Nature of the Cone ON-Pathway Dysfunction in Melanoma-Associated Retinopathy

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PURPOSE. To establish the basis for an ON-pathway abnormality of the cone system in melanoma-associated retinopathy (MAR) through analysis of the electroretinogram (ERG) and visual evoked potential (VEP).

METHODS. Two patients with MAR syndrome whose sera produced immunolabeling of retinal bipolar cells participated in the study. Full-field ERGs were recorded in response to brief flashes, to rapid-on and rapid-off sawtooth stimuli at a temporal frequency of 8 Hz, and to sine-wave stimuli at temporal frequencies ranging from 8 to 96 Hz. Fundamental responses to the sine-wave stimuli were evaluated within the context of a vector-summation model of the depolarizing bipolar cell (DBC) and hyperpolarizing bipolar cell (HBC) contributions to the response fundamental. VEPs were recorded to the onset of luminance increments and decrements that had contrasts of 10%, 20%, and 50%. The patients’ results were compared with those of age-similar control subjects.

RESULTS. The patients with MAR showed abnormal ERG responses to luminance increments, consisting of a marked attenuation of the initial portion of the b-wave, but their ERG responses to luminance decrements were normal in amplitude and timing. The ERG temporal response functions of the patients with MAR had normal amplitudes at frequencies of 32 Hz and higher, with a constant phase lag across these frequencies, but larger-than-normal amplitudes at frequencies below 32 Hz, and a phase lead at 8 Hz. Their VEP responses showed a marked delay to increments but only a minimal delay to decrements.

CONCLUSIONS. Within the context of the vector-summation model, the ERG findings in the patients with MAR are more consistent with an attenuation of the DBC contribution to the ERG response than with a DBC response delay. The delayed VEP responses of the patients with MAR to luminance increments may represent a late response of the OFF system to increment onset. (Invest Ophthalmol Vis Sci. 2002;43: 1189–1197)
Therefore, it is possible that the ERG ON-response deficit in patients with MAR syndrome represents a delay in the DBC response relative to that of the HBC response, rather than an attenuation of signal transmission within the DBC pathway, as proposed previously. A response delay within the DBC pathway would not explain the night blindness of patients with MAR, but as Sieving has noted, it is not necessarily true that a given retinal abnormality would affect both the rod pathway and the cone ON pathway in the same way.

Based on a recent study, it should be possible to distinguish between a response delay and a response attenuation within the cone DBC pathway in patients with MAR by analyzing their ERG responses to sinusoidal flicker within the framework of a vector-summation model of the primate ERG. According to this model, the fundamental of the ERG response evoked by sinusoidal stimulation is the vector sum of the massed fundamental responses of the cone photoreceptors, DBCs, and HBCs. The amplitudes and phases of the response components of the model were derived from the monkey retina by means of pharmacologic isolation. At temporal frequencies near 32 Hz (the frequency typically used clinically), the model predicts that a reduction in the DBC response amplitude alone would have little effect on the amplitude of the fundamental of the ERG response but would produce a substantial phase lag. Conversely, a delay in the DBC response relative to the responses of the photoreceptors and HBCs would increase the fundamental response amplitude at 32 Hz compared with normal, but would introduce only a minimal phase lag.

The vector-summation model also predicts that a DBC response attenuation and a DBC response delay would have quite different effects on the shape of the temporal response function at temporal frequencies below 32 Hz. The normal ERG temporal response function has a peak near 32 Hz and a minimum near 10 Hz. The response minimum has been attributed to a relative cancellation between the out-of-phase responses of the DBCs and HBCs at this frequency. If there were an attenuation of the DBC contribution to the ERG, then the model predicts that the fundamental response would be enhanced compared with the normal response at frequencies near 10 Hz. This would result in a flattened temporal response function across the lower frequency range. Conversely, the vector-summation model predicts that a delayed DBC response would have little effect on response amplitudes at frequencies near 10 Hz but would increase response amplitudes at higher frequencies. This would result in a more strongly bandpass temporal response function over the frequency range from 10 to 52 Hz. (Illustrations of quantitative predictions of the model for a DBC response attenuation and a DBC response delay across a range of temporal frequencies are presented in Fig. 6.)

