Principles and Practice of Clinical Electrophysiology of Vision

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Electroretinographic Detection of Female Carriers (Heterozygotes) of X-Linked Recessive Retinitis Pigmentosa

Paul A. Sieving

This chapter describes the clinical electrophysiology of female carriers of X-linked recessive retinitis pigmentosa (XLRP heterozygotes). These carriers often show ophthalmoscopic evidence of retinal pathology that includes disc pallor and constricted retinal arteries (Fig 101–1, Plate 23) as well as patches of atrophy of the retinal pigment epithelium, and pigmentary clumping in the form of bone spicules (Fig 101–2, Plate 24). The retinal changes can occur in isolated regions and cause minimal visual symptoms or, occasionally, become geographically extensive and cause marked visual field constriction and markedly reduced electroretinogram (ERG) responses. Females are affected less severely than males. Historically, this led to the term "intermediate sex-linked" retinitis pigmentosa (RP).[6, 8] One variant of ophthalmoscopic findings in female heterozygotes is a tapetal-like reflex within the posterior pole that appears as an iridescent sheen or metallic luster in the macula.[4]

One question of clinical importance is whether the full-field ERG is sufficiently sensitive to identify female carriers who are only mildly affected. Second, which full-field ERG tests are most sensitive? These questions are addressed in this chapter.

REVIEW OF STUDIES

Full-field ERG recordings have been described as abnormal in 50% to 96% of X-linked RP carriers.[1, 2, 5, 7] The first comprehensive study of XLRP heterozygotes found a 96% sensitivity of detection when using full-field ERG recordings of 23 obligate carriers from nine pedigrees.[2] These investigators could be certain of the clinical state in only 14 of 23 (61%) of these obligate carriers by ophthalmoscopic examination alone.

In this study patients were dark-adapted for 45 minutes before testing in a Ganzfeld ERG bowl with a 10-μs xenon flash (PS series photostimulator, Grass Instrument Co., Quincy, Mass). Three stimulus conditions were used: a blue flash (Wratten 47 + 47A + 47B, with an 8-ft-L-sec/flash unattenuated xenon flash), dark-adapted; a white flash (8-ft-L-sec/flash), dark-adapted; and a white (8-ft-L-sec/flash) flicker at 30 Hz. Rod and cone ERG amplitudes ranged from normal to nondetectable in these XLRP heterozygotes.

The most sensitive ERG test conditions were the single white flash, dark-adapted, for which 83% of XLRP heterozygotes were subnormal, and the response implicit time to 30-Hz flicker, for which 75% of carriers were prolonged. Twenty-two of the 23 obligate carriers had reduced amplitudes to either dark-adapted white flash, delayed cone flicker implicit times, or both. Only three carriers showed delays in cone flicker implicit times despite normal ERG amplitudes.

A second study of XLRP heterozygotes found abnormal ERG responses in approximately 50% of 36 XLRP heterozygotes, 22 of whom were obligate car-

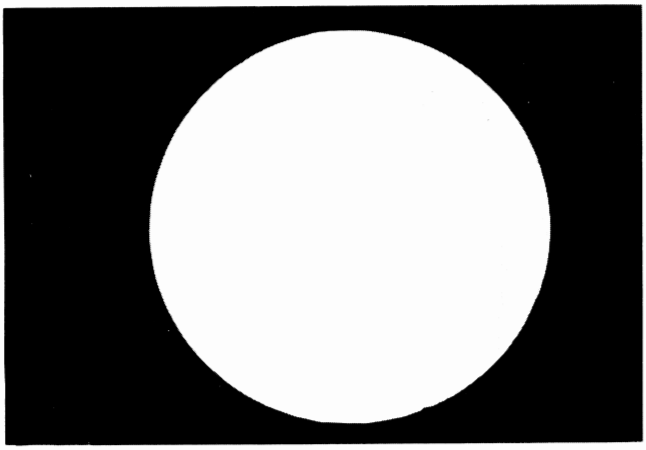

FIG 101–1.
Fundus photograph of a 43-year-old XLRP heterozygote with "waxy pallor" of the optic disc and constricted retinal arterioles. **(See also Color Plate 23.)**

riers.[1] Fifty percent of the obligate heterozygotes had subnormal amplitudes to dark-adapted blue flashes, while 57% had prolonged response latency on white 30-Hz flicker. Compared with the study by Berson and colleagues,[2] one difference of potential importance in the methodology was the stimulus presentation. Arden et al.[1] placed an opal plastic screen 4 to 6 cm from the subject's eye and back-illuminated it by the flash (Grass PS-photostimulator). While this approximates a wide-field stimulus, it may not illuminate the peripheral retina entirely or as uniformly as a true Ganzfeld bowl. Since many XLRP carriers show fundus pathology in the far periphery, true full-field stimulation of the peripheral retina may be critical to high sensitivity of heterozygote detection by ERG testing.

