Role of Multifocal Electroretinography in the Diagnosis of Idiopathic Macular Hole

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Purpose. To analyze the preoperative results of multifocal electroretinography (mfERG) in the fellow eyes of patients with idiopathic unilateral macular hole and to evaluate the usefulness of this method in predicting the likelihood of macular hole formation in the fellow eye.

Methods. Over a period of 5 years, 80 eyes of 40 patients (mean age, 64.9 years) with unilateral idiopathic macular hole were examined. The diagnosis of idiopathic macular hole was confirmed by optical coherence tomography (OCT). The fellow eyes were intact in all cases. All patients underwent vitreoretinal surgery. Before the surgery, both eyes of the patients were examined by mfERG. During the follow-up period, the 40 fellow eyes were also observed by OCT, and the changes in the vitreofoveal attachment were investigated. The preoperative response densities and ring ratios of mfERG were analyzed in both eyes, and discriminant analysis was used to calculate the best separator function.

Results. Preoperative mfERGs demonstrated significantly lower mean response densities in the central area of the 40 eyes with macular hole than in the fellow eyes. During the follow-up period, macular hole was diagnosed in 13 fellow eyes by OCT. The preoperative values of the mfERGs in these eyes were significantly lower than in the other 27 cases. The mfERG ring ratios were significantly lower in the fellow eyes in which macular holes developed than in those that remained intact.

Conclusions. The analysis of ERG in the fellow eyes of patients with macular hole seems clinically useful. The lower amplitude may forecast the propensity for subsequent development of a macular hole. Patients with low central ERG amplitude and lower ring ratios in the healthy fellow eyes should have stricter follow-up. (*Invest Ophthalmol Vis Sci.* 2010;51:1666–1670) DOI:10.1167/iovs.09-4375

The idiopathic macular hole is a full-thickness dehiscence at the fovea that affects the neuroretina, sparing the retinal pigment epithelium. Recent studies have shown that macular holes are more common in elderly women and occur with a prevalence of 1 in 3300 usually in the sixth and seventh decades of life. According to the literature, during a follow-up period of an average of 36 months, patients with unilateral macular hole have a risk of 3% to 56% of having the disorder develop in the fellow eye as well, depending on the presence of any predisposing foveal lesions.[1–11]

The complete pathogenesis of macular hole remains unknown. It was Gass who first suggested that idiopathic macular hole is caused by progressive tangential vitreoretinal traction at the fovea. Johnson and Gass[12] described the biomicroscopic classification of macular hole in 1988, and Gass[13] published a reappraisal in 1995. With the help of optical coherence tomography (OCT), which is a modern, noncontact imaging technique for the morphologic examination of the retina, Gaudric et al.[14] have recently shown the initial stages of macular hole formation. OCT is not only effective in diagnosing macular hole, it is also useful for monitoring the postoperative period in both the surgically treated and fellow eyes.[15]

Multifocal electroretinography (mfERG), developed by Sutter and Tran[16] in 1992, is a noninvasive, objective method and is used to detect the regional functional changes of the central retina by measuring the electrophysiological responses. Studies have shown that the mfERG responses in eyes with macular hole are decreased at the fovea. After surgery, after the hole is closed, the responses start improving again.[17–20] According to these studies, mfERG seems to be a sensitive method of registering function due to morphologic changes.

Our purpose in this study was to evaluate the usefulness of mfERG for predicting the likelihood of macular hole formation in the fellow eye.

Methods

In this retrospective study, 40 patients with unilateral idiopathic macular hole (admitted in our clinic between November 2001 and December 2006) were evaluated. The age of the patients ranged from 50 to 80 years (mean, 64.9) at the time of their first visit. OCT (Stratus OCT, Humphrey Instruments, Carl Zeiss, Inc., Dublin, CA) was performed on both eyes to verify the diagnosis. Only patients with asymptomatic fellow eyes at the first visit were included in the study. The normal retinal and vitreoretinal morphology in the fellow eye was also confirmed by OCT.