The goal of the present study was to determine whether a response attenuation within the DBC pathway or a DBC response delay is responsible for the abnormal cone ERG response defect in MAR. We first measured cone ERG ON and OFF responses in two patients with MAR syndrome to confirm the presence of an abnormal ON response and to investigate the characteristics of the OFF response. The stimulus used to elicit ON and OFF responses was sawtooth flicker rather than the long-flash stimuli used in previous studies of MAR, to minimize the potential eye movement artifacts that can obscure the waveform morphology of the ERG OFF response when long-duration flashes are used. We then analyzed the patients’ ERG responses to sinusoidal flicker within the context of the vector-summation model. Finally, we measured the VEP responses of the patients with MAR to luminance increments and decrements to determine whether there was evidence of a relative delay in the VEP response to increments similar to that observed previously in two patients with night blindness and cone ERG ON-response deficits.

**METHODS**

**Subjects**

Two patients with MAR syndrome participated in the study. Their characteristics are presented in Table 1. A malignant melanoma had been removed from the back of each patient. Each reported night blindness, which was confirmed psychophysically in MAR patient 1 by means of dark-adapted static perimetry described previously (patient 2 was apprehensive about being in the dark and declined testing). Both patients reported seeing characteristic shimmering lights or photopsias. Of note, 21 months after the onset of visual symptoms, patient 1 reported spontaneously that the photopsias had disappeared, although there was no evidence of any change in visual function. Both patients had normal visual acuity but had a marked reduction in large-letter contrast sensitivity (Table 1). The two patients showed a selective reduction of the b-wave amplitude of the brief-flash ERG under both dark-adapted and light-adapted conditions (see Fig. 1 for the light-adapted ERG waveforms). The sera of both patients produced strong, specific immunolabeling of retinal bipolar cells that is typical of MAR, using a procedure described previously.

**TABLE 1. Patients’ Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MAR 1</th>
<th>MAR 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first visit (y)</td>
<td>59</td>
<td>55</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>Age at diagnosis of melanoma (y)</td>
<td>58</td>
<td>49</td>
</tr>
<tr>
<td>Age at onset of visual symptoms (y)</td>
<td>59</td>
<td>55</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Bipolar cell autoantibodies present</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Fundus</td>
<td>Normal</td>
<td>OU: 1-disk-diameter atrophic lesion, inferotemporal retina</td>
</tr>
<tr>
<td>Goldmann visual fields</td>
<td>OD: enlarged blind spot; OS: normal</td>
<td>OU: Small relative central scotoma</td>
</tr>
<tr>
<td>Color vision</td>
<td>OD: tritan defect; OS: anarchic pattern</td>
<td>Not tested</td>
</tr>
<tr>
<td>Visual acuity</td>
<td>OD: 20/15; OS: 20/15</td>
<td>OD: 20/100 (amblyopic); OS: 20/20</td>
</tr>
<tr>
<td>Contrast sensitivity*</td>
<td>OD: 1.05; OS: 1.00</td>
<td>OD: not tested; OS: 1.17</td>
</tr>
</tbody>
</table>

* Pelli-Robson chart (normal range, 1.65–1.95)
The findings from the patients with MAR were compared with those from three groups of control subjects. For the brief-flash ERG, the patients’ results were compared with those of a group of 101 visually normal control subjects, ages 7 to 73 years. For the sinusoidal and sawtooth stimuli, the ERG responses of the patients with MAR were compared with those from a group of 10 visually normal control subjects who had a mean age of 46.5 years (age range, 34–56 years). The VEP findings from the patients with MAR were compared with those from a group of 10 control subjects who had a mean age of 47.2 years (age range, 28–56 years). Four control subjects participated in both the sinewave/sawtooth ERG study and the VEP study. All control subjects had best corrected visual acuity of 20/20 or better in the tested eye, clear ocular media, and normal-appearing fundi in ophthalmic examination. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of the University of Illinois at Chicago. Informed consent was obtained from all subjects after the nature and possible consequences of the study had been explained to them.

