Principles and Practice of Clinical Electrophysiology of Vision

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Detection of the Carrier State of X-Linked Retinoschisis

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Among the X-linked ophthalmic genetic disorders, X-linked retinoschisis (XLR) is distinguished by the lack of detectable abnormalities in the obligate female carriers.[4] The variable mosaicism of X-linked genes, as predicted by the Lyon hypothesis, which has been demonstrable for such conditions as X-linked ocular albinism, choroideremia, and X-linked retinitis pigmentosa, has not been apparent for XLR.[6]

In 1988, we reported the first consistent abnormality in XLR carriers.[3] Using a psychophysical approach, we found in 11 obligate carriers of XLR from six pedigrees that there was a complete absence of the modulation of cone flicker thresholds by increasing rod stimulation (the Frumke effect). All of these patients had normal visual acuity and lacked any discernible ophthalmic pathology. We hypothesized that XLR might be the result of abnormal retinal development associated with Müller cell dysfunction. This abnormal retinal development is responsible for the macular schisis seen in 100% of affected individuals as well as the peripheral schisis seen in up to 25% of patients.[4] The classic absence of the b-wave in the electroretinogram would be a reflection of Müller cell dysfunction.[7,8] The relatively stable course of the disorder is consistent with the concept that XLR is a developmental defect rather than an ongoing degenerative process. In the otherwise normal obligate carrier female, the degree of abnormal retinal development is minimal and results in normal retinal morphology but causes a retinal disturbance affecting the intraretinal communication responsible for the rod-cone interaction measured by this psychophysical method.

METHOD

Prior to evaluation, each subject was assessed by visual acuity and indirect ophthalmoscopy in order to rule out ocular pathology. The right pupil was dilated with 1% tropicamide and patched for 45 minutes of dark adaptation. In the initial studies, no refractive correction other than the patients' regular glasses were used. We have shown that moderate refractive errors up to 3.00 D do not significantly alter the patients' relative changes in threshold response. The testing apparatus consists of a modified Lister perimeter with a light-emitting diode (LED) testing target that has been described previously.[5] The key feature of the LED control is the preservation of linearity of light output over a 9-log-unit range by driving the LEDs with a variable frequency of short current pulses. An area 10 degrees nasal to fixation was tested, with fixation maintained on a dim red LED target. While the original apparatus lacked fixation monitoring, patients were carefully instructed, tested, and reminded to maintain appro-

priate fixation. The consistency of responses confirmed the adequacy of fixation since cone flicker thresholds are dramatically lower for foveal vs. parafoveal target areas. Newer versions of the testing system do include infared television monitoring of fixation.

The absolute rod threshold for the test location was determined by using a 5-degree annular blue target illuminated by blue LEDs surrounding a red LED target subtending 30 seconds of arc. The flicker frequency was calibrated to 15 Hz with 100% modulation. The patient was instructed to indicate the appearance of flicker rather than detection of the extrafoveal red light. The method of ascending limits was used to simplify the task, limit the testing time, and avoid target intensities that would be significantly above thresholds and cause rod bleaching. We have compared the use of ascending limits with a forced-choice psychometric paradigm and have obtained similar results, although the psychometric method is considerably longer to perform.

For each set of test conditions, the cone flicker thresholds were measured at least three times. Inconsistent responses were noted, and the patient was prompted to properly maintain fixation and rest if necessary. The cone flicker thresholds are measured over a large range of blue target luminances (up to 6 log units above the patient's rod threshold