The electrophysiological function of both eyes (n = 80) of the patients was separately recorded by mfERG (Retiscan ver. 3.1; Roland Consult, Wiesenbaden, Germany) at the first visit (and during the follow-up as well). The examinations were performed according to the guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV).[21,22]

In the eye with macular hole, pars plana vitrectomy was performed with the peeling of the inner limiting membrane in all cases, after administration of 0.5% membrane blue vital dye (Dorc Int., Rotterdam,

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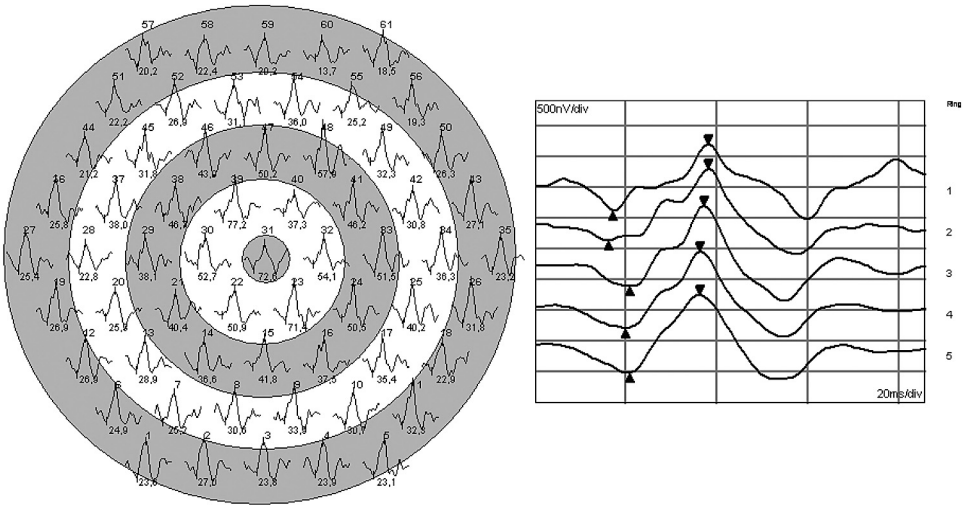

FIGURE 1. Sixty-one-hexagon mfERG. The hexagons are arranged into five concentric rings.

The Netherlands). Vitrectomy was performed through either 20- or 23-gauge ports.

During the follow-up period, the retinal morphology of both eyes was recorded by OCT, every 3 to 6 months. mfERGs were also recorded at the follow-up visits.

In this study, 61 hexagon-stimuli mfERGs were recorded, resulting in five concentric rings (Fig. 1). The central hexagon (1.8°, ~500 μm) covered the region matching to the anatomic extension of the macular hole (~400 μm). The preoperative mean response densities in the four central rings (R1–R4) obtained at the first visit were compared in the affected eyes with those of (intact) fellow eyes. (R5 was considered too far from the point of interest in eyes with macular hole.)

The mean period of follow-up was 24.1 months (range, 24–36 for fellow eyes that remained intact, 3–19 months for fellow eyes in which macular hole developed). According to the OCT results, during the postoperative follow-up period, normal macular structure remained in 27 fellow eyes, whereas signs of macular hole developed in 13 fellow eyes (stages I–IV,[13]). The preoperative mean central mfERG response densities (obtained at the first visit) in fellow eyes with macular hole were compared with that of intact ones.

As macular hole affects only the most central region of the visual field, comparing the response of the central part of the macula with those in the peripheral regions could enhance the disease-specific features of the mfERG. Ring ratios would be defined as the ratios of the central ring response density (R1) to the peripheral ones (R1/R2, R1/R3, and so on).[23]

We compared the preoperative R1/R2, R1/R3, and R1/R4 (obtained at the first visit) of fellow eyes with later-developing macular hole with the same ratios in those eyes that remained intact. We also looked for the best predictive mfERG-based parameters of the significant separation that signals formation of macular hole in the fellow eye.

