The Effects of Retinal Abnormalities on the Multifocal Visual Evoked Potential

John Y. Chen,1,2 Donald C. Hood,1 Jeffrey G. Odel,2 and Myles M. Behrens2

PURPOSE. To examine the effects on the amplitude and latency of the multifocal visual evoked potential (mfVEP) in retinal diseases associated with depressed multifocal electroretinograms (mfERG).

METHODS. Static automated perimetry (SAP), mfERGs, and mfVEPs were obtained from 15 individuals seen by neuro-ophthalmologists and diagnosed with retinal disease based on funduscopic examination, visual field, and mfERG. Optic neuropathy was ruled out in all cases. Diagnoses included autoimmune retinopathy (n = 3), branch retinal arterial occlusion (n = 3), branch retinal vein occlusion (n = 1), vitamin A deficiency (n = 1), digoxin/age-related macular degeneration (n = 1), multiple evanescent white dot syndrome (n = 1), and nonspecific retinal disease (n = 5). Patients were selected from a larger group based on abnormal mfERG amplitudes covering a diameter of 20° or greater.

RESULTS. Fourteen (93%) of 15 patients showed significant mfVEP delays, as determined by either mean latency or the probability of a cluster of delayed local responses. Thirteen of 15 patients had normal mfVEP amplitudes in regions corresponding to markedly reduced or nonrecordable mfERG responses. These findings can be mimicked in normal individuals by viewing the display through a neutral-density filter.

CONCLUSIONS. Retinal diseases can result in mfVEPs of relatively normal amplitudes, often with delays, in regions showing decreased mfERG responses and visual field sensitivity loss. Consequently, a retinal problem can be missed or dismissed as functional, if a diagnosis is based on an mfVEP of normal or near-normal amplitude. Further, in patients with marked mfVEP delays, a retinal problem could be confused with optic neuritis, especially in a patient with a normal appearing fundus. (Invest Ophthalmol Vis Sci. 2006;47:4378 – 4385) DOI: 10.1167/iovs.06-0242

The multifocal visual evoked potential (mfVEP), introduced by Baseler et al.,1 is a useful tool for evaluating optic nerve disease and visual defects secondary to optic nerve or retinal ganglion cell damage (see Refs. 2,3 for reviews). The diagnostic utility of the mfVEP can be enhanced by combining it with the multifocal electroretinogram (mfERG).4 If the mfVEP is abnormal, the mfERG can be used to exclude outer retinal disease.

For example, the mfERG can be used to distinguish between branch retinal arterial occlusion (abnormal mfERG) and ischemic optic neuropathy (normal mfERG), both of which can cause altitudinal visual field defects and abnormal mfVEPs. On the contrary, if the mfVEP and fundus exams are normal and the visual field is abnormal, then the cause is assumed to be nonorganic or functional.5 Typically, in such cases, an mfERG is not performed, as it is assumed to be normal. In general, this analysis assumes that there is good correspondence between mfERG and mfVEP amplitudes when retinal disease is present.

However, relatively little is known about how local mfERG and mfVEP responses compare. Recently, two studies compared mfVEPs to mfERGs from patients with retinitis pigmentosa.6,7 Although there was a suggestion of a greater loss in the mfERG than in the mfVEP for the responses from the central retina, in general, the agreement between the mfERG and mfVEP appeared reasonably good. Smaller mfERGs were associated with smaller mfVEPs.

Of course, diseases such as RP that destroy large regions of photoreceptors should, in general, produce good agreement. When there is no signal coming from a region of receptors, it would be surprising to record mfERG or mfVEP responses from that region. In the present study, we examined the effects of retinal disease on the relationship between mfERG and mfVEP responses in patients without a known disease of the receptors. Many of these patients showed relatively large mfVEP responses in regions with depressed mfERG amplitudes; these mfVEP responses were typically delayed in latency. These findings have implications for the clinical use of the mfVEP, as well as for understanding the nature of local damage brought about by these retinal disorders.