**Stimuli and Instrumentation**

**ERG.** Brief-flash ERGs were measured in response to achromatic (xenon) strobe flashes that were presented in a ganzfeld (Nicolet, Madison, WI). ERG responses to sinusoidal and sawtooth stimuli were measured with instrumentation that has been described previously. In brief, the stimulus consisted of achromatic full-field flicker that was superimposed on an achromatic rod-desensitizing adapting field, both presented within an integrating sphere (Oriel, Stratford, CT). The flickering stimulus and adapting field were provided by two separate optical channels, each with a light source consisting of a 300-W tungsten–halogen bulb (each housed within a projector; Eastman Kodak, Rochester, NY), and each with infrared blocking filters. The light from the two optical channels was combined with a "y" fiber-optic light guide (Oriel) that was introduced into a side port of the integrating sphere.

**Temporal modulation of the test field** was controlled by a ferroelectric liquid crystal (FLC) shutter (Displaytech, Longmont, CO) and driver (DR-95; Displaytech). The driver was controlled by a signal-processing board (DAS-801; Keithley, Cleveland, OH) housed within a microcomputer. The FLC shutter was driven at a constant temporal frequency of 1 kHz and was pulse-width modulated under computer control, with the duty cycle governed by a linearized look-up table. A shutter and driver (Vincent Associates, Rochester, NY) within the second optical channel controlled the adapting field presentation. Luminances were calibrated with a photometer (LS-110; Minolta, Osaka, Japan).

**VEP.** The stimulus for the VEP was based on that of Zemon et al., and has been described previously. In brief, the stimulus consisted of a 12° × 12° grid of squares, presented on a computer monitor against a background of 1.5 log cd/m² and controlled by a stimulus presentation and data acquisition system (Venus; NeuroScientific Corp., Farmingdale, NY). The squares were each 0.3° in width and were 0.4° apart. Each stimulus cycle consisted of 200 ms of the incremental squares (luminance higher than the background) followed by 800 ms of the decremental squares (luminance lower than the background) and another 800 ms of the background alone. This stimulus cycle was repeated continuously until the requisite number of sweeps had been obtained (described later). Stimuli of 10%, 20%, and 50% Weber contrast were used, with luminances controlled by a linearized look-up table.

**Procedure**

**ERG.** For all recordings, the pupil of the tested eye was dilated with 2.5% phenylephrine hydrochloride and 1% tropicamide drops, and the cornea was anesthetized with proparacaine drops. The subject’s head was held in position with a chin rest and forehead bar. ERG responses were recorded using a signal averaging system (Viking IV; Nicolet). For the brief-flash ERG, responses to flashes of 0.9 log cd/m² were recorded from the test eye with a monopolar Burian-Allen contact lens electrode, with a forehead electrode as the reference and an earlobe as the ground, after 10 minutes of light adaptation to a rod-desensitizing adapting field of 1.5 log cd/m². The flashes were presented at 1-second intervals, and responses to four flashes were averaged.