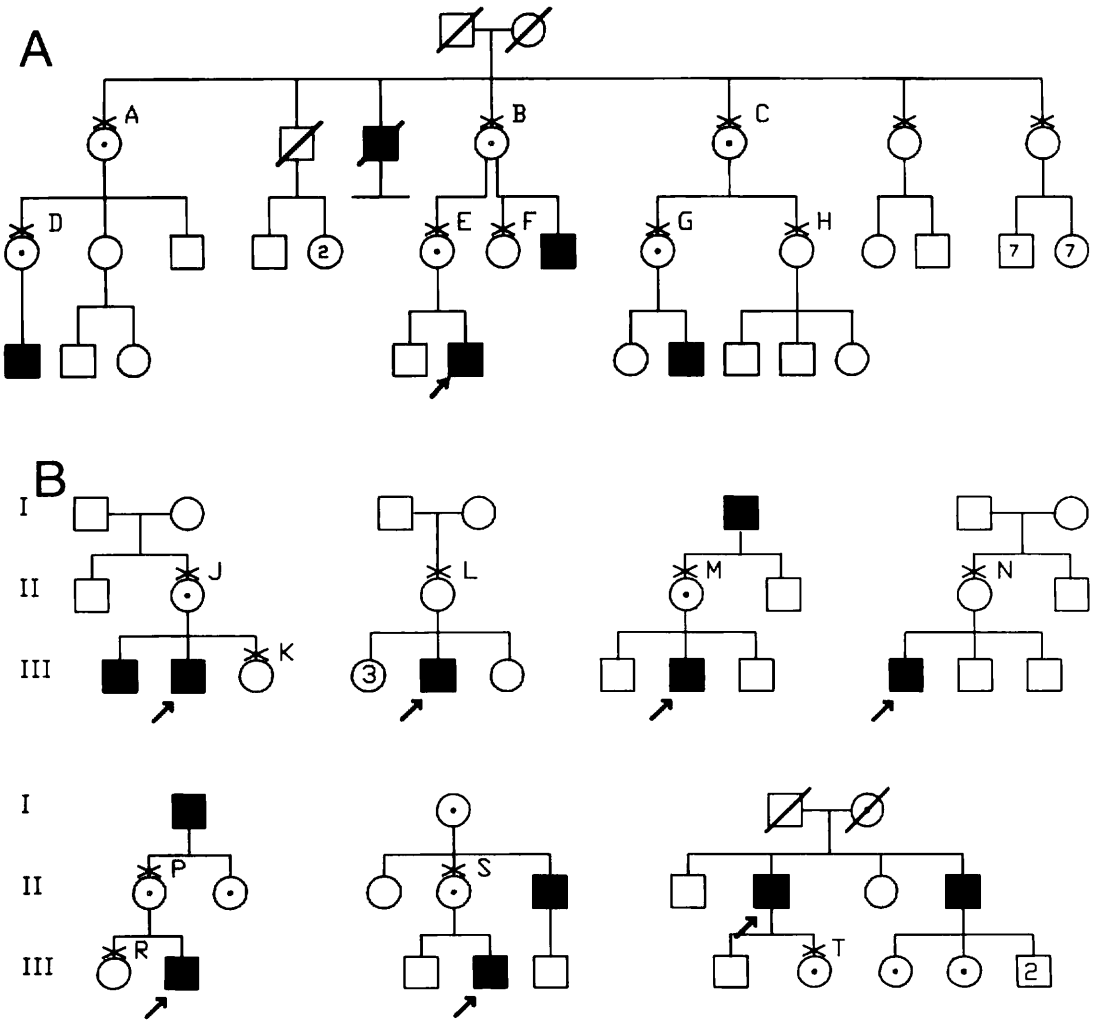

FIG 103–1.
Pedigrees of the families with XLR. The symbols conform to the standard conventions: male, *square;* female, *circle;* deceased, *slash;* affected, *shaded;* normal or unknown, *open;* obligate carrier, *central dot;* and examined, *X.* The *arrow* indicates the proband for whom the diagnosis was confirmed. The letters assigned to the tested individuals correspond to the labeling of the results shown in Figures 103–3 and 103–4. (From Arden GB, Gorin MB, Polkinghorne MD, et al: *Am J Ophthalmol* 1988; 105:590–595. Used by permission.)

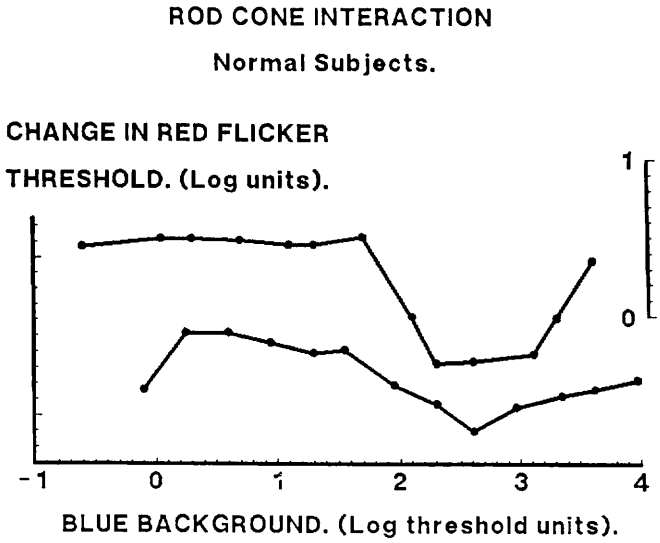

FIG 103–2.
The rod-cone interaction of two normal subjects. The cone flicker threshold (ordinate) is plotted against the intensity of the blue light background (abscissa). Note the decrease in the threshold of the cone flicker threshold as the intensity of the red stimulation by blue background is increased. (From Arden GB, Gorin MB, Polkinghorne MD, et al: *Am J Ophthalmol* 1988; 105:590–595. Used by permission.)

level, with adequate time between each blue illumination to reestablish a consistent level of rod adaptation. The results are displayed graphically as log cone flicker thresholds vs. log rod background illumination.

