Contrast-Processing Deficits in Melanoma-Associated Retinopathy

Kenneth R. Alexander,¹,² Claire S. Barnes,¹ Gerald A. Fishman,¹ Joel Pokorny,⁵ and Vivianne C. Smith³

PURPOSE. To evaluate the hypothesis that patients with melanoma-associated retinopathy (MAR) have a selective functional loss within the magnocellular (MC) pathway of the cone system, with sparing of parvocellular (PC) pathway function.

METHODS. Two patients with MAR, ages 57 and 61 years, with normal Snellen visual acuity, participated in the study. Contrast sensitivity was measured at spatial frequencies ranging from 0.25 to 8 cycles per degree (cpd), using two paradigms (steady pedestal and pulsed pedestal) designed to assess the functional integrity of the MC and PC pathways, respectively. Results in patients with MAR were compared with those in 10 visually normal observers, aged 23 to 57 years.

RESULTS. Both patients with MAR showed a loss of contrast sensitivity compared to normal observers, but the pattern of loss differed for the two testing paradigms. For the steady-pedestal paradigm (presumed MC-pathway mediation), the patients' sensitivity loss was greatest at the lowest spatial frequency (0.25 cpd) and the sensitivity loss decreased systematically with increasing spatial frequency. For the pulsed-pedestal paradigm (presumed PC-pathway mediation), the sensitivity loss was greatest at an intermediate spatial frequency of 1 cpd. For both paradigms, the patients' sensitivities were within the normal range at the highest spatial frequency (8 cpd), consistent with their normal visual acuity.

CONCLUSIONS. The contrast sensitivity deficits of patients with MAR under photopic conditions are not specific to the MC pathway, as proposed previously, but instead are related to the spatial frequency of the test target. The overall pattern of contrast sensitivity loss shown by the patients with MAR is consistent with the dysfunction at the level of the retinal bipolar cells that is presumed to underlie the MAR syndrome. (Invest Ophthalmol Vis Sci. 2004;45:305-310) DOI:10.1167/iovs.03-0840

Melanoma-associated retinopathy (MAR) is a form of paraneoplastic visual disorder that can occur in individuals who have metastatic malignant cutaneous melanoma.¹ MAR is characterized by night blindness, photopsias or the perception of shimmering lights, and characteristic abnormalities in the electroretinogram (ERG) of both the rod and cone systems.¹⁻⁵ These ERG abnormalities include a selective reduction in the amplitude of the b-wave of both the rod and cone systems with preservation of the a-wave, so that the ERG has a negative shape, and a decreased ERG ON response of the cone system with a normal cone OFF response. The serum of patients with MAR produces selective immunolabeling of retinal bipolar cells,¹ and the intravitreal injection of MAR IgG into the monkey eye produces ERG abnormalities that resemble those of patients with MAR.⁶ It is assumed that MAR is the result of autoantibodies that are generated against a melanoma and that cross-react with bipolar cells, impairing their function,¹,⁶ although the identity of the antibody is not known at present.

The ERG waveforms of patients with MAR are similar to those recorded from the monkey retina when signal transmission from photoreceptors to depolarizing (ON) bipolar cells (DBC) is blocked by intravitreal injections of L-2-amino-4-phosphonobutyrate (L-AP4).⁶,⁷ This has led to the proposal that the antibodies in MAR produce a selective response attenuation within the DBCs,⁵ which is supported by a recent analysis of the flicker ERG of the cone system of patients with MAR.⁸ A blocked signal transmission from photoreceptors to DBCs would account both for the abnormal ERG ON response of the cone system in MAR, and for the patients' night blindness and reduced rod b-wave amplitude, given that rod bipolar cells are of the depolarizing type.⁹ Therefore, the evidence from immunolabeling studies and from the ERG abnormalities indicates that the retinal ON bipolar cells are the primary site of pathophysiology in patients with the MAR syndrome.

Recently, it has been proposed that patients with MAR have a response deficit within the magnocellular (MC) pathway of the cone system, with sparing of the parvocellular (PC) pathway.¹¹ This hypothesis is based on the findings that patients with MAR have a greatly reduced large-letter contrast sensitivity, substantially reduced temporal contrast sensitivity for contrast-reversing Gaussians of low spatial frequency and markedly increased displacement thresholds for a low-contrast, low-spatial-frequency grating. These are visual tasks that are thought to be mediated by the MC pathway. The patients with MAR in that study also had normal or modestly reduced visual acuity and normal or somewhat reduced chromatic contrast sensitivity, visual tasks that are thought to be mediated by the PC pathway.