Responses to sinusoidal and sawtooth stimuli were recorded in a separate session. Subjects were light adapted to room illumination before testing and were then adapted for 2 minutes to a rod-desensitizing adapting field of 1.2 log cd/m². The left eye was tested in all subjects. Recordings were made with a bipolar Burian-Allen contact lens electrode grounded at the earlobe. The signal-averaging system was triggered by a transistor–transistor logic (TTL) signal generated by the signal-processing board (DAS-801; Keithley) and synchronized with the onset of each stimulus cycle. ERG recordings were made at sine-wave temporal frequencies of 8, 16, 32, 64, and 96 Hz, with the sine waves presented at maximum amplitude and in sine phase. Recordings were also made at a sawtooth stimulus frequency of 8 Hz, at maximum amplitude and in both rapid-on and rapid-off phase. Each cycle of rapid-on sawtooth flicker consisted of an abrupt increment in luminance, to emphasize an ON response, followed by a linear decrease in luminance. Each cycle of rapid-off flicker consisted of an abrupt decrement in luminance, to emphasize an OFF response, followed by a linear increase in luminance. These sawtooth stimulus waveforms are illustrated in Figure 2. The maximum luminance of the sinusoidal and sawtooth stimuli was 2.6 log cd/m² and the minimum luminance was 0.1 log cd/m². In the absence of the adapting field, these luminances produced a modulation of 99%. Against the adapting field, the modulation was 91.2%.

Recordings of responses to sinusoidal and sawtooth stimuli were begun after the subjects had adapted to each waveform for approximately 30 seconds. For each condition, two or three 500-ms recordings were obtained to determine reproducibility. Each recording was the average of four sweeps, and the recordings were averaged offline. Response amplitudes at the stimulus fundamental frequencies were derived from power spectral densities of the averaged waveforms, and response phases were obtained from fast Fourier transforms (FFTs) by computer (using the MatLab Signal Processing Toolbox; The MathWorks, Natick, MA). The fundamental response amplitudes that are plotted in the figures represent the full peak-to-trough amplitudes. The phases are given in cosine phase.

**VEP.** Monocular VEPs were recorded in a dimly lit room. The tested eye was chosen at random, except that the nonamblyopic left eye of patient 2 was stimulated. Subjects viewed the display through the best optical correction in a trial frame, with the untested eye occluded. Responses were recorded from an electrode positioned 3

![Figure 1](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933593/ on 04/10/2017)
waves were within (55.3 μV, MAR 1; 72.7 μV, MAR 2) the normal range (34.9–71.6 μV), and their d-wave implicit times (23 ms, MAR 1; 24 ms, MAR 2) were within the normal range (21–25 ms). Furthermore, the shapes of the patients’ d-wave responses were within the range of variation exhibited by normal subjects. Abnormal ON responses were also apparent in the patients’ ERG responses to 8- and 16-Hz sinusoidal stimuli, as illustrated in Figure 3. At these two temporal frequencies, control subjects typically show two response peaks per stimulus cycle. These peaks have been labeled in Figure 3 as “ON” and “OFF” responses, respectively, to indicate that they corresponded to the regions of increasing and decreasing luminance in the sinusoidal stimulus. By comparison, the ERG responses of the patients with MAR showed only one peak at each frequency, corresponding to an OFF response, with only a minor inflection in the waveform at the time of the normal ON response.

To determine whether the patients’ abnormal ON responses, shown in Figures 2 and 3, represented a response attenuation or a response delay within the DBC pathway, we first examined the amplitudes and phases of the patients’ ERG fundamental responses to 32-Hz sinusoidal flicker. The ERG waveforms of the patients at this temporal frequency are shown in Figure 4A, together with the response of the same control subject as in Figure 3. Of note, there was little apparent difference between the waveform shapes of the patients with MAR and the control subject at 32 Hz, in contrast to the marked differences between their ERG waveforms at the lower temporal frequencies (Fig. 3). The log amplitudes and phases of the fundamentals of the 32-Hz ERG responses of the patients with MAR are presented in Figure 4B (filled symbols) in the form of a polar plot. For comparison, the amplitudes and phases of the responses of the individual control subjects are also plotted in this figure (open triangles). The amplitudes of the response fundamentals of the patients with MAR were within the range of normal. However, the patients with MAR showed a phase lag that was approximately 25° beyond the range of normal and approximately 50° beyond the normal mean (corresponding to response delays of 2.2 and 4.3 ms, respectively, assuming that the phase lag was due entirely to a response delay). According to the vector-summation model, this pattern of results is most consistent with a response attend-
within the DBC pathway, which would introduce a phase lag but would have little effect on the amplitude of the response fundamental.