The distribution of the data was checked by the Shapiro-Wilks W test. Parametric (two-sample *t*-probe), and nonparametric (Kolmogorov-Smirnov) tests and analysis of variance (ANOVA) were used for comparisons (statistical analyses performed by Statistica 7.0; StatSoft Inc., Tulsa, OK, and SPSS ver. 15; SPSS Inc., Chicago, IL). Statistical significance was set at $P < 0.05$. For separation, Fisher's linear discriminant function was calculated.[24]

The research adhered to the tenets of the Declaration of Helsinki.

RESULTS

In accordance with the literature, at the first visit, we found that the mfERG response densities of eyes with macular hole were significantly lower in the central (R1) and the first paracentral (R2) rings than those of the fellow eyes. Although these values of R3 and R4 were also slightly lower, the difference was not significant (Table 1).

TABLE 1. Comparison of Preoperative mfERG Response Densities in Eyes with Macular Holes and Asymptomatic Fellow Eyes

Response Densities (nV/deg^2)	R1	R2	R3	R4
Eyes with macular hole (n = 40)	**55.2** ± 20.9	**43.9** ± 15.3	35.5 ± 11.8	26.3 ± 8.0
Fellow eyes (n = 40)	**79.2** ± 29.4	**54.2** ± 15.4	40.0 ± 11.1	29.0 ± 8.7
P	**<0.001**	**0.003**	0.08	0.1

Data are expressed as the mean ± SD. Significant data and probabilities are in bold.

TABLE 2. Multifocal ERG Response Densities of Fellow Eyes Developing Macular Hole during the Follow-up, Those Remaining Intact, and Normal Control Eyes

Response Densities (nV/deg^2)	R1	R2	R3	R4
Fellow eyes with macular hole (MH, n = 13)	**65.6** ± 26.7	53.1 ± 13.9	39.4 ± 10.6	29.5 ± 8.8
Fellow eyes remaining intact (INT, n = 27)	85.7 ± 28.8	54.7 ± 16.3	40.2 ± 11.5	28.8 ± 8.8
Normal control eyes (CO, n = 40)	102.2 ± 24.8	65.6 ± 14.8	49.4 ± 11.8	36.4 ± 8.4
$P1$ (MH - INT)	**0.03**	0.75	0.82	0.79
$P2$ (MH - CO)	**0.01**	0.06	0.08	0.07
$P3$ (INT - CO)	0.18	0.06	0.07	0.08

Data are expressed as the mean ± SD. Post hoc test; significant probabilities are in bold.

