Multifocal ERG Reveals Several Patterns of Cone Degeneration in Retinitis Pigmentosa with Concentric Narrowing of the Visual Field

Márta Janáky,1 Andrea Pálffy,1 Andrea Deák,1 Mónika Szilágyi,1 and György Benedek2

PURPOSE. To analyze multifocal ERGs (mfERGs) in patients with retinitis pigmentosa (RP), with constricted visual fields and visual acuity satisfactory for steady fixation.

METHODS. The mfERGs of 86 eyes of 43 patients with various forms of inheritance and durations of RP were analyzed. A retinal scanning system with a 20-in. monitor was used to map central cone function. Electrical signals of the retina were detected by using DTL fiber electrodes.

RESULTS. The site of the best response density of the mfERGs in the patients with RP was found in a central or eccentric position of the trace array. Depending on the position of the best response density in the two eyes, the patients were categorized into three groups. In the first group, the best response density was recorded from the central hexagon in both eyes, producing a central peak surrounded by very low responses in the three-dimensional presentation. In the second group of patients, the best responses were found to correspond to the central hexagon on only one side. In the fellow eye, however, the best response density appeared to be in an eccentric position. The patients in the third group did not present a central peak in the mfERG on either side. In scattered parts of the trace arrays, several acceptable responses were observed in all three groups that might represent patches of functioning retinal cone receptors.

CONCLUSIONS. The results suggest highly variable central responses and groups of cones with preserved function in areas previously considered nonresponsive. The high variability of the central responses could be a result of variable foveal cone density, with differences in inheritance- and duration-related cone degeneration at the time of the examination. The authors stress the value of step-by-step analysis of the trace array of the mfERGs, which can reveal the still-functioning groups of cones. (Invest Ophthalmol Vis Sci. 2007;48:383–389) DOI: 10.1167/iovs.06-06061

Retinitis pigmentosa (RP) is a hereditary, progressive retinal photoreceptor dystrophy in which the final consequences of cone degeneration on the central vision are rather variable. Some patients maintain good visual acuity throughout life although their full-field electroretinograms (ERGs) are not measurable, and the visual field is constricted to 5° to 10°. Others, however, lose central vision, even at a young age, and are therefore much more disabled. These observations are in line with the widely held notion that RP is not a homogeneous disease; instead, it can reveal differing manifestations. Several morphologic,2–4 psychophysical,5–7 and electrophysiologic8–9 studies have been performed to reveal the course and nature of the photoreceptor loss in RP. The relationship between visual abilities and electrophysiologic indicators seems to be an important practical problem in the follow-up of patients with RP.

It is well known that the full-field ERG (i.e., the gross electrical response of the retina) can be extinguished in the early stage of the disease, when the central visual acuity is still entirely preserved.10,11 Because the traditional ERG does not seem to be sensitive enough to indicate the condition of the central retina, other methods have been sought. First, several attempts were made to use focal electroretinography for estimation of the residual function of the central retina in RP.9,12 These techniques, however, require special procedures to minimize the effect of stray light, and in addition it is rather time-consuming to obtain responses from more than one region.

