Photopic Flicker Sensitivity Losses in Simplex and Multiplex Retinitis Pigmentosa

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Psychophysical tests for flicker sensitivity were conducted on a group of retinitis pigmentosa patients classed as either simplex or multiplex on the basis of the familial incidence of this disease. The results were compared with those obtained from normal observers. A similar pattern of losses, predominantly at high temporal frequencies, was shown by all patients. The pattern cannot be reproduced in normal observers by reducing the luminances of the test stimuli; nor can it be explained by a simple reduction in the signal-to-noise ratio of the visual system. Invest Ophthalmol Vis Sci 25:1035–1042, 1984

Retinitis pigmentosa (RP) is the name for a group of retinal diseases in which progressive retinal degeneration is accompanied by migration of pigment cells into the retina.1 The clinical diagnosis used in our study was based on the following diagnostic symptoms. Typically, initial ophthalmoscopic changes occur in the postequatorial fundus with atrophy preceding pigment migration, which often gives rise to bone spicule patterns in the fundus. The disease becomes more widespread as it progresses. When it is well established, blood vessels usually are attenuated, and the disc assumes a pale, waxy, yellow color. Other signs often seen in established RP are the presence of posterior subcapsular lens opacities and vitreous cells. Patients show reduced fields and frequently complain of night blindness. The disease often is associated with a history of similar complaints in the family. The majority of cases of RP are thought to be genetic, following one of the three major inheritance patterns: autosomal dominant, autosomal recessive, or X-linked. Inheritance may be deduced from the familial pattern of incidence.

This report concerns those patients showing simplex and multiplex incidence. The simplex category consists of those families where only one sufferer has been identified over at least three generations. The multiplex category consists of those families containing siblings who are sufferers but no other affected individuals over at least three generations. The simplex and multiplex groups are likely to contain predominantly, though not exclusively, cases of autosomal recessive RP.2,3

The purpose of our study was to determine the temporal characteristics of retinal loss in simplex and multiplex RP. In subsequent papers, a summary of which has appeared already,4 the losses in the other classes of RP will be examined. It has been shown for one genetic type of RP (X-linked heterozygotes) that sensitivity losses occur across a broad range of temporal frequencies in peripheral, scotopic vision.5 For another retinal disease—glaucoma—there are photopic sensitivity losses in both central and peripheral retina deemed unaffected by perimetric studies.6 In this case, the losses predominated at a specific temporal frequency of about 30 Hz. It was, therefore, of interest to determine whether a particular pattern of losses is characteristic of simplex and/or multiplex RP.

Current evidence suggests that RP is not solely a disease of rods, but affects cones as well.7 In many cases, cone function is at least as much disturbed as rod function.8 Furthermore, in advanced stages of the disease, the rods may be so drastically affected that only cone function is measurable. Finally, temporal sensitivity for photopic flicker shows interesting complexity in normals and might be expected to provide more differential information between the genetic types of RP. We therefore used the temporal visuogram method9 to measure photopic sensitivity losses for the simplex and multiplex groups. We also measured the critical flicker frequency (CFF) as a function of light adaptation level. This allowed comparison of cone threshold elevation, adaptation sensitivity, and photopic modulation sensitivity in the same dystrophic retinae.
Materials and Methods

The patients were drawn from a population diagnosed as having simplex or multiplex RP by the Genetics Clinic of Moorfields Eye Hospital (London). In each case, information was available on three or more generations of the family. Only those patients with childhood onset of the disease and with Goldmann fields greater than 2° with the IV₄ target were selected. The sample included nine simplex and four multiplex patients, all of whom gave their informed consent to participate in the study. Usually only the right eye was investigated, but in several cases measurements were made on both eyes, making a total sample of 18 eyes. The ages, sex, diagnosis, corrected visual acuities, condition of the ocular media and relevant static perimetry data collected at the time of the investigation are given in Table 1.