METHODS

Subjects

Fifteen patients (six men and nine women) with retinal disease were selected for this study (Table 1). Nine patients had unilateral disease, whereas six had bilateral disease. The diagnoses included autoimmune retinopathy (n = 3), branch retinal arterial occlusion (n = 3), branch retinal vein occlusion (n = 1), vitamin A deficiency (n = 1), digoxin/age-related macular degeneration (n = 1), multiple evanescent white dot syndrome (n = 1), and nonspecific retinal disease (n = 5). These patients were all seen by a neuro-ophthalmologist for the purposes of diagnosing optic nerve or retinal disease. The diagnosis of retinal disease was based primarily on the combined results of the funduscopic examination, visual field, and the mfERG. Some of the patients had additional diagnostic tests including the full-field ERG, retinal antibody studies, and fluorescein angiogram. None of the patients had clinically significant cataracts or any other ocular or systemic diseases, and a diagnosis of optic neuropathy was ruled out in all cases. In addition, none of these patients had a disease known to affect large numbers of photoreceptors, such as RP. The patients were chosen from a larger pool of patients with retinal disease based on the presence of abnormal mfERG responses affecting an area greater than 20° in diameter.

The patients had a mean age of 66.6 ± 14.6 years. The control group for the mfVEP consisted of 50 subjects with normal visual acuity...
and normal findings in ophthalmic examination with a mean age of 58.7 ± 9.0 years. All subjects gave informed consent to participate after a full explanation of the procedure. The tenets of the Declaration of Helsinki were followed, and informed consent was obtained after the nature and possible consequences of the study were explained. The Institutional Review Board of Research Associates of Columbia University approved the research.

Static Automated Perimetry
Threshold visual fields, as well as foveal thresholds, were obtained in all patients with the Humphrey visual field analyzer (program 24-2; model HFAII series 750; Carl Zeiss Meditec, Dublin, CA). Threshold visual fields, as well as foveal thresholds, were obtained in all patients with the Humphrey visual field analyzer (program 24-2; model HFAII series 750; Carl Zeiss Meditec, Dublin, CA).

mfERG
The mfERG technique has been described in detail elsewhere. Briefly, the stimulus was an array of 103 hexagons scaled with eccentricity. The display extended 46° horizontally and 39° vertically at a viewing distance of 32 cm, with a central X used for fixation. On each frame, every hexagon had a 50% probability of being white or black. The luminance of the white hexagons was 200 cd/m²; the surround luminance was 100 cd/m². Pupils were dilated using 1% tropicamide, and corneas were anesthetized with 0.5% proparacaine. A bipolar Burian-Allen electrode was used to record the mfERG, and the forehead served as the ground. The mfERG signal was amplified (P511J preamplifier; Grass-Telefactor, West Warwick, RI), sampled at 1200 Hz and band-pass filtered between 10 and 300 Hz. Pupil position was monitored with a CCD camera (see Refs. 7 and 9 for details).

mfVEP
Stimulus. Figure 1 is a schematic of the scaled, dartboard display, which had a diameter of 44.5° and contained 60 sectors each with 16 checks: 8 white (200 cd/m²) and 8 black (<1 cd/m²). The display, a standard option produced by the system software (VERIS; Dart Board 60 with Pattern; Electro-Diagnostic Imaging [EDI], San Mateo, CA), was viewed through natural pupils with the appropriate refractive correction. The display appeared on a black and white monitor driven at a frame rate of 75 Hz. On each frame change, the checkerboard of each of the 60 sectors had a 0.5 probability of reversing in contrast or staying the same. The contrast reversals of the 60 sectors were independently modulated according to a pseudorandom sequence. This display has been used in previous studies. (See Ref. 15 for a review of the general multifocal technique and Ref. 2 for a review of the mfVEP technique.)

Recording. Three channels of continuous VEP (EEG) records were obtained with gold cup electrodes. For the midline channel, electrodes were placed 4 cm above the inion (active), at the inion (reference), and on the forehead (ground). For the other two channels, the same ground and reference electrodes were used, but the active electrodes were placed 1 cm above and 4 cm lateral to the inion on either side. By taking the difference between pairs of channels, three additional “derived” channels were obtained, resulting in effectively six channels of recording representing the six possible pairs of the four recording electrodes.2,14

The records were amplified with the high- and low-frequency cutoffs set at 3 and 100 Hz with a preamplifier (one half amplitude; preamplifier P511; Grass Telefactor), and were sampled at 1200 Hz (every 0.83 ms). In a single session, two 7-minute recordings were obtained from monocular stimulation of each eye. The mfVEP responses were extracted with the system software (VERIS ver. 4.x; EDI). Technically, these mfVEP responses are the first slice of the second-order kernels. (For more details, see Refs. 2 and 14.)

