another possibility for the discrepancy between the abnormal mfERG results and normal retinal thickness in area 3 is that the idiopathic epimacular membrane affected the inner retina and induced abnormal mfERG results. Thus, Tanikawa et al reported abnormal oscillatory potentials in eyes with an idiopathic epimacular membrane. Hood et al suggested that activity in the inner retina contributed to the first-order kernel of mfERGs. The results of studies examining the correlation between visual acuity and the focal ERG from the central retina are contradictory in eyes with an idiopathic epimacular membrane. Tanikawa et al studied 30 patients with unilateral idiopathic epimacular membranes using focal macular ERGs and reported that there was a significant correlation between the relative b-wave amplitude (affected eye vs fellow eye) and the visual acuity. In contrast, Moschos et al reported that the correlation between the mfERGs in area 1 and the visual acuity was not significant. Our results revealed that correlation between the visual acuity and amplitude ratio (affected eye vs fellow eye) was not significant.

One possible explanation for the discrepancy between visual acuity and mfERG in area 1 may be the size of the stimulus used in these different studies. The diameter of the center stimulus in mfERGs was 4.1°. The foveal pit was 0.5 mm in diameter and consisted only of photoreceptor cells, and the visual acuity is closely related to the function of the central fovea. If a smaller stimulus size was used, a correlation might have been found. However, a previous study using 61 hexagonal elements failed to find a correlation between focal ERG in area 1 and the visual acuity, but Tanikawa et al found a significant correlation, even with a 10° focal stimulus.

If our mfERG was altered by the dysfunction induced by swollen cone cells, there should have been a good correlation of mfERGs to the visual acuity. The possible cause for this discrepancy is that mfERG changes in area 1 were caused not only by cone cell dysfunction but also by other changes of the retina, such as the ILM changes or inner retinal damages.

In conclusion, retinal edema in eyes with an idiopathic epimacular membrane is mainly in the photoreceptor layer. The visual acuity was significantly correlated with the swelling of the photoreceptors in the fovea. On the other hand, the reduction of the mfERGs demonstrated physiological changes in the retina, possibly including cone cell dysfunction and ILM changes or inner retinal dysfunction.

Submitted for publication March 5, 2003; final revision received November 6, 2003; accepted April 21, 2004.

Correspondence: Shoji Kishi, MD, Department of Ophthalmalmology, Gunma University School of Medicine, 3 Showamachi, Maebashi, Gunma 371-8511, Japan (kishi@med.gunma-u.ac.jp).

REFERENCES

6. Li J, Tsu MO, Lam TT. Reduced amplitude and delayed latency in foveal response of multifocal electroretinogram in early age related macular degenera-
7. Palmovskis AM, Sutter EE, Bearse MA Jr, Fung W. The multifocal electroreti-
nogram in the diagnostic and verlaufskontrolle lokalisierter Netzhautfunk-
tionsstorungen: fallbericht eines Patienten mit chorioretinopathia centralis se-
8. Fiao CH, Kondo M, Tanikawa A, Terasaki H, Miyake Y. Multifocal electroretino-
9. Si VJ, Kishi S, Aoyagi K. Assessment of macular function by multifocal electro-
retinogram before and after macular hole surgery. Br J Ophthalmol. 1999;83:
420-424.
11. Jurklies B, Weismann M, Husing J, Sutter EE, Bornfeld N. Monitoring retinal func-
12. Vajaranant TS, Syz JP, Frishman GA, Giesser JP, Slipole W. Localized retinal dys-
13. Johnson CA. Recent developments in automated perimeter in glaucoma diag-
14. Chau HHL, Brown E. Pilot study of the multifocal electrotretinogram in ocular hy-
15. Buckland L. The spatial distribution of ERG losses across the posterior pole of glau-
17. Fortune B, Schnack ME, Adams A. Multifocal electroretinogram delays reveal lo-
419.
analyses of diabetic macular edema by optical coherence tomography and multi-
electroretinogram of mosaic retinal dysfunction in carriers of X-linked retinitis 
pigmentosa.

22. Hasegawa S, Ohshima A, Hayakawa Y, Yagi M, Abe H. Multifocal electrotretinogram-
23. Moschos M, Apostolopolous M, Ladas J, et al. Assessment of macular function by multifocal electroretinogram before and after epimacular membrane sur-
25. Hood DC, Frishman LJ, Sazizk S, Sunvathanthan S. Retinal origins of the primate 
26. Horiguchi M, Suzuki S, Kondo M, Tanikawa A, Miyake Y. Effect of glutamate ana-
alogues and inhibitory neurotransmitters on the electroretinograms elicited by ran-
27. Newman EA, Frishman LJ. The b-wave. In: Principle and Practice of Clinical Elec-
29. Terasaki H, Miyake Y, Nomura R, et al. Focal multifocal ERGs in eyes after re-