We examined this conclusion further by analyzing the fundamental response amplitudes and phases of the patients with MAR and control subjects at temporal frequencies ranging from 8 to 96 Hz, with the results shown in Figure 5. Both log amplitude (Fig. 5, top) and phase (Fig. 5, bottom) were plotted against log temporal frequency, according to convention. The shaded regions show the ranges for the 10 control subjects. The patients' amplitudes (Fig. 5, top) were within the normal range at the three highest temporal frequencies, but were larger than normal at the two lower frequencies. Further, the response functions for the patients did not show the strong bandpass shape that was characteristic of the function for the control subjects, but instead had a relatively flat shape from 8 to 32 Hz. The phases of the response fundamentals of the patients with MAR (Fig. 5, bottom) were more negative than those of the control subjects, representing a phase lag, except at the lowest temporal frequency of 8 Hz, where there was a relative phase advance. Over the frequency range from 16 to 96 Hz, the average phase lag of the patients with MAR was approximately 20° compared with the lower limit of the normal range and approximately 44° compared with the normal mean.

The ERG temporal response functions of the patients with MAR and the control subjects were compared with the predictions of the vector-summation model for two conditions: a response attenuation within the DBC pathway, and a response delay within the DBC pathway. The model predictions (Fig. 6) were obtained by vector summation of the amplitudes and phases of the primate ERG response components that were plotted in Figure 4 of Kondo and Sieving. The model predictions are shown for the specific temporal frequencies that were tested in our study. (No data were plotted at 96 Hz, because the data of Kondo and Sieving did not extend to that frequency.) The open circles in Figure 6 represent the fundamental response amplitude (top) and phase (bottom) for the normal primate ERG. The amplitude function has a peak at 32 Hz and a response attenuation at lower temporal frequencies. The phase function has a slight phase increase between 8 and 16 Hz and a systematic decrease in phase at the three higher frequencies. These temporal response functions for the normal primate ERG fundamental are quite similar in overall shape, although not in magnitude, to the human control ERG data shown in Figure 5. Therefore, the primate data represent a...
satisfactory model for the shape of the normal human ERG temporal response function.

The filled circles (Fig. 6, left) indicate the fundamental response amplitude (top) and phase (bottom) to be expected if there were a complete attenuation of the DBC contribution to the ERG response fundamental. The filled triangles (Fig. 6, right) represent the fundamental response amplitude (top) and phase (bottom) if the DBC response were delayed by 5 ms compared with the responses of the cone photoreceptors and HBCs. The amplitude and phase functions for the patients (Fig. 5) were more similar in shape to the predicted effect of a response attenuation within the DBC pathway (Fig. 6, left) than with a DBC response delay (Fig. 6, right). That is, the amplitude functions of the patients were relatively flat across the frequency range from 8 to 32 Hz, and their phase functions had a phase lead at 8 Hz and a phase lag at the higher temporal frequencies. These results support the hypothesis that the ERG ON-response deficits in patients with MAR syndrome represent an attenuation of signal transmission within the retinal ON pathway.

VEP Responses

The VEP responses of the two patients with MAR and a representative control subject are shown in Figure 7. This figure plots VEP responses to luminance increments (Fig. 7, left) and luminance decrements (Fig. 7, right) at a stimulus contrast of 50%. Two averaged responses are presented for each subject, to illustrate reproducibility. As observed previously, the normal VEP responses to increments and decrements each show a dominant positive peak, termed P1 and indicated by the arrows in the figure. In the control subjects, the peak latencies for P1 at 50% contrast were approximately 110 ms for both increments and decrements. (The normal ranges are indicated by the shaded regions in the figure.) In the two patients with MAR, the responses to luminance increments (Fig. 7, left) were markedly delayed, and the response waveforms were broader than normal. The response latencies for luminance decrements (Fig. 7, right), however, were normal (MAR 2) or just at the upper limit of the normal range (MAR 1). Of note, the patients’ responses to both increments and decrements occurred before the termination of the 200-ms stimulus and therefore did not represent responses to stimulus offset.