Table 1. Clinical evaluations of the patients tested

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Corrected visual acuity</th>
<th>Log threshold elevation</th>
<th>Condition of media</th>
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<tr>
<td>1</td>
<td>27</td>
<td>F</td>
<td>SP</td>
<td>6/12</td>
<td>&gt;3; &gt;3</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>F</td>
<td>SP</td>
<td>6/9</td>
<td>0; 0.9</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>M</td>
<td>SP</td>
<td>6/9 (R)</td>
<td>0.9; 1.4</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>M</td>
<td>SP</td>
<td>6/18 (L)</td>
<td>X</td>
<td>N</td>
</tr>
<tr>
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<td>39</td>
<td>M</td>
<td>SP</td>
<td>6/5</td>
<td>0.6; 0.4</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>M</td>
<td>SP</td>
<td>6/6</td>
<td>0.3; 0.6</td>
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</tr>
<tr>
<td>7</td>
<td>49</td>
<td>F</td>
<td>SP</td>
<td>6/9</td>
<td>X</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>F</td>
<td>SP</td>
<td>6/24</td>
<td>1.1; 1.6</td>
<td>P</td>
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<tr>
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<td>48</td>
<td>F</td>
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<td>6/9 (R)</td>
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<td>N</td>
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<tr>
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<td>48</td>
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<td>MP</td>
<td>6/9</td>
<td>X</td>
<td>N</td>
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<tr>
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<td>62</td>
<td>F</td>
<td>MP</td>
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<td>X</td>
<td>A</td>
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<td>F</td>
<td>MP</td>
<td>6/36 (R)</td>
<td>X</td>
<td>P</td>
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<tr>
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<td>F</td>
<td>MP</td>
<td>6/24 (L)</td>
<td>X</td>
<td>P</td>
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Abbreviations: M = male; F = female; SP = simplex; MP = multiplex; R = right eye; L = left eye; N = normal; P = posterior subcapsular lens opacity; A = aphakia; X = observation not made. Log relative thresholds are the log of the average threshold elevation relative to normal values. They were obtained in dark-adapted conditions at 0° and 5° eccentricity along the horizontal meridian in the temporal field with a spot of light subtending 0.9° and having a dominant wavelength of 560 nm.

Apparatus

The flicker apparatus consisted of a square array of 25 high-luminance 575-nm, light-emitting diodes (LEDs). These light sources have current/luminance function, which is approximately linear. A steady DC signal maintained the mean luminance at 40 cd/m² (measured with a photometer) and a two-decade, 10-turn, logarithmic potentiometer controlled the amplitude of sinusoidal modulation. An additional one-decade range switch permitted control of the modulation over a factor of 1,000, which is important because good observers can give readings in the range of 0.3–0.5% under optimal conditions. The dial readings on the potentiometers were calibrated by measuring the light output from the LED display with a photometer.

The field of 25 LEDs was set behind a circular diffusing sheet in a tube with a white inner surface, so as to give the appearance of a uniform field, 2.5 cm in diameter. This field was placed in a large (40 cm), equiluminant, steady field made by back-projection of DC illumination from four, incandescent bulbs through a diffusing surface. There was a 1-mm, dark border around the flickering field. The maximum modulation that could be obtained from the LED display was 86% because of scatter from the surround. The apparatus was viewed from a forehead and chin rest at a distance of 28.6 cm, so that the flickering field subtended 5°.

Measurement of CFF Functions

In order to measure CFF, which we defined as the maximum resolvable frequency at 86% modulation, the experimenter adjusted the temporal frequency. Starting at a low value, frequency was increased beyond the point at which the patient reported that flicker had disappeared, then decreased slowly until flicker was first reported again.

Luminance was altered by insertion of neutral density filters in front of the light source in 0.6 log unit steps from −3.14 to 1.66 log cd/m². The neutral density filters were calibrated for 570 nm with a spectrophotometer. To avoid pupil size changes with luminance, patients and normal controls were dilated with cyclopentolate and phenylephrine, and dark-adapted for 20 min prior to the test. Their pupils were all between 8
and 9 mm in diameter. Starting at the lowest luminance, two measurements of CFF were taken at each luminance level; if no flicker was visible at 3 Hz, the luminance was increased to the next level. Before each pair of measurements, the luminance of the DC surround was adjusted to be of equal brightness with the narrowband test-field, as judged by the individual patient. The need for this adjustment was a manifestation of the Purkinje shift of spectral sensitivity from rods to cones, as discussed below.