The multifocal (mf)ERG technique, which allows a high-resolution mapping of the macular area of the retina,13 initially seemed to be a more promising method for detection of the remaining foveal cone function in some patients with RP. The first experiences obtained with this method, however, showed that there were no detectable mfERG responses in a substantial proportion of patients with RP, even if they had good visual acuity.14–17 Most of the later investigators introduced rather strict inclusion criteria for participation in their mfERG studies. Nonetheless, mfERG alterations reflecting a progressive constriction of the visual field and generally regarded as typical of RP were found in only a proportion of the recordings. For example, only 27 (71%) of the selected 38 patients produced a recordable, “typical” mfERG in the study performed by Seeliger et al.14 This result raises the question of the sensitivity of the method. It is rather difficult to regard an alteration as typical if it is found in only a proportion of patients with RP. Difficulty in maintaining fixation during recording is unlikely to have been the cause of the abnormal responses, because these patients were young and had good visual acuity. Alternatively, the insufficient sensitivity of the method could be responsible for its ineffectiveness in detecting residual function in this hereditary retinal degeneration. Finally, the solution of this problem could lie in the peculiar characteristics of the degenerating cone receptors. In a search for the answers to these questions, we analyzed the mfERG recordings of all our patients with RP who had sufficient visual acuity to maintain fixation. To cover the whole patient population, we analyzed the responses irrespective of whether they were of good or poor quality. Another difference relative to the earlier studies is that we repeated the stimulation monocularly in the cases in which the best responses were not in the central position (31st hexagon).
Electrophysiology of Vision) guidelines for multifocal ERG record-
alyzed according to the ISCEV (International Society for Clinical
patient with monocular stimulation and compared the two recordings.
the best response density in an eccentric position, we retested the
and 100 Hz.
electrodes. For a 50,000
luminance was 51.8 cd/m2, whereas the frame rate was 75 Hz.
fixation. The radius of the central hexagon was 2°. A
GmbH, Wiesbaden, Germany) with a 20-in. monitor was used to map
before the mfERG was recorded, the appropriate refraction was
amplification, the filters were set between 5
/11003
Gender Genotype Visual acuity
Male 14 U 7
AD 10
Female 29 AR 12
S 14
Group I 14 Male 2 U 4
AD 5
Female 12 AR 3
S 2
Group II 16 Male 7 U 2
AD 3
Female 9 AR 4
S 7
Group III 13 Male 5 U 1
AD 2
Female 8 AR 5
S 5

Clinical Data of the 43 Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>n Gender Genotype Age at Testing</td>
<td>Visual acuity n Visual Field</td>
</tr>
<tr>
<td>Total 43 Male 14 U 7 Mean 31.44 Range 6–64</td>
<td>Mean 0.63 86 5–10°</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I 14 Male 2 U 4 Mean 28.64 Range 14–55</td>
<td>Mean 0.86 28 5–10°</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Group II 16 Male 7 U 2 Mean 34.37 Range 11–55</td>
<td>Mean 0.65 32 5–10°</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Group III 13 Male 5 U 1 Mean 31.33 Range 6–33</td>
<td>Mean 0.4 26 5–10°</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n, number of patients or eyes in the corresponding group. U, Usher syndrome; AD, autosomal dominant; AR, autosomal recessive; S, simplex.

METHODS

The mfERGs of 86 eyes of 43 patients with different forms of inheri-
tance and durations of RP were analyzed. All these patients had been
under the care of the same ophthalmologist in the Department of
Ophthalmology for at least 5 years. Examination of the retina included
both direct and indirect ophthalmoscopy and also (in individual cases)
slit-lamp biomicroscopy with Goldmann contact lenses. The visual
acuity of the patients was at least 0.2 in the worse eye, allowing
fixation. Visual field remnants of at least 5° to 10° were detectable by
Goldmann perimetry (III.4 white stimulus).

The clinical characteristics of the patients are listed in Table 1. A
Group of 21 age-matched individuals with good (1.0 or corrected to
1.0) visual acuity and no ophthalmoscopic or visual field alterations
were divided into three groups. The study was performed in full accordance
with the standards laid down in the Declaration of Helsinki.

Before the mfERG was recorded, the appropriate refraction was
measured and corrected for the testing distance. Pupils were dilated
with the standards laid down in the Declaration of Helsinki.

A retinal scanning system (Retiscan; Roland Consult Instrument
GmbH, Wiesbaden, Germany) with a 20-in. monitor was used to map
the central cone function. The room light was on during stimulation.
The screen–patient distance was 28 cm.

The stimulus consisted of 61 hexagons covering a visual field of 30°
around the fixation site. The radius of the central hexagon was 2°. A
red central-fixation cross 2 mm in diameter was used. During stimula-
tion, each element was either black or white (93% contrast). The mean
luminance was 51.8 cd/m2, whereas the frame rate was 75 Hz.