The P1 latencies of the patients with MAR as a function of stimulus contrast are illustrated in Figure 8, together with the ranges of the normal latencies (shaded regions). For luminance increments (Fig. 8A, open symbols), the patients’ P1 latencies were considerably longer than normal at the two highest contrasts. No clear response peak was discernible at the lowest contrast. In comparison, the patients’ peak latencies to luminance decrements (Fig. 8B) were within (MAR 2) or at the upper limits (MAR 1) of the normal range for the two highest contrasts and were slightly beyond the normal range in both patients at the lowest contrast.

The data that are illustrated in Figures 8A and 8B show the patients’ response latencies to increments and decrements...
is that it minimizes the potential eye movement artifacts that can affect the shape of the ERG OFF response to long-duration flashes. Using the sawtooth waveform, we found that the patients’ d-wave responses had a normal amplitude and timing. The patients did not show the enhancement of d-wave amplitude that has been reported to occur when L-AP4 is applied to the monkey retina to eliminate the response of the DBC system. We note, however, that the application of the IgG of patients with MAR to the monkey retina also did not enhance the d-wave of the ERG OFF response, although the b-wave of the ON response was markedly attenuated. The explanation for this apparent discrepancy between the effects of L-AP4 and MAR IgG on the OFF response remains to be clarified. Nevertheless, it is apparent from our data that the ERG OFF response of patients with MAR can be within the normal range despite a marked abnormality in their ERG ON response.

To determine whether the ERG ON-response abnormality represents an amplitude reduction or a response delay within the DBC pathway, we examined the ERG fundamental response to sine of a flicker within the context of a vector-summation model of the generators of the primates ERG. The patients with MAR showed a fundamental response at 52 Hz that was normal in amplitude but had a phase lag of approximately 50° relative to the normal mean (Fig. 4). According to the vector-summation model, this result is more consistent with a reduction in the amplitude of the DBC response than with a DBC response delay, which would have increased the ERG fundamental response amplitude substantially but would have had little effect on the response phase (Fig. 6).

Other features of the temporal response functions of the patients with MAR (Fig. 5) were also more consistent with an attenuated DBC response than with a DBC response delay. First, the patients’ relatively enhanced fundamental response amplitudes at the lower temporal frequencies and the flattening of their amplitude functions (Fig. 5, top) are consistent with this explanation. That is, for normal subjects, the vector summation of nearly out-of-phase DBC and HBC components is thought to reduce the amplitude of the response fundamental at these lower temporal frequencies. Therefore, an attenuated DBC response would enhance the fundamental response amplitude at low temporal frequencies compared with normal, as is seen in the patients’ amplitude functions. Second, according to the vector-summation model, an attenuated DBC response would result in a phase advance at 8 Hz and a phase lag at higher frequencies, as is observed in the patients’ phase plot (Fig. 5, bottom). As noted previously, an attenuated response within the DBC system would account not only for the abnormal ERG responses of the patients with MAR, but also their reduced rod b-wave amplitude and their night blindness, given that rod bipolar cells are of the depolarizing (ON) type.