Analyzing the mfVEP. After exporting mfVEP responses from the custom software (VERIS; EDI), monocular and interocular measures of both amplitude and latency were produced. For the monocular measures, the amplitude and latency measures were compared to monocular recordings from 100 normal control subjects.16 –18 For the interocular measures, the analyses compared the eyes of a patient and related the resultant measures to a similar analysis of control subjects' eyes. These methods have been described in detail for both the amplitude2,14,16 –18 and latency measures.19,20

Probability Plots and an Example of the mfVEP Analysis. Figure 2C shows the mfVEP records for patient P10, a 41-year-old male who presented with a complaint of a “smudge” in his vision in the left eye for the past 4 months. Ophthalmoscopy revealed unremarkable

<table>
<thead>
<tr>
<th>Subject</th>
<th>Eye</th>
<th>Age</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Visual Acuity</th>
<th>Fundus Findings</th>
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<tr>
<td>P1</td>
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<td>35</td>
<td>F</td>
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<td>OS</td>
<td>65</td>
<td>F</td>
<td>BRVO</td>
<td>20/20 OD, 20/25 OS</td>
<td>Parafoveal microaneurysm on FA</td>
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<td>F</td>
<td>Unknown</td>
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<td>OD</td>
<td>66</td>
<td>M</td>
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<tr>
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<td>Unremarkable</td>
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<td>BRAO</td>
<td>20/40 +3 OD, 20/40 +2 OS</td>
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<td>OU</td>
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<td>Autoimmune retinopathy</td>
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<td>20/20 OD, 20/20 OS</td>
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<td>80</td>
<td>F</td>
<td>ARMD/digoxin toxicity</td>
<td>20/40 OD, 20/50 OS</td>
<td>Macular drusen, RPE defects</td>
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sponses for P10. The significant points in the SAP fields (total deviation from the two eyes.19 On the interocular latency plot, red points represent points where the right eye is slower than the left. Blue represents points where the left eye is slower than the right. The color indicates whether the responses did not meet the amplitude criterion19,20 indicating the 1% level, whereas the lower hemifield of the right eye had a cluster of six points, with four exceeding the 1% level. Based on a group of 100 normal individuals,19,20 these clusters are significant at greater than 1%.

In addition to examining clusters, the mean value of relative latencies was calculated for each eye. To obtain the mean relative latency, latency values for only those sectors that meet reliability criteria were averaged to give a single value. For the 50 age-matched control subjects, the mean relative mfVEP latency was 3.4 (4.3 SD) ms. In patient P10, the mean latency in the right eye was 15.3 ms and 13.4 ms in the left. The 95% CI for age-matched control subjects was 11.9 ms, thus the results exceed the 95% CI.

RESULTS

The results for patient P5 in Figures 4 to 6 provide an example of the basic findings. Patient P5 is a 71-year-old man who presented with a complaint of a “donut-shaped” field defect in his right eye that he had had for approximately 10 years. Best-corrected visual acuities were 20/20 in each eye. SAP showed a generalized decrease in visual field sensitivity for the right eye (Fig. 4A). Ophthalmoscopy revealed flat discs with normal vessels and macula. His mfERG results for each eye are shown in Figure 4B. In Figure 5 (right column), the mfERG responses from the left (red) and right (blue) eyes are superimposed. There is a marked decrease in amplitude relative to his left eye. In addition, the implicit times (i.e., time to peak response) of the mfERG from the left eye are delayed. This is best seen in the inset comparing a set of mfERG responses from both eyes in Figure 5B (right column).

Consistent with the mfERG, the mfVEP (Fig. 4C, left column) from the left eye showed normal amplitudes and latencies, as indicated by the probability plots in the first column of Figure 6A (amplitude) and 6B (latency). For the right eye, there were clear delays in the mfVEP as can be seen in the records (Figs. 5A, 5B, left column) and on the probability plot in Figure 6B. The latency probability plots shown in Figure 6B revealed a large, significant cluster in the right eye. The mean relative latency of P5 was 21.6 ms, indicating a large delay compared with the control values. This delay in implicit time of the mfVEP was the first of our two major findings.