The tests of MC-pathway function in the patients with MAR examined by Wolf and Arden¹² were focused on performance at low spatial frequencies, whereas the tests of PC-pathway function were oriented toward performance at high spatial frequencies. Therefore, it is possible that the deficits of the patients with MAR were related more to stimulus spatial frequency than to dysfunction within the MC pathway per se. The purpose of the present study was to evaluate this possibility using a new testing protocol that exploits the different contrast-response properties of the MC and PC pathways.¹¹ Specifically, contrast sensitivity was measured for spatially localized, narrow-band targets (sixth spatial derivatives of Gaussians or D6 patterns)¹² using steady-pedestal and pulsed-

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pedestal paradigms. The steady-pedestal paradigm, which entails a brief presentation of the test stimulus against a continuously presented luminance pedestal, favors the MC pathway because the test target is presented for only a few milliseconds. The pulsed-pedestal paradigm, in which there is the simultaneous brief presentation of both the test stimulus and luminance pedestal, favors the PC pathway, because the abrupt onset of the luminance pedestal saturates the MC pathway. As reported previously, the contrast-response properties of these two paradigms correspond to those described for the primate MC and PC pathways.

**METHODS**

**Subjects**

Two patients with the MAR syndrome, ages 61 (MAR patient 1) and 57 (MAR patient 2), participated in the study. The characteristics of these patients were described in a previous report and are summarized in Table 1. Each patient had undergone the surgical removal of a malignant melanoma from his back. Each of the patients had the typical symptoms of MAR, including night blindness and a selective reduction in his large-letter contrast sensitivity from 1.0 to 1.3 over this period, but no change in the ERG response of either the rod or cone system. Each patient had reported seeing characteristic shimmering lights, or photopsias. Of note, 21 months after the onset of his visual symptoms, MAR patient 1 reported that the photopsias had disappeared. There was an increase in his large-letter contrast sensitivity from 1.0 to 1.3 over this period, but no change in the ERG response of either the rod or cone system. Each patient had a visual acuity of −0.04 log MAR (20/18 Snellen equivalent) in the tested (left) eye. The sera of both patients produced a constant proportion of the peak spatial frequency of the D6 pattern of positive contrast was presented briefly (45 ms), with either a vertical or horizontal orientation, chosen randomly. The test target was presented in the center of a square pedestal that subtended 7.6° on a side and had a luminance of 12.5 cd/m². The pedestal in turn was presented in the center of a steady-adapting field.

**Test Stimuli**

The test stimuli and procedures were based on those used previously. The stimuli were generated by a Macintosh computer (PowerPC 7500/100; Apple, Cupertino, CA) and were presented on an Apple high-resolution gray-scale display. A 10-bit video board (Thundervox 30/1600; Radius, Sunnyvale, CA) and a linearized lookup table controlled the stimulus luminances, which were calibrated with a photometer (IS-110; Minolta, Osaka, Japan). The stimulus configuration is illustrated in Figure 1. The test stimulus was a one-dimensional D6 pattern, which has a spatial frequency bandwidth of approximately one octave at half-height. The D6 pattern was defined by a sixth spatial derivative of a Gaussian in one direction and a Gaussian in the orthogonal direction. The space constant of the orthogonal Gaussian was a constant proportion of the peak spatial frequency of the D6 pattern, so that the test target was approximately circular.

![Figure 1](image.png)

**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>MAR Patient 1</th>
<th>MAR Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at first visit (y)</strong></td>
<td>61</td>
<td>57</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td><strong>Age at diagnosis of melanoma (y)</strong></td>
<td>58</td>
<td>49</td>
</tr>
<tr>
<td><strong>Age at onset of visual symptoms (y)</strong></td>
<td>59</td>
<td>55</td>
</tr>
<tr>
<td><strong>Metastasis</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Bipolar cell autoantibodies present</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Fundus</strong></td>
<td>Normal</td>
<td>1 disc diameter atrophic lesion in the inferotemporal retina</td>
</tr>
<tr>
<td><strong>ERG</strong></td>
<td>Selective b-wave reduction</td>
<td>Selective b-wave reduction</td>
</tr>
<tr>
<td><strong>Goldmann visual fields</strong></td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Color vision (FM 100-Hue)</strong></td>
<td>Anarchic pattern</td>
<td>Small relative central scotoma</td>
</tr>
<tr>
<td><strong>Visual acuity (logMAR)</strong></td>
<td>−0.04</td>
<td>−0.04</td>
</tr>
<tr>
<td><strong>Contrast sensitivity</strong></td>
<td>1.30</td>
<td>1.20</td>
</tr>
</tbody>
</table>

Visual characteristics refer to the tested (left) eye.