Temporal Visuograms

The second approach to flicker sensitivity was to measure modulation sensitivity as a function of temporal frequency, at a fixed mean luminance level. Modulation sensitivity is defined as the reciprocal of the modulation threshold. Modulation depth of a sinusoidally flickering light was adjusted to perceptual threshold for various frequencies. The frequency range chosen was from 5 Hz upwards, both because pilot data below 5 Hz showed greater variability than above this frequency and because it is above the range in which pupil responses are elicited. Normal pupils were used for comparison with previous results. At each frequency tested, the experimenter adjusted the log potentiometer until flicker had just disappeared, then increased until the patient first reported that flicker reappeared. Usually, each point was measured twice, but at some intermediate frequencies only one reading was taken. In addition, readings always were obtained for the maximum modulation (86%); in this case, modulation was fixed and frequency varied as above. Twelve normal observers with a mean age of 27 years (SD = ±7 years) were tested with the same technique to provide control data. (Individuals with a high consumption of alcohol or tobacco were eliminated from the sample as this may affect the results of the test, and none of the patients had high consumption levels.) The normal flicker sensitivity profile as a function of temporal frequency is shown in Figure 1A (dashed line). Error bars represent 1 SD of the variability across normal observers, which increases towards the higher frequencies in this sample. As reported previously for temporal modulation up to age 70, the sensitivities showed insignificant correlation with age in these normals (R = −0.05, 0.01, 0.24, 0.10, 0.32, and 0.52 at 5, 10, 15, 20, 30, and 40 Hz, respectively). Almost all patients showed good reliability under the method of experimenter adjustment, with

Fig. 1. A, Flicker modulation sensitivity plotted in terms of percent modulation at threshold as a function of temporal frequency. Inset shows sinusoidal modulation of luminance as a function of time at 100% (full line) and 30% (dashed line) modulation, to emphasize that changing modulation does not alter the mean luminance. Dashed lines: mean of 12 normal observers for central observation of a 5° field. Error bars represent ± standard deviation of the normal mean. Filled circles, full line: simplex RP patient 2. B, Temporal visuogram of sensitivity loss relative to normal for patient 2 (full line, filled circles). Dashed lines show 2.3 X standard deviation at each frequency. Points outside this region are significantly different from normal at P > 0.01 in this and subsequent graphs. C, Temporal visuograms of sensitivity loss in undilated eyes relative to dilated eyes in four normal observers. Full lines: central 5°. Dashed lines: 20° peripheral observation.
a mean standard deviation of only 1.2 dB (15%) of the mean threshold across all patients and temporal frequencies.

The genetic chart for a representative patient (no. 2) is given in Figure 2. This patient came from a large family of 13 unaffected individuals over three generations and, therefore, represents a well defined simplex case. The sensitivity data for this patient (Fig. 1A, full line) show a markedly reduced flicker sensitivity, especially at the high frequencies. Fig. 1B shows the ratio of the patient’s sensitivity relative to the mean value for normal observers at each frequency measured. The functions comprising such ratios are called temporal visuograms. The dashed lines indicate the criterion of 2.3 SD of the variability of the normal data. Values outside this range are significantly different from normal at \( P = 0.01 \). This patient showed a marginally significant loss above 30 Hz. Note that the visuogram plot emphasizes specific aspects of the loss function, which are not clearly evident in the sensitivity functions themselves, owing to the changing slope of the normal curve.

As mentioned, the temporal visuograms were obtained with the patients’ natural pupil (3–4 mm), while the CFF functions were measured with the pupil dilated (8–9 mm). To determine the effect of the state of dilation on the temporal visuogram, we measured flicker sensitivity for four normal observers, ages ranging from 24–38, with normal (4 mm) pupils to 8 mm, when dilated with Tropicamide in each case. Figure 1C shows a temporal visuogram, where the ordinate represents the ratio of the mean sensitivities of the observers when their pupils were undilated to the mean values they gave when their pupils were dilated. Although the pupil area has increased by a factor of 4, sensitivity does not vary greatly either in central vision (filled circles) or at another retinal location 20° in the temporal field on a 45° meridian (open circles). The greatest effect of pupil size is observed in the 30–40 Hz range, but is less than a factor of 2 at any frequency.