Electrical signals of the retina were detected by using DTL fiber
electrodes. For a 50,000X amplification, the filters were set between 5
and 100 Hz.

In all testing, binocular stimulation was used, but when we found
the best response density in an eccentric position, we retested the
patient with monocular stimulation and compared the two recordings.

The results obtained with the retinal scanning equipment were
analyzed according to the ISCEV (International Society for Clinical
Electrophysiology of Vision) guidelines for multifocal ERG record-
ing. Data were analyzed with two-way ANOVA for group and for
category. When ANOVA showed significant differences, post hoc anal-
ysis was performed with the Dunnett test. P < 0.05 was considered
significant.

RESULTS

On the basis of the best response density of the mfERGs, the
patients were divided into three groups.

The patients in group I (n = 14) presented typical mfERGs
and typical visual field constrictions on both sides. The best
response density was obtained from the 31st hexagon, produc-
ing a central peak surrounded by very low responses in the
three-dimensional presentation (Fig. 1). In the peripheral rings,
one to two good responses were almost always obtainable (e.g., in hexagons 10, 11, or 51). The amplitudes of the scalar
products in the first ring of the multifocal recordings in the
patients with RP (mean: 43.06 nV/deg², range: 17.2–82.2) were
mostly below the normal values (mean: 109.62 nV/deg²,
range: 51.3–136). The differences between these two variables
are significant (P < 0.00001). In both the control subjects and
the patients with RP, the amplitudes of the responses declined
rapidly in the outward direction toward the outer rings.

In the patients with RP, the best average amplitudes were
in the second and third quadrants. This finding is in concert with
the generally accepted type of progressive visual field loss.

Most of the patients in this group had autosomal dominant
inheritance or Usher syndrome. The severity of the alterations
did not correlate well with the age of the patients. Some young
patients had a low central peak of the mfERG, and there were
older patients with only a mild sensitivity loss. Their mean
visual acuity was 0.86, and only three patients had a visual
acuity of 0.5 in the worse eye (Table 1).

In group II (n = 16) of the patients with RP, the best
response was found in the 31st position of the trace array on
only one side. In the fellow eye, the best response density
appeared in an eccentric position (Fig. 2). This alteration could
not be a consequence of a fixation problem, as the fusion
phenomenon keeps the eyes in a motionless position during
binocular stimulation. No laterality differences were found in
the patients with RP, the amplitudes of the responses declined
rapidly in the outward direction toward the outer rings.

In cases in which the best response density was found in an
eccentric position, we repeated the stimulation monocularly,
as well. In both conditions, the best responses were found

outside the central position. In this group, the averaged mean amplitudes of the responses in the first ring of the mfERGs were lower than in group I, although some eyes had a very good central peak. Accordingly, we analyzed the mfERG findings of this group in two subgroups, depending on the site of the best responses. Group II.A comprised the mfERGs of the eyes with a central response, and group II.B those of the fellow eyes with an eccentric best position. The amplitudes of the responses in the first ring of the group II.A eyes (mean, 47.41 nV/deg²) were almost the same as those in group I. The eyes with eccentric best responses (group II.B) produced lower amplitudes in the first ring (mean, 24.36 nV/deg²). The results are presented in Figure 3 (second and third sets of columns).

No significant side differences between the two eyes were found in the amplitudes of the third, fourth, and fifth rings or in the four quadrants.

The patients in group II had a mean visual acuity of 0.65. Altogether, 25 of the 32 eyes displayed visual acuity better than 0.5 (Table 1).