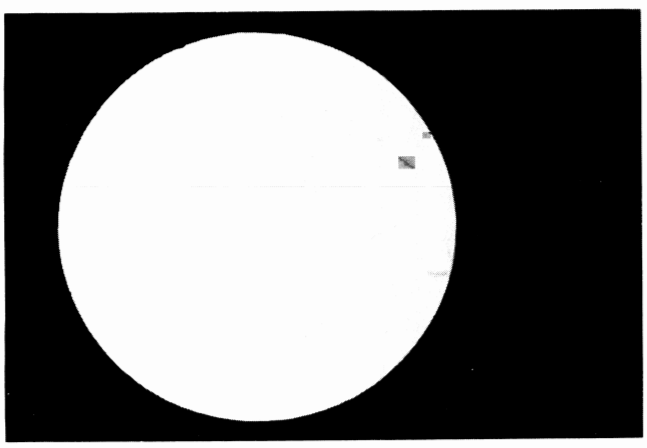

FIG 101–2.
The *peripheral retina* of the XLRP carrier in Figure 101–1 with intraretinal "bone spicule" pigmentation. **(See also Color Plate 24.)**

A third study analyzed ERG responses from 43 XLRP heterozygotes, including 33 obligate carriers,[5] by using a 10-μs flash (Grass PS-photostimulator) in a Ganzfeld bowl. Four test conditions were a white flash (Grass intensity I-16) light-adapted with a 7-ft-L background; a white flash I-16 after 30 minutes[1] dark-adaptation; a blue flash I-4, dark-adapted; and an orange-red stimulus flickering at 30 Hz (intensity not specified), without background light. Eighty-six percent of the XLRP heterozygotes had abnormal amplitudes on one or more test conditions that ranged from 74% subnormal for white flash, dark-adapted, to 81% subnormal for white flash, light-adapted. Only 51% had prolonged flicker implicit times.

This study indicates that subnormal ERG amplitudes are a sensitive ERG criterion for detecting heterozygotes, with the single-flash photopic condition only slightly more sensitive than dark-adapted white or blue stimuli or 30-Hz flicker. The 86% overall detection rate by ERG alone was comparable to the approximately 87% of carriers identified by fundus changes alone. With the combination of ERG plus fundus changes these authors could identify "virtually 100% of cases."

A fourth study involved 22 XLRP heterozygotes, some of whom were obligate carriers in known XLRP pedigrees, while others showed fundus changes typical of the carrier state and had a father or son with RP.[7] Ganzfeld stimuli were used (Nicolet Pathfinder II and GS2000 Stimulator). Test conditions included blue flash (Wratten 47 + 47A + 47B; Nicolet intensity setting, 0.25), dark-adapted; red flash (Wratten 26; intensity setting, 1.0), dark-adapted; blue flash series (Wratten 47B); white flashes, light-adapted (0.64 cd-sec/m^2 with a background of 34 cd/m^2); and 29-Hz flicker with a background of 6.9 cd/m^2. The most sensitive test to distinguish XLRP heterozygotes from normal was the latency of flicker responses (91% prolonged). Amplitude reductions were a less sensitive index, with flicker amplitudes abnormal for 73% and rod b-wave amplitudes abnormal for 76%.

In this study the amplitude and latency criteria for detecting heterozygotes were set by a criterion of the most efficient discriminator between populations. This is probably the best (literally, "most efficient") method to handle such data for statistical detection of the XLRP heterozygote population. However, these criteria caused 2 of 22 normal controls to show "abnormal" latencies to 29-Hz flicker, and at least

one was "abnormal" on rod b-wave amplitude and on 29-Hz flicker amplitude. In a clinical setting, these normal controls would risk being told they carry the gene for XLRP.

This study also evaluated the asymmetry of ERG responses between the two eyes of each heterozygote and found greater variability and larger intraocular differences (IODs) than in the normal population. Some heterozygotes had abnormal IODs between eyes despite both eyes having amplitudes that were individually within the "normal" range.

To summarize these four studies, ERG abnormalities are prevalent in XLRP heterozygotes. ERG reductions are comparable under dark-adapted and light-adapted conditions. Prolonged flicker latency is a sensitive indicator of the XLRP carrier state, which is intriguing since it suggests that abnormalities of the cone system are readily identified in these XLRP carriers. However, in the study by Fishman et al.,[5] cone flicker latency was a much less sensitive criteria for detecting heterozygotes than was the amplitude of flicker or single-flash responses. Their study was alone in using orange-red stimuli for the flicker, whereas the other studies used white flicker with or without an adapting background. One possible explanation of the different findings involves effects of rod stimulation on cone timing.[3] In this form of rod-cone interaction, the latency of cone responses depends on the relative preservation of rod function as judged by rod b-wave amplitude. Since an orange-red light will stimulate rods less relative to cones than will a white light, this may explain the different results on ERG flicker testing of XLRP heterozygotes found by the Illinois study as compared with the remaining three.

RECOMMENDATIONS

Studies to date concur that the full-field ERG is a sensitive and objective test to identify carriers of XLRP. The sensitivity is generally high, independent of the test condition, whether single flash or flicker, scotopic or photopic conditions. Using more than one condition increases the sensitivity of ERG testing. A Ganzfeld bowl is recommended. The ERG sensitivity critically depends on defining an appropriate normal population for comparison. Intraocular ERG differences may also provide a clue to the presence of the carrier state.

By clinical examination with retinal ophthalmoscopy, from 60% to nearly 90% of XLRP heterozygotes show peripheral retinal degeneration. These retinal changes may be quite subtle. More importantly, the changes are nonspecific since similar retinal lesions may result from congenital or inflammatory causes. However, nondegenerative lesions rarely cause reduced ERG responses, and the ERG provides an essential adjunct to ophthalmoscopy alone. Thus ERG evaluation of suspected heterozygotes is to be highly encouraged, even in seemingly obvious cases from families showing an X chromosomal inheritance pattern.

And finally, both ERG testing and ophthalmoscopic examination have false positives as well as false negatives. Since the ERG findings may be used to provide genetic counseling to individuals wondering whether to have children, it seems essential that a qualified retinal diagnostician be involved in the ERG testing or at least be knowledgeable about its limitations.

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