RESULTS

In the test subjects and controls, the rod threshold at 10 degrees nasal to fixation varied from 8.1 (10^{-7}) to 9.7 (10^{-9}). The cone flicker thresholds var-

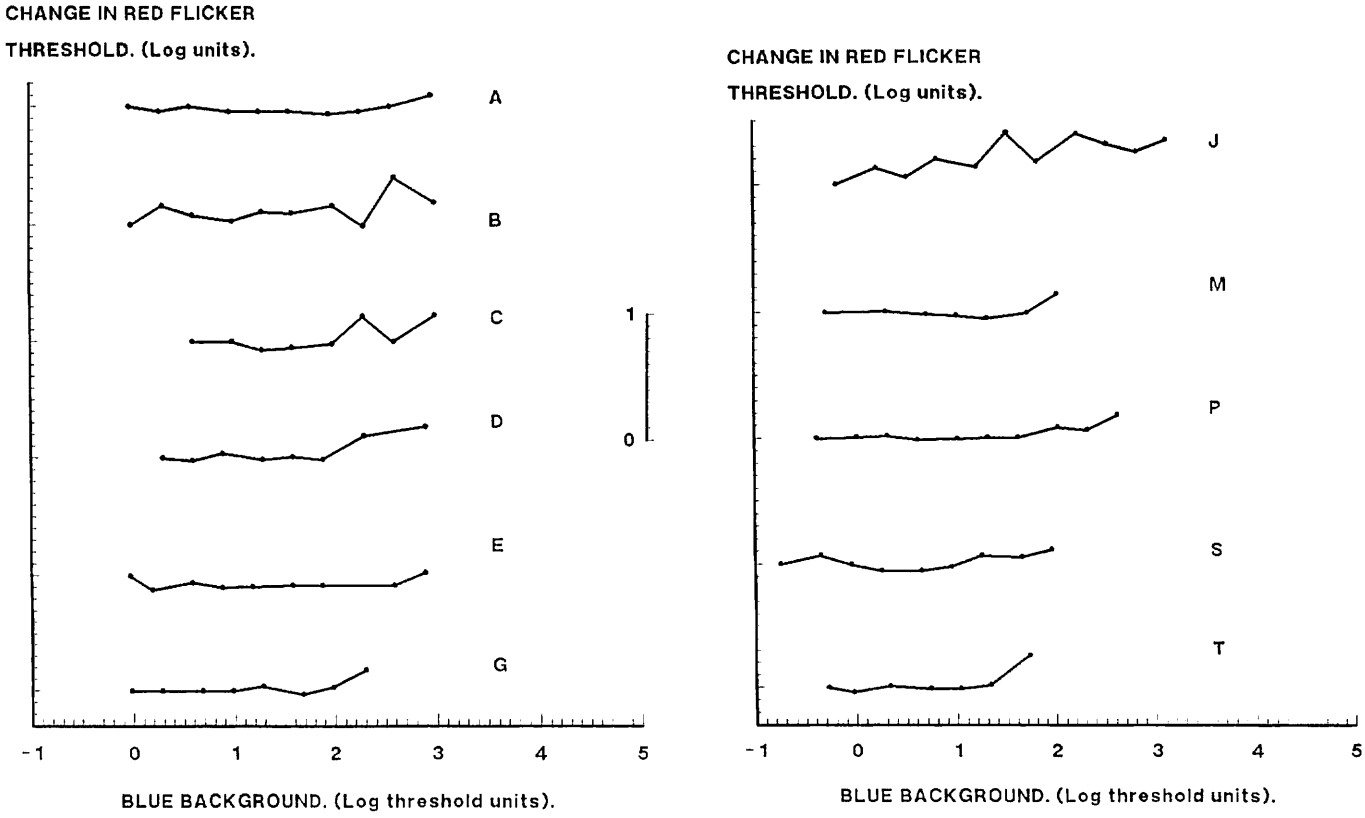

FIG 103–3.
The rod-cone interactions of the 11 obligate carriers of XLR. The ordinate and abscissa correspond to those of Figure 103–1. (From Arden GB, Gorin MB, Polkinghorne MD, et al: *Am J Ophthalmol* 1988; 105:590–595. Used by permission.)