Why is the effect of dilation so small? For large pupil apertures, the Stiles Crawford effect of the directional selectivity of the retina towards the central pupil means that effective retinal illuminance is changed by a much smaller proportion than pupil area. (Since the extrafoveal regions have a stronger Stiles-Crawford effect than the fovea, the increase in sensitivity with dilation should be less in peripheral than central vision, as is evident in the data of Figure 1C.) We therefore conclude that change from dilated to undilated pupils in the temporal visuogram is rather small in relation to the loss exhibited for the patients in the remainder of this paper.

Results

Normal CFF Functions

The form of the function of CFF with luminance level is well established as showing a duplex form. In the scotopic region, CFF rises approximately linearly with log luminance until it reaches a plateau region and levels off. At photopic luminances, the curve rises approximately linearly once more (the Ferry-Porter region) and will reach a second plateau. These features are evident in our data for three normal observers (Fig. 3, filled circles), using the protocol described above. For our field conditions, the rod plateau occurs at about 12 Hz, and the cone portion appears at about \(-1.9 \log \text{cd/m}^2\) or 5 photopic td. At our highest luminances, the cone plateau has not yet appeared, so that the normal cone portions are approximately linear.

Fitzke and Massof have shown that the intercept of the linear portion of the photopic function at zero CFF provides a good estimate of the absolute cone threshold for the same stimulus. On this criterion, cone threshold occurred at a mean value of \(-2.9 \log \text{cd/m}^2\) for our normal observers.

CFF Functions in Simplex RP

The data for patient 2 (Fig. 3, open circles) show a pattern of changes that typify the simplex group. The rod portion of the CFF curve is absent. The cone portion shows a normal slope and no significant loss of extrapolated cone sensitivity at \(-2.8 \log \text{cd/m}^2\). Thus, it can be said that cone function is normal in the medium luminance range. For the higher test luminances, however, an interesting phenomenon occurs. The function clearly shows a tendency to reach a plateau as luminance was increased. Thus, the early effects of this type of RP seem to begin with loss of sensitivity at high luminance, rather than at threshold.

Similar features are evident in the data of nine simplex cases (Fig. 4) in which the mean normal data are represented as the dashed line. Seven of the patients...
showed no rod portion of the curve, while the other two showed reduced rod function (dotted lines). We did not have sufficient resolution in the scotopic region to characterize the rod function in any detail, however.

Of the three relevant aspects of cone function (extrapolated threshold, slope, and tendency to plateau), the least affected was the slope of CFF versus luminance. No patient showed a significant departure from the normal slope in the lower photopic range.

Nevertheless, substantial departures from normal are evident in the zero-intercept of the functions, providing an extrapolated estimate of cone threshold. Our normal population is insufficient to determine the normal variability, but four patients have threshold increases greater than 1 log unit, and one shows more than 2 log units threshold elevation. It therefore appears that cone threshold may be elevated at an advanced stage of the disease.

The third feature of these functions is that they show some tendency toward a high luminance plateau at luminances lower than normal, even when there is little change in the cone threshold. It is unfortunate that the LED system was unable to follow this effect to higher luminances, but even the present data clearly indicate that there is a specific loss in CFF at high luminances. We therefore measured the full temporal sensitivity curve at our highest luminance to determine whether the loss was also specific to high frequencies or was a general effect at all temporal frequencies.

Temporal Visuograms in Simplex and Multiplex RP

Temporal visuograms were obtained as described in Methods for 11 eyes of the same simplex RP patients (and for seven eyes of four patients with multiplex RP). The sensitivity losses as a function of flicker frequency are shown for the simplex patients in Figure 5A (left eyes shown as dashed lines). In every case, the most pronounced loss occurred at the highest frequency. All showed a progressive loss as frequency was increased above 10 Hz. All except the two patients who were affected most had flicker sensitivity within normal limits up to 10 Hz. Finally, the less affected patients appear to show a tendency toward supernormal sensitivity at the lowest temporal frequency. In six of the eyes, the sensitivity at 5 Hz is significantly higher than normal at the 1% level of probability.