The patients in group III (n = 13) presented no central peak in the mfERG on either side. These cases were classified in the earlier studies as “undetectable mfERGs” or as “just noise.” However, in some parts of the trace array, we found satisfactorily intact responses in all these patients (Fig. 4). In these plots, the best responses were found at rather variable sites (e.g., hexagons 17 and 47). In some cases, there were two or three peaks of low amplitude in the three-dimensional presentation of scalar products, making them “uneven,” “patchy” in appearance, or “unrecordable.” The mean amplitude in the first ring of the mfERGs in this group was rather low (19.28 nV/deg²). The appearance of some characteristic, though small, responses convinced us that these mfERG recordings could not be attributed merely to artifacts or noise. Repeated examinations gave almost corresponding results. It is noteworthy that these patients also had satisfactory visual acuity (0.9–0.2, mean, 0.4). Three eyes had a visual acuity of 0.9, and 12 one had 0.5 or better (0.7–0.5).

We did not find any relationship between our groups on the basis of the mfERG recordings and the heredity pattern of the patients.

For further statistical comparison of the data, we normalized the results of ring analysis, taking the value in the 31st hexagon as 1.0 and calculating the sum of the responses in each other ring proportional to it. In this analysis, significant differences between the groups were found in only a few cases. Group I exhibited significantly smaller ring-3 values compared with those in the central hexagon in the healthy control subjects (P < 0.05), and the ring-1 values relating to those of the central hexagon were significantly larger in group III than in the control subjects (P < 0.05).

**DISCUSSION**

Recording of the mfERG is a relatively new electrophysiological method of mapping the functional capacity of cones in the central retinal area. This is generally regarded as a useful diagnostic tool in a wide range of clinical conditions (e.g., in various forms of macular dystrophy, diabetic retinopathy, central retinal vein occlusion, autosomal dominant optic atrophy, cone dystrophy, and RP). Our results suggest that several patterns of mfERG alterations can be found in patients with RP with satisfactory visual acuity. We dealt with patients with a severely narrowed visual field and analyzed not only the typical mfERGs but also the “undetectable” mfERGs.
In our normal control group, all the recordings had the best responses in the 31st position. Among the patients with concentric constriction of the visual field, we could distinguish three groups, depending on the site of the best response density in the recordings. In a large number of patients, we obtained the results found to be typical in earlier studies. Both eyes of 14 (32%) patients in group I and one eye of the 16 (37.2%) patients in group II had mfERGs with a typical central peak and diminished or extinguished peripheral responses. This number amounts to 69.7% of the eyes involved in the study, a total similar to that found in the study by Seeliger et al. Among the extinguished local ERGs, we observed one to two subnormal responses with a normal wave form in the peripheral rings of the recordings in our group I. These scattered responses, which indicate a preserved function, may escape the attention of an observer who concentrates only on the typical central peak of the trace array. However, in the two-dimensional presentation of the trace array, obvious, circumscribed areas of the retina appear that indicate remnant visual functions and make the periphery of the three-dimensional presentation "uneven." These small peripheral areas could be of prognostic significance if an attempt is made to check the retinal function for replacement therapy.

In group II, the best response density appeared eccentrically in one eye, and centrally in the fellow eye. Finally, in group III, no central peak was seen, but patches of regular responses proved the existence of retinal areas with preserved cone function at parafoveal sites.

In accordance with the earlier study, we did not find any relationship between our groups on the basis of the mfERG recordings and the hereditary pattern of the patients. Thus, our results suggest highly variable central responses and patches of cones with preserved function in areas previously considered nonresponsive. This could be the reason why comparisons of the normalized data and hence elimination of the "multiplication effect" revealed much lower differences between the proportions of the values of ring analysis in the patients with RP and control subjects that could have been expected on ophthalmoscopy or estimation of the visual field.

A comparison of our results and those involving a "non-detectable" mfERG in a substantial proportion of patients with RP raises several questions concerning the method used and the nature of cone degeneration in this disease.

First, we must consider the effectiveness of our method. There are two systems for recording mfERGs: the VERIS (Electro-Diagnostic Imaging, Redwood, CA) and the Retiscan (Roland Consult Instrument GmbH). In most of the earlier studies, VERIS systems were used. We used Retiscan equipment, as no substantial differences in effectiveness have been found between the two systems. Further, there were differences in the active electrodes used. We recorded the retinal responses with DTL fiber electrodes. The signal-to-noise ratio of DTL electrodes may be worse than that of the Burian-Allen electrodes preferred in earlier studies. Further, there is a prismatic effect of the contact lens, and correction of the refraction differences due to the lenses is also difficult. We additionally prefer to use DTL electrodes in our clinical routine examinations, because they are better tolerated by the patients, especially in childhood, or when the test has to be repeated.