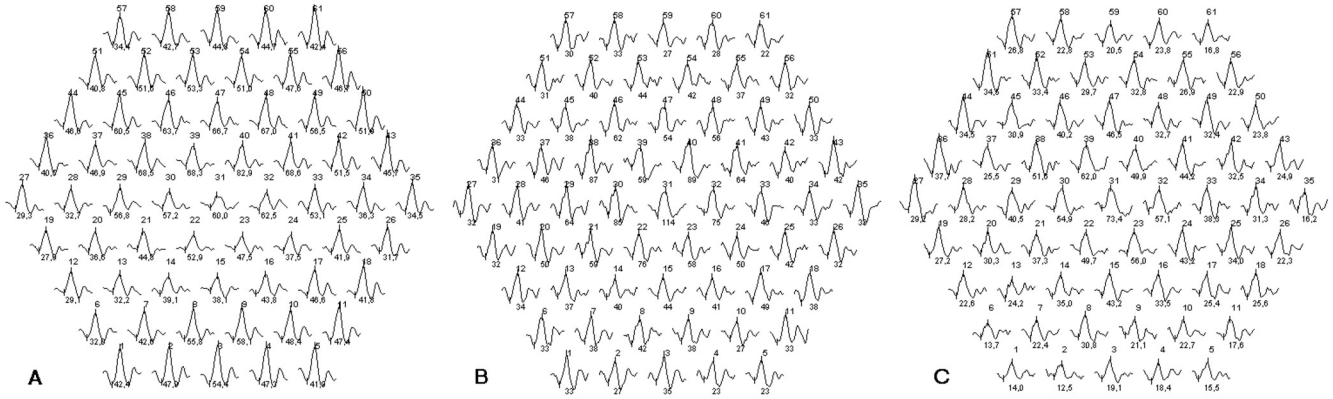

FIGURE 2. Preoperative mfERG of an eye with macular hole (**A**), a fellow eye that remained intact during the follow-up period (**B**), and a fellow eye in which a macular hole developed during the follow-up period (**C**).

During the follow-up, OCT showed signs of macular hole in 13 previously intact fellow eyes. The response density of the central ring (R1) was considerably lower in these fellow eyes than that in the 27 intact ones and in normal control eyes (Table 2, Fig. 2). In areas R2, R3, and R4, the response densities were not significantly different in the groups.

All R1/R2, R1/R3, and R1/R4 ring ratios were also significantly lower in the fellow eyes with later-developing macular hole than in intact fellow eyes and control eyes (Table 3). There was no significant difference between the ratios in the intact fellow eyes and those in the control eyes.

Employing the best separator ring ratios, we estimated the linear functions that would best discriminate between the data points, to predict whether the fellow eye would be affected later. Using the ring ratios as variables (i.e., predictor parameters), we applied Fisher's discriminant analysis to build two linear functions and to calculate their coefficients for the best classification of the cases into the previously defined groups.[24–27] Each linear function provides numerical results that are used for the statistical separation of the cases. The separation is then evaluated for misclassification, giving the probability of selecting the correct group for each case.

Considering only the best separating R1/R2 as the predictor parameter for the discriminant function, 80% of the given cases were classified correctly (Table 4). Applying all three ring ratios as variables, we got a slightly better result (82.5%), as displayed in Table 5; 81.5% of the cases were predicted correctly for the unaffected group, whereas 84.6% of cases were correct for the patients with macular hole formation. The constants and the coefficients for each predictor parameter in Fisher's linear discriminant functions are shown in Table 6.

TABLE 3. Ring Ratios of Fellow Eyes Developing Macular Hole during the Follow-Up, Those Remaining Intact, and Normal Control Eyes

Ring Ratios	R1/R2	R1/R3	R1/R4
Fellow eyes with macular holes (MH, $n = 13$)	**1.22** ± 0.33	**1.67** ± 0.56	**2.28** ± 0.93
Fellow eyes remaining intact (INT, $n = 27$)	1.59 ± 0.38	2.13 ± 0.46	3.07 ± 0.99
Normal control eyes (CO, $n = 40$)	1.59 ± 0.08	2.29 ± 0.35	3.23 ± 0.54
*P*1 (MH - INT)	**0.02**	**0.01**	**0.01**
*P*2 (MH - CO)	**0.01**	**<0.01**	**<0.01**
*P*3 (INT - CO)	0.57	0.62	0.31

Data are expressed as the mean ± SD. Post hoc test, significant probabilities are in bold.

DISCUSSION

mfERG is used to detect functional changes in the macula.[16] Studies have shown that, in eyes with macular hole, the retinal response densities are decreased. Several studies have shown that macular response improves after surgery, when the hole has closed.[17–20]

In this study, we analyzed the mfERGs of 40 patients with unilateral macular hole. Before surgery, the central response densities (R1, R2) showed a marked decrease in the eyes with macular hole compared with the amplitudes in asymptomatic fellow eyes, as reported in several studies.[18–24] We did not find significant differences according to the perifoveal areas (R3–R4), in that the holes were concentrated in the central areas.