The most noteworthy feature of these results is the similarity between the loss functions in this group of patients, although each patient is at a different stage of the disease, and they would, therefore, be expected to show varying degrees of loss. This is further borne
Fig. 5. A, Temporal visuograms showing sensitivity loss as a function of frequency for eleven eyes with simplex RP. B, Same for seven eyes with multiplex RP. Solid lines: right eyes; dashed lines: left eyes. Note dissimilarity of loss function from that produced by luminance reduction (Fig. 6A).

In addition to the degradation of rod function in all simplex patients, the effects on cone function in our simplex and multiplex patient group are as follows: (1) All patients showed a loss of high temporal frequencies significant at the 1% probability level. (2) The low frequency region was the last to show any sensitivity loss. Of the 18 eyes tested, only the six most affected overall showed significant losses at low temporal frequencies and the performance of seven eyes was significantly better than normal at 5 Hz. (3) Where tested, the high frequency loss was greatest at our highest luminance, implying a relative reduction in the maximum resolvable frequency. (4) Most simplex patients showed an elevation in extrapolated cone thresholds, as indicated by the shift of the CFF curve to the right on the luminance axis. (5) The slope of the CFF versus log luminance function, which is a measure of light adaptation, was normal in the mid-luminance range, even in those most severely affected.

Discussion

In general, the simplex classification probably includes not only inherited disease predominantly of the autosomal recessive variety but also nongenetic cases. In view of the similarity of the losses in our simplex group it is worth reviewing its homogeneity by other criteria. All cases showed an early onset of the disease (before age 20). The simplex classification was based on investigation of an average of 15 family members over three or four generations. Only two patients were found to show residual rod function. Except for these cases, the remainder of the simplex patients therefore would fall into Type I category of Massof and Finkelson, for which the most likely basis is a genetic transmission of the disease. The multiplex classification based on sibship is a more tightly defined group, with a high probability of genetic transmission.
the stimulus, since her CFF values lie close to the normal cone data and extrapolate to a normal cone threshold. In other patients who do have a definite increase in extrapolated cone threshold, it also can be shown that this factor is not the explanation of their anomalous temporal visuograms. Figure 6A shows the effect of luminance reduction on the temporal visuogram. The original 2°-field data of de Lange16 have been reanalyzed in the form of a visuogram. The values from two observers for a luminance of 31.8 cd/m² (100 photopic td) have been used as the reference for values obtained at three lower luminances. The pattern of sensitivity loss with luminance reduction is similar for the three luminances and increases progressively with temporal frequency up to 20-30 Hz, then diminishes substantially at higher frequencies. A similar effect of luminance was seen in the comparison of undilated with dilated pupils in normal observers (Fig. 1C). None of the visuograms of the simplex patients show such a pattern.

These normal results may now be applied to the interpretation of the patients' data. Although the CFF/luminance data on their own are compatible with a luminance reduction hypothesis, the temporal visuograms of the simplex group do not show the loss in the mid-frequencies expected for a luminance reduction. Here, a luminance reduction hypothesis cannot explain the visuogram results.

One possible explanation for the shape of the simplex/multiplex visuogram is an overall slowing of visual processing, together with a decrease of signal-to-noise ratio in the advanced cases. Figure 6B shows the sort of effect slowing could have. The flicker sensitivity curve has been shifted leftwards on the frequency axis by a factor of 1.6. The resulting visuogram (lower panel) has a form similar to those seen in most of the present group of patients, including an increase in sensitivity at low temporal frequencies and a progressive loss with increasing frequency to about 1 log unit at 40 Hz. A decrease in signal-to-noise ratio would reduce sensitivity equally at all temporal frequencies and would appear as a uniform downward vertical shift of both flicker sensitivity curves and visuograms. The patient data therefore can be explained by an initial slowing of the retinal response, together with a reduction in signal-to-noise ratio at an advanced stage.

As mentioned in the introduction, the slowing pattern of loss differs from that found in other retinal diseases6,10,17 and even from the patterns found in other genetic types of RP.4 Full consideration of the differ-
ences with RP must await presentation of the data for autosomal dominant X-linked hemizygous and X-linked heterozygous groups in a companion study.

**Key words:** photopic flicker, retinitis pigmentosa, temporal modulation, CFF

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**References**