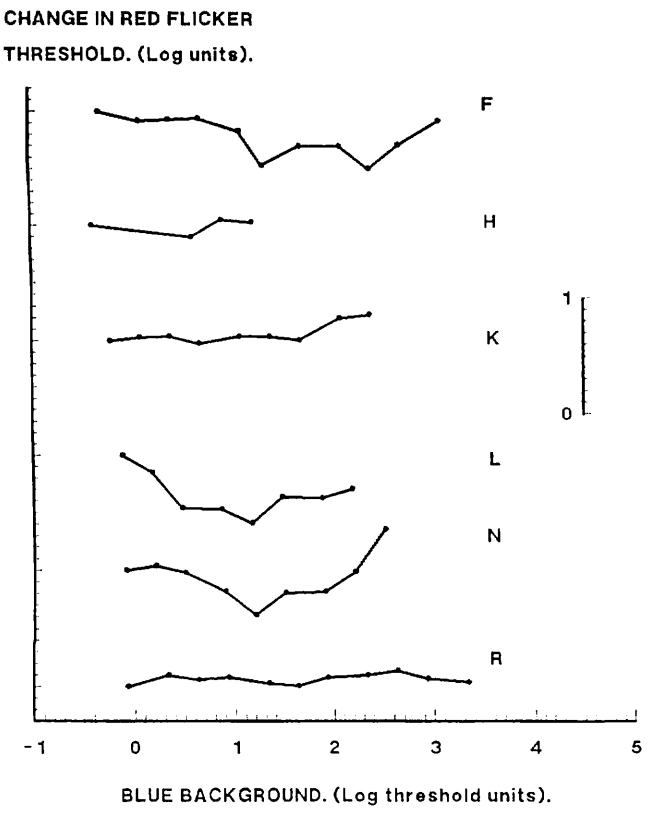

FIG 103–4.
The rod-cone interactions of the potential carriers of XLR. The results from the two potential carriers (sisters) who gave technically inconsistent results have been omitted. The ordinate and abscissa correspond to those of Figure 103–1. (From Arden GB, Gorin MB, Polkinghorne MD, et al: *Am J Ophthalmol* 1988; 105:590–595. Used by permission.)

ied greatly from patient to patient due to the subjective end point; however values were highly reproducible for a given subject. In the normal subject, the cone flicker thresholds were constant for backgrounds between −0.5 and 1.0 log units above absolute rod threshold (Fig 103–1). With higher intensities of background illumination, the cone flicker threshold would abruptly fall about 0.5 to 1.0 log units and then subsequently rise as the blue light became suprathreshold for the cone system.

A total of 11 obligate carriers and 8 individuals at risk were examined and tested from eight unrelated families. Two of the individuals at risk were unable to give reliable responses to the testing conditions and were excluded from the analysis. The pedigrees, indicating the affected males and the women who were evaluated, are shown in Figure 103–2.

In the 11 obligate XLR carriers there was no evidence of modulation of the cone flicker thresholds (Fig 103–3), while two patterns of response were evident among the carriers at risk (Fig 103–4), as would be expected from the probabilities of the carriers at risk being normal or true carriers.

DISCUSSION

As discussed in Chapter 59, there are numerous parameters that can be modified in the testing environment. The particular conditions used in our testing (regarding the target and annulus size as well as the retinal locus) were established on the basis of the prior experience of the research unit and our ability to compare our test results with previous studies of normals and other disorders. It is reasonable to think that the lack of rod-cone interaction in XLR carriers should be demonstrable by other methods. However, Alexander and Fishman[1] were able to detect a rod-cone interaction in a patient with XLR and have not found an abnormality in XLR carriers (personal communication). Their method does not address the rod-cone interaction directly but relies on the changes in cone flicker thresholds over a series of retinal loci during dark-adapted and light-adapted states of the entire retina. Additional testing, including the application of different methods to the same patient population, will be necessary to resolve this discrepancy. Arden and Frumkes[2] have raised the possibility of measuring the rod-cone interaction by using electrophysiological techniques. The application of this approach would minimize the subjective elements in the psychophysical paradigms and allow a more objective quantification of the interactions.

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