Our second major finding was a relatively small change in the mfVEP amplitude in some patients with depressed mfERG amplitudes. In the case of P5, as indicated in the center column of Figure 6B, there were regions of the field with relatively normal mfVEP amplitudes despite the mfERG being markedly reduced throughout the entire field (Fig. 4B). The contrast between the mfERG and mfVEP results is best seen in Figure 5. Here the mfVEP and mfERG from the two eyes from Figure 4 are superimposed with sample traces enlarged for ease of viewing. Although the mfERG in the right eye was markedly reduced in amplitude, the mfVEP in the right eye was only marginally reduced.

Latency of mfVEP

Like P5, many of the eyes with retinal disease showed significant delays on mfVEP. Table 2 shows the mean relative latency for each of the affected eyes. Based on the 95% CI for age-
matched control subjects (11.9 ms), 13 (62%) of 21 eyes with retinal problems and 10 (67%) of 15 patients showed significant average delays on mfVEP. When cluster criteria and the latency probability plots were used, as described in the Methods section, 16 (76%) of 21 eyes and 13 (87%) of 15 patients showed delays. Finally, 18 (86%) of 21 eyes and 14 (93%) of 15 patients showed delayed mfVEP records on either the mean latency or the cluster criterion. The mean relative monocular latency in the 21 affected eyes was 11.5 ms, significantly higher ($P < 0.001$) than the mean latency in the 50 age-matched control eyes (3.4 ms).

**Figure 3.** mfVEP monocular and interocular probability plots of (A) amplitude and (B) latency for P10. The area enclosed between the green circles denotes the approximate region of depressed mfERG responses (see Fig. 2B).

**Figure 4.** (A) SAP fields, (B) mfERG responses, and (C) mfVEP responses for P5. The significant points in the SAP fields (total deviation plots) ranged from −4 to −28 dB.

**Figure 5.** (A) Superimposed right and left eye responses for the mfVEP and mfERG of P5. Responses from equivalent locations on the mfVEP and mfERG are enclosed by the green circles and enlarged in (B).
Normal mfVEP Amplitudes in Regions of Poor mfERG

Like P5, many of the eyes with retinal disease showed relatively large mfVEP amplitudes in regions where the mfERG showed markedly decreased to nonrecordable responses. In particular, although mfVEP amplitudes were typically abnormal in the affected eyes of the patients, 13 (87%) of 15 patients showed mfVEP amplitudes that were normal in regions that corresponded to abnormal regions of the mfERG. Figure 7 shows another example (P3). Every one of the 103 mfERG responses of the left eye (Fig. 7A, left panel) showed decreased amplitude. However, the mfVEP, which covers approximately the same region of the field as the mfERG, showed amplitudes that were normal to near normal (Fig. 7B). When the responses were superimposed as in Figures 7C and 7D, there was relatively little difference in amplitude of the mfVEP from the two eyes compared with the mfERG where the two eyes show marked differences.

Can a Neutral-Density Filter Mimic the Effects of a Retinal Disease?

It is well known that decreasing retinal illuminance increases the latency of the VEP. For example, Sherman et al.21 reported that reducing retinal illuminance with a neutral-density filter delays the VEP from a normal eye while causing only minimal reduction in amplitude. Thus, we asked whether a neutral-
density filter would mimic the effects observed in some of the patients with retinal disease.

Figure 8A shows the visual fields from SAP of a normal subject after placement of a 1.1 log unit (11 dB) filter in front of the right eye. The filter decreased the sensitivity of the eye 3 to 8 dB, as shown in Figure 8A. Figure 8B shows the mfERGs obtained when decreasing the amount of luminance entering a normal subject’s right eye by the same amount. The mfERG responses from the right eye are decreased in amplitude and delayed in implicit time, similar to the mfERGs of 13 of the 15 patients, including the mfERGs of P3 and P5, displayed in Figures 7A and 4B, respectively. These effects on the mfERG are easier to see in Figures 9B and 9C (right column) where the mfERG responses from the two eyes are superimposed.