After surgery, during the follow-up period of 2 years, the fellow eye remained intact in 67.5% of cases, whereas we diagnosed macular hole in the rest, confirmed by OCT. This rate of 32.5% is in accordance with the data in the literature. In our study, the follow-up period was at least 24 months for eyes remaining intact (mean, 28.4 months), in the other group, a macular hole developed within 15.2 months, on average. The overall average of the follow-up was 24.1 months.

Patients were divided into two groups on the basis of the development of the macular hole during the follow-up period. The main objective of this study was to find out whether the 13 fellow eyes in which macular hole developed were distinguishable from the intact fellow eyes before morbidity by measuring the central amplitudes.

On the basis of the analysis of the preoperative mfERGs, we can verify that the amplitudes in the central area (R1) can discern eyes with macular hole and intact fellow eyes. Amplitudes measured in R2 are also informative to a significant

TABLE 4. Discriminant Analysis Based on R1/R2 as Predictor

R1/R2	Predicted Group Membership: No Macular Hole	Predicted Group Membership: Macular Hole
Fellow eye remained intact	21	6
Macular hole developed	2	11

TABLE 5. Discriminant Analysis Based on the Ring Ratios as Predictors

	Predicted Group Membership	
R1/R2; R1/R3; R1/R4	No Macular Hole	Macular Hole
Fellow eye remained intact	22	5
Macular hole developed	2	11

extent. We found that R3 and R4 regions are not apt to predict the development of a macular hole.

The ratios of R1/R2, R1/R3, and R1/R4 were also investigated in patients' fellow eyes. Since the outer part of the macula (corresponding to rings R3–R5) is not affected by the formation of a macular hole, analyzing the ratio of the central ring (R1) to these rings could enhance the disease specificity of the mfERGs. The use of this ratio has been described in drug-induced maculopathy. The results of the statistical analysis point out significant differences for the ring ratios R1/R2, R1/R3, and R1/R4 between the fellow eyes of the patients who will have macular hole formation compared with the patients in whom one eye will remain intact. The discriminant analysis showed that these three ring ratios together could be used as good predictors of any new case based on the mfERG data of the fellow eye.

We found that macular holes occur considerably more frequently in fellow eyes with lower ring ratios. Based on the analysis of the normative data of our laboratory, the normal ring ratios are 1.59, 2.29, and 3.23 for R1/R2, R1/R3, and R1/R4, respectively. Patients with unilateral macular hole having an R1/R2 lower than 1.42 (mean − 2 SD) have a relative risk (RR) of 7.445 of having a macular hole develop in the fellow eye within 2 years. Patients with ratios below the lower limit of normal (mean − 2 SD) at all three examined ring ratios have an RR of 23.97 and an odds ratio of 312. Thus, our conclusion is that ratios of R1 to any of the outer rings (R2–R4) are strongly predictive of the development of macular hole.

As a result of this comprehensive investigation, we suggest that preoperative mfERG examination is clinically useful in both eyes in patients with unilateral macular hole. The decreased electrical response densities and the significantly lower values of R1/R2, R1/R3, and R1/R4 can forecast the risk of macular hole, when OCT cannot detect any changes in the retinal cross section. It is recommended that the patients who have decreased responses in the asymptomatic fellow eyes before surgery be kept under strict supervision during the follow-up period. There are conclusive reports in the literature of surgery for impending macular holes. We do not recommend pre-emptive surgery based only on the mfERG findings, but with the help of a stricter follow-up, a forming macular hole could be detected earlier, and surgery could be performed at an earlier stage, presumably resulting in a better visual outcome.

TABLE 6. Coefficients for Fisher's Linear Discriminant Function

	Fellow Eye Remains Intact	Macular Hole Develops
R1/R2	6.1388206	3.8224662
R1/R3	6.7039432	6.7919408
R1/R4	1.0172088	1.3836593
Constant	11.199968	7.1212316

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