*Pelli-Robson chart. Normal range, 1.65–1.95.
that subtended 10.5° horizontally by 9.1° vertically and had a luminance of 25 cd/m². As depicted in Figure 1, the pedestal produced a luminance decrement against the adapting field. The remainder of the screen (vertical bars with a width of 0.6° to either side of the adapting field) was set to 20 cd/m² (80% of the adapting field luminance). The D6 pattern was of positive contrast, such that the maximum luminance correctly was assigned a value of 0.05 log unit, and contrast sensitivity of the letters in a set of three correctly. Each letter that was read several seconds before responding, as recommended by the testing were uncertain. No time limit was given, and, particularly at the lower were instructed to read each letter on the chart and to guess, if they correction in a phoropter at a test distance of 1 m. Fixation was guided by four thin black diagonal lines that extended from the edges of the pedestal to a region just outside the D6 pattern.

**Procedure**

Before testing, the visual acuity of all observers was assessed with a Lighthouse Distance Visual Acuity Test (Lighthouse International, New York, NY). The chart was transilluminated, with an interletter luminance of 2.3 log cd/m², and it was viewed through the best optical correction in a phoropter at a test distance of 4 m. The observers were asked to attempt to read every letter on the chart and to guess if they were uncertain. No time limit was given. Testing was terminated when none of the letters on a line could be identified correctly. Each letter that was identified correctly was assigned a value of 0.02 log MAR, and visual acuity was defined as the total log MAR score, according to the recommendation of Bailey et al. Letter contrast sensitivity was then measured with a Pelli-Robson contrast sensitivity chart that was illuminated by overhead lighting so that the interletter luminance was 2.0 log cd/m². The chart was viewed through the best optical correction in a trial frame at a distance of 1 m, with an appropriate correction for the testing distance. Observers were instructed to read each letter on the chart and to guess, if they were uncertain. No time limit was given, and, particularly at the lower contrast levels, observers were encouraged to view the letters for several seconds before responding, as recommended by the testing instructions. Testing was terminated when the subject identified none of the letters in a set of three correctly. Each letter that was read correctly was assigned a value of 0.05 log unit, and contrast sensitivity was defined as the total score, as recommended by Elliott et al. For both chart tests, measurements were made twice, with a different version of the chart used for each of the measurements. The two scores for each test were averaged.

The psychophysical procedure was then explained, and observers were given a brief practice series. Two testing paradigms were used. In the steady-pedestal paradigm (Fig. 1A), the luminance pedestal was presented continuously. During the test period, the D6 pattern was presented briefly against the luminance pedestal. In the pulsed-pedestal paradigm (Fig. 1B), the luminance pedestal and D6 pattern were presented briefly and simultaneously during the test period. For both paradigms, the test stimulus duration was 45 ms (three video frames). A 50-second period of adaptation preceded each test condition.

The observer initiated each trial by pressing a button on a response pad (GamePad; Gravis, San Mateo, CA). After a brief warning tone, the stimulus was presented. The observer’s task was to judge whether the D6 pattern was vertical or horizontal on that trial and to record the response by pressing the corresponding button on the response pad. The order of conditions was 1, 0.5, 2, 4, 0.25, and 8 cpd. Within each condition, the order of the steady- and pulsed-pedestal paradigms was randomized. Thus, there were 12 test conditions within an experimental session (six spatial frequencies × two testing paradigms). In a pilot study, a spatial frequency of 16 cpd was also included, but no control observer was able to respond correctly at the highest contrast at this spatial frequency and duration. Additional testing showed that the difference between this result and that of Leonova et al. was due to the use of circular rather than elongated D6 patterns.

Contrast thresholds were measured with a two-alternative forced-choice procedure using an accelerated stochastic approximation. There were two randomly interleaved staircases: one for vertical and one for horizontal orientation of the D6 pattern. The staircase steps were defined by the relationship:

\[ X_{n+1} = X_n - \frac{c}{2 + m_{\text{shuf}}} (Z_n - \theta), \quad n > 2 \]

where \( X_n \) is the step size in trial \( n \), \( c \) is the initial contrast value, \( m_{\text{shuf}} \) is the cumulative number of reversals, \( Z_n \) is the observer’s response (0 or 1), and \( \theta \) is the targeted percent correct value (80% in the present experiment). Each staircase was terminated after the 12th reversal. The threshold for each orientation was defined as the mean of all data points for that orientation beginning with the sixth reversal. There were no systematic differences between the contrast thresholds for the two stimulus orientations for any of the observers, so the results for the two orientations were averaged.