Figure 9A shows the mfVEP records from the left (left column) and right (right column) eye obtained with the filter in front of the right, but not the left, eye. The mfVEPs from the right eye are delayed relative to those from the left. This can be seen in the superimposed mfVEP records in the left columns of Figures 9B and 9C, as well as in both the monocular and interocular latency probability plots in Figure 10B. In contrast, the subject had normal amplitudes for the right eye as seen in the records of Figures 9B and 9C, as well as in the amplitude probability plots of Figure 10A. These relatively normal amplitudes can be contrasted with the decreased mfERG amplitudes in Figures 9B and 9C (right column).
DISCUSSION

The purpose of the study was to examine the relationship between local abnormalities of the mfERG and the amplitude and latency of the mfVEP. Under extreme conditions, where large regions of receptors are destroyed with diseases such as RP, one should expect good agreement between the mfERG and mfVEP measures as neither of them should be present. However, in this study we excluded patients with diseases such as RP and cone–rod dystrophy, which are known to result in widespread photoreceptor degeneration. There were two main findings.

First, nearly all patients showed delayed cortical responses on mfVEP. Delays as large as demyelinating optic nerve disease have been shown with conventional pattern VEP (PVEP) in patients with macular lesions, just as the Pulfrick stereoiilusion that reflects delays seen in optic neuritis has also been found in central serous retinopathy. However, to our knowledge, this is the first study to show local delays in retinal disease using the mfVEP. This demonstration was made possible by the recent development of techniques for measuring mfVEP latency. Using these techniques, 18 (86%) of 21 eyes and 14 (93%) of 15 of patients showed significant mfVEP delays.

The increased mfVEP latencies observed with retinal disease are in the range seen with optic neuritis/multiple sclerosis. The range of latencies observed here for the retinal patients (11.5 ± 6.7 ms) overlaps that (11.7 ± 5.8 ms) observed in 23 eyes with optic neuritis (Odel JG, et al. IOVS 2005;46:ARVO E-Abstract 642). The clinical implications are clear: Delays in optic neuritis are statistically indistinguishable from those in our subset of retinal patients, and in some cases, may be less than those of mfVEP responses in retinal disease. Clinicians should be careful to rule out a retinal origin in the presence of a delayed mfVEP before a diagnosis of optic neuritis is made based on the mfVEP.

The second major finding is the relatively large mfVEP amplitudes in regions with diminished mfERGs. More specifically, in 13 of 15 patients the local mfVEP responses are normal to near normal in areas of the field where the mfERG was moderately to severely depressed in amplitude. Clinically, it is clear that an ERG test is advisable in patients with abnormal fields but normal findings in fundus and mfVEP examinations, before a nonorganic or functional diagnosis is made.

It is not entirely clear why these patients with retinal disease had relatively large, but delayed, mfVEP responses in regions of the field with markedly depressed mfERGs. What is most striking is that, simply by decreasing the luminance entering a normal eye, both findings can be mimicked in a control subject. That is, by decreasing the amount of luminance entering a normal subject’s right eye, the mfERG responses (Fig. 8B) are diminished in amplitude and the mfVEP responses (Fig. 9A) show delayed responses (Fig. 10B) and normal amplitudes (Fig. 10A).

The similarity of the results obtained from the patients to the neutral-density filter results does not mean that the diseases in question are physically decreasing the intensity of the light. We do not expect the mechanism responsible for the delays in any of our patients to be due to a filtering of the light. However, we cannot rule out a decrease in the number of quanta absorbed through shortened outer segments and/or disoriented cone outer segments. Although this would act as a neutral density filter, we suspect this does not account for most of the findings. A third possibility, and the one we favor, is that the quantal absorption by the receptors is normal, but the signal from the photoreceptors and/or bipolar cells is decreased by the disease process. Decreasing the output of the cells (i.e., receptors/bipolar cells) before the gain and adaptation mechanisms present at the amacrine and ganglion cell and cortical levels produces effects similar to a neutral-density filter.

FIGURE 10. mfVEP monocular and interocular probability plots of (A) amplitude and (B) latency from a normal subject after placement of a 1.1 log unit (11-dB) filter in front of the right eye.
In any case, from a clinical perspective, a retinal problem can be missed or dismissed as functional if a diagnosis is based on an mfVEP of normal or near-normal amplitude. Further, as these patients can have marked delays in the mfVEP, a retinal problem can be confused with optic neuritis or multiple sclerosis, especially in a patient with a normal-appearing fundus.

**Acknowledgments**

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**References**