Although the ERG data of the patients with MAR are more consistent with a relative attenuation of the DBC response than with a DBC response delay, the patients showed a marked delay in the VEP response to luminance increments (Fig. 7, bottom). The explanation for this finding is presently uncertain, but we note that a similar type of late response to luminance increments has been observed in the light-evoked field potentials of the superior colliculus of the mGlur6-deficient mouse. The metabotropic glutamate receptor mGlur6 mediates synaptic transmission from photoreceptors to DBCs, so that mGlur6-deficient mice have a marked ON-pathway defect. Sugihara et al. suggested that the late response to luminance increments in these knockout mice may represent the response of the ON-surround of OFF-center ganglion cells to light onset. Consistent with this possibility, Massey et al. reported that some OFF-center ganglion cells of the rabbit retina responded to light onset with a delayed response from the antagonistic surround that was approximately 90 ms later than...
the response of ON-center ganglion cells to the same stimulus. We hypothesize that the delayed VEP response to luminance increments in our patients with MAR may similarly represent a late response of the ON-surround of OFF-center cells.

As noted in the introduction, Wolf and Arden\(^{15}\) concluded that there was no specific damage to the ON-pathway in patients with MAR syndrome, based on the observation that their three patients showed no threshold asymmetry for identifying letters of positive versus negative contrast, or for detecting increment versus decrement Gaussian patches. However, these tests are not likely to be entirely appropriate for assessing ON-pathway dysfunction. It has been shown that letter identification is based on a limited band of object frequencies,\(^{26,27}\) and within that critical band, letter stimuli contain regions of both positive and negative contrast.\(^{28}\) Therefore, it is not likely that this task preferentially stimulates ON versus OFF pathways. Further, the detection of briefly presented incremental Gaussian patches by their patients with MAR could have been based on stimulus offset (effectively a luminance decrement) rather than stimulus onset.

In agreement with Wolf and Arden,\(^{15}\) the patients with MAR syndrome in our study showed a marked loss of contrast sensitivity for large letters but had normal high-contrast visual acuity (Table 1). Although a selective magnocellular pathway defect was invoked previously to account for this finding,\(^{15}\) a loss of contrast sensitivity at low spatial frequencies accompanied by normal visual acuity is also consistent with an ON-pathway defect. For example, the intravitreal injection of L-AP4 to inactivate the retinal ON pathway of monkeys greatly reduced their contrast sensitivity at low spatial frequencies but had little effect on their visual acuity.\(^{29}\) Therefore, an ON-pathway deficit could account for this finding in patients with MAR, as well.

Wolf and Arden\(^{15}\) reported that their patients with MAR had the greatest loss of sensitivity under test conditions that involved transient stimuli (i.e., temporal contrast sensitivity and low-contrast displacement thresholds). They hypothesized that this might be due to selective damage within the magnocellular pathway, although the locus of this damage was not specified. It has been reported recently that the sustained and transient properties of the visual pathway are first organized at the level of the retinal bipolar cells.\(^{30}\) This raises the intriguing possibility that the visual disability experienced by patients with MAR may represent the effect of an antitumor antibody on a specific class of cone ON bipolar cells: those with transient response properties. The exact mechanism by which an autoantibody might affect the function of a particular class of retinal bipolar cells remains to be resolved, however.

In conclusion, the two patients with MAR syndrome who were investigated in this study showed an ON-response deficit of the ERG of the cone system that was manifested as a selectively reduced b-wave response to brief luminance increments, an abnormal response to rapid-on (incremental) sawtooth flicker with a normal response to rapid-off (decremental) sawtooth flicker, and a reduction in the first (ON) component of the ERG response to low-frequency sinusoidal flicker. They also showed ERG responses to 32-Hz sinusoidal flicker that were of normal amplitude but had a relative phase lag. Analysis of their ERG responses to sinusoidal flicker at a range of temporal frequencies within the framework of a vector-summation model\(^{16}\) indicated that the ON-response deficits of the cone ERG were more consistent with an attenuation of the DBC response component than with a DBC response delay. Nevertheless, these patients showed profoundly delayed VEP responses to luminance increments with relatively normal responses to luminance decrements. The delayed VEP responses to increments may represent the response of OFF-center cells to light onset, as has been proposed for the delayed light-evoked field potentials of the superior colliculus in mGluR6 knockout mice.\(^{22}\)

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\section*{References}