**RESULTS**

The mean results for the control observers for the steady-pedestal (Fig. 2, circles) and pulsed-pedestal (Fig. 2, triangles) paradigms are shown in Figure 2. The error bars represent the 95% confidence limits for the control data. In agreement with a previous study, the mean contrast sensitivity function for the steady-pedestal paradigm had a low-pass shape, whereas the function for the pulsed-pedestal paradigm was band-pass in shape. As a consequence, the greatest difference in contrast sensitivity occurred at the lowest spatial frequency, and then

**Figure 2.** Mean contrast sensitivity functions for the control observers for the steady-pedestal and pulsed-pedestal paradigms. Error bars: 95% confidence limits for the data of the control observers.
contrast sensitivities tended to converge at the highest spatial frequency. By a repeated-measures analysis of variance, there was a statistically significant difference between the mean contrast sensitivities for the two paradigms for the control observers ($F = 538.51, P < 0.001$). Post-hoc $t$-tests with a Bonferroni correction for multiple comparisons showed significant differences between the two paradigms at all spatial frequencies ($t = 21.97, 17.83, 14.63, 8.96, 4.71, 2.52; all P < 0.05$; for 0.25, 0.5, 1, 2, 4, and 8 cpd, respectively).

The results for the two patients with MAR are presented in Figure 3. For clarity, the contrast sensitivity functions for the steady-pedestal and pulsed-pedestal paradigms are plotted separately. For the steady-pedestal paradigm (Fig. 3, top), both patients with MAR showed a substantial reduction in contrast sensitivity at low spatial frequencies, but their contrast sensitivity was within the 95% confidence limits for the control observers at the highest spatial frequency. For the pulsed-pedestal paradigm (Fig. 3, bottom), the patients with MAR showed a loss of contrast sensitivity at intermediate spatial frequencies (MAR patient 2) or all but the highest spatial frequency (MAR patient 1).

The sensitivity losses of the patients with MAR relative to the mean of the control observers are illustrated by the visuograms in Figure 4. For the steady-pedestal paradigm (Fig. 4, top), the sensitivity loss of both patients with MAR was greatest at the lowest spatial frequency, and then the magnitude of the sensitivity loss decreased systematically with increasing spatial frequency. For the pulsed-pedestal paradigm (Fig. 4, bottom), the patients' sensitivity losses were nonmonotonic across spatial frequency. The greatest sensitivity loss occurred at 1 cpd, with less sensitivity loss at lower and higher spatial frequencies.

To determine whether visual performance was more compromised under test conditions that favor the MC or PC pathway, we plotted the log ratios of the contrast sensitivities for the steady- and pulsed-pedestal paradigms in Figure 5. For the control observers (Fig. 5, shaded region), the vertical distance between the two functions was greatest at the lowest spatial frequency, and the difference decreased systematically with increasing spatial frequency (see Fig. 2). In this plot, log ratios near zero (Fig. 5, dashed line) indicate that the PC pathway probably mediates contrast sensitivity for both testing paradigms. Data points that lie below the shaded region would represent a relatively
greater sensitivity loss for the steady-pedestal paradigm (inferred greater sensitivity loss within the MC pathway), whereas data points above the shaded region would represent a greater sensitivity loss for the pulsed-pedestal paradigm (inferred greater sensitivity loss within the PC pathway).

The two patients with MAR showed a high degree of similarity in the pattern of results (Fig. 5, symbols), despite differences in overall levels of contrast sensitivity. For the lowest spatial frequency of 0.25 cpd, the patients’ log sensitivity ratios were considerably below the 95% confidence limits of the control observers, consistent with a greater sensitivity loss within the MC pathway. At higher spatial frequencies, the patients’ log sensitivity ratios were generally within the 95% confidence limits of the control observers, although their data points tended to be at the lower limit of normal. Overall, then, there was a tendency for the patients with MAR to show a greater sensitivity loss under conditions that favor the MC pathway, with the loss most pronounced at the lowest spatial frequency.

DISCUSSION

In addition to the typical symptoms of MAR, which include night blindness, photopsias, and a selectively reduced ERG b-wave, the two patients with the MAR syndrome in this study also had reduced large-letter contrast sensitivity (Table 1), reduced contrast sensitivity at low spatial frequencies (Fig. 3, top), normal visual acuity (Table 1), and normal contrast sensitivity at high spatial frequencies (Fig. 3, bottom). In these respects, the patients’ visual performance was similar to that of three patients with MAR reported previously by Wolf and Arden.10

Wolf and Arden10 proposed that the reductions in the visual performance of their patients with MAR were due to a selective deficit within the MC pathway, with preservation of PC-pathway function. However, our results demonstrate that the PC pathway is in fact also affected in MAR. The patients with MAR in the present study showed a reduced contrast sensitivity at intermediate spatial frequencies when tested using a pulsed-pedestal paradigm that favors the PC pathway. Therefore, our findings indicate that the functional impairment in MAR is related more to the spatial frequency of the test stimulus than to whether the test stimulus favors the MC or PC pathway. Of note, two of the patients with MAR tested by Wolf and Arden10 showed some deficits in chromatic discrimination (the third patient was a deuteranope), indicating that the PC pathway was not entirely normal in those patients. Similarly, the two patients with MAR in the present study also had color vision defects (Table 1).