There were differences in the stimulating conditions, too. In earlier studies, monocular stimulation of the better eye was used. We used binocular stimulation, which made it possible that the better eye could stabilize the fixation of the weaker eye. Even though our patients had no history of strabismus, and there were no substantial differences in the visual acuity of their eyes, some of them (in groups II and III) exhibited the best response density in an eccentric position on one or on both sides. We therefore repeated the test by monocular stim-
ulation on these eyes. We obtained almost the same results in the two conditions. In 42 (48.8%) of the 86 eyes, the best responses were not located centrally, irrespective of the stimulation technique.

The patients in group III gave very poor mfERG responses in both eyes, but all their recordings revealed two to three characteristic responses of low amplitude, in scattered sites of the trace array. Because of their typical form and their latency values, we accepted these as valid responses instead of regarding these mfERGs as nonrecordable.

After excluding the possibility that our findings could be caused by methodological differences, we have to take the problem of cone degeneration into account. There is ample evidence suggesting the involvement of cone degeneration in the foveal area of patients with RP. Among others, sophisticated psychophysical analysis has demonstrated that the contrast sensitivity function could be abnormal in early stages of RP, despite the visual acuity’s being normal. A reduced contrast sensitivity in RP has also been attributed to the damage to the cone receptors. There are several potential mechanisms for this disturbance, including the loss of photopigment or abnormalities of the membranes of the central cones. However, these were ruled out by a study conducted by Seiple et al., who suggested that the functional deficits may be caused by the scattered, spatially independent loss of the receptors, with the remaining cones having normal adaptation properties.

In addition to the loss of central cone receptors, the high variability of the cone density both in the normal and in the diseased retina could contribute to our findings. The peak foveal cone density is highly variable among individuals (100,000 to 324,000 cones/mm²). The site at which the cone density is most variable is at the center of the fovea, where the coefficient of variation is 46%. The extent of the zone with a high density of cones could also vary in size. This striking variability in the cone density of the normal fovea may be related to variability in the rate, timing, or extent of the migration of cones during development. Another factor that leads to variations in cone density is the age-related loss of photoreceptors. As a third factor of variability, we may consider the disease- and inheritance-related differences of photoreceptor degeneration in RP. Because of the known relationship between visual acuity and cone density, these factors together may result in a high variability of the central responses of mfERGs.

Certainly, these deviations in cone density, including foveal cone spacing, could be limiting factors of the visual resolving power. Foveas with higher cone density may be capable of resolving higher frequencies. This could be the explanation for the high variability of visual resolving power both in the normal and in the diseased retina, in the range of 30 to 60 cyc/deg.

These facts explain why some patients can lose numerous central cones without measurable visual acuity disturbances, whereas others, with a cone degeneration of the same degree, have more severe visual loss.

Overall, we assume that

1. The highly variable central responses in the mfERG could be a result of variable foveal cone density, a phenomenon present both in normal and diseased retinas.

2. The differences in disease-related cone receptor degeneration (determined by inheritance and by the different
durations of the disease) may enhance the variability of the mfERG results.

3. A scattered, spatially independent loss of photoreceptors in RP could be responsible for the patchy appearance of the remnant mfERG in the patients in our groups II and III.

As a general conclusion, we want to stress the value of step-by-step analysis of the trace array of mfERGs, which can reveal the still functioning patches of cones. The responses in these patches may not attain a level that could alter the average values in ring analysis.

Acknowledgments

The authors thank Kati Mayer and Gabriella Dósa-Molnár for their valuable technical assistance and Péter Liszli for all his kind help.

References