The patients’ contrast sensitivity deficits for the pulsed-pedestal paradigm in the present study resemble the contrast sensitivity deficits of monkeys whose ON pathway is inactivated by intraretinal injections of l-AP4.18 In a study of the effect of l-AP4 on contrast discrimination at various spatial frequencies, Schiller et al.18 required monkeys to make a saccadic eye movement to a homogeneous stimulus presented together with a set of five checkerboard patterns, all of the same spatial frequency. This task is similar to the original pulsed-pedestal paradigm of Pokorny and Smith,13 which favors the PC pathway. After the application of l-AP4, the monkeys’ saccadic performances were normal at the highest tested spatial frequency (5 cpd) and near normal at the lowest spatial frequency (0.8 cpd), but their percent correct values were reduced and saccadic latencies were increased at intermediate spatial frequencies (1-3 cpd). This pattern of response deficits is similar to the pattern of contrast sensitivity loss shown by the patients with MAR using the pulsed-pedestal paradigm (Fig. 4, bottom). Therefore, the normal visual acuity and normal contrast sensitivity at high spatial frequencies of the patients with MAR, together with their reduced contrast sensitivity at intermediate spatial frequencies using the pulsed-pedestal paradigm, is consistent with the ON-pathway dysfunction that is presumed to underlie the MAR syndrome.4–6

Even though the two patients with MAR in the present study showed a reduced contrast sensitivity for both the pulsed-pedestal and steady-pedestal paradigms, which is indicative of deficits within both the PC and MC pathways, the sensitivity loss tended to be greater under conditions that favor the MC pathway. This was particularly the case at the lowest spatial frequency, as shown in Figure 5. Similarly, Wolf and Arden10 observed that the visual performance of their patients with MAR was severely compromised for tests that favored the MC pathway when using stimuli of low spatial frequency.

The apparently greater loss of contrast sensitivity under conditions favoring the MC pathway could represent the consequence of the ON-pathway deficit that is thought to underlie the MAR syndrome. For example, although Schiller et al.18 did not report the effect of l-AP4 on contrast sensitivity under conditions favoring the MC pathway, they suggested that l-AP4 interferes with a normal push–pull interaction between the ON and OFF pathways. Disturbance of this interaction due to an attenuated signal within the ON pathway in MAR is likely to be particularly detrimental for the MC pathway, which is insensitive to contrast polarity at threshold,19 implying inputs from both the ON and OFF pathways. An attenuated signal within the ON pathway would also be likely to have a more pronounced effect at low spatial frequencies, at which there is a greater pooling of neural signals within the cortical analyzers that are presumed to mediate spatial contrast sensitivity, which could account for the substantially reduced steady-pedestal contrast sensitivity of the patients with MAR at low spatial frequencies (Fig. 4, top). Alternatively, given the recent evi-
dence that the transient (MC-like) and sustained (PC-like) properties of the visual pathway are first organized at the bipolar cell level, the greater sensitivity loss of the patients with MAR at low spatial frequencies under conditions favoring the MC pathway may represent greater damage to retinal bipolar cells that have transient properties. In either case, the patients’ contrast processing deficits, together with their ERG abnormalities described in a previous study, and the specific immunolabeling of retinal bipolar cells by their IgG, are consistent with pathophysiology at the level of the retinal bipolar cells, affecting primarily the DBCs, and perhaps emphasizing bipolar cells with transient response properties.

In conclusion, our results indicate that visual deficits in patients with MAR are not limited to the MC pathway, but are also apparent under test conditions that favor the PC pathway. Nevertheless, there is a tendency for a greater functional impairment under conditions that emphasize the MC pathway, particularly at low spatial frequencies. The present findings illustrate the value of using steady-pedestal and pulsed-pedestal paradigms to distinguish mechanisms of contrast sensitivity loss in retinal disease. Further, the deficits in contrast sensitivity shown by the patients with MAR emphasize the importance of identifying visual impairment that may not be evident through the clinical measurement of Snellen visual acuity alone.

Acknowledgments

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References