Principles and Practice of Clinical Electrophysiology of Vision

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X-Linked Recessive Cone Dystrophy

Richard G. Weleber

HISTORY OF THE DISEASE

The cone dystrophies are a group of genetically determined retinal degenerations that primarily involve cones and, unless an early acquired form, by definition have abnormal cone-mediated responses on electroretinographic (ERG) testing.[12] Usually the cone ERG will be markedly subnormal to nonrecordable, even at a time when the visual acuity is relatively good, a condition referred to as peripheral cone disease.[7] Since the ERG is a panretinal response, an abnormal cone ERG indicates generalized cone dysfunction throughout the retina.

X-linked recessive inheritance (excluding blue cone monochromatism) is relatively rare in cone dystrophies, with only three pedigrees reported, all of whom did not have a tapetal-like retinal sheen.

Heckenlively and Weleber in 1986 reported the findings on four affected males from two families with X-linked recessive cone dystrophy in which affected males demonstrated a golden yellow to yellowish green tapetal-like sheen over large areas of the fundus (Fig 105–1, Plate 26).[3] One of the carrier women showed a macular tapetal-like reflex similar to that seen with X-linked retinitis pigmentosa (Fig 105–2, Plate 27). Jacobson et al.[4] reported a detailed evaluation of clinical features from nine affected males, three of whom also showed a tapetal-like retinal sheen, and six female carriers in a large four-generation family with X-linked cone dystrophy.

The cone-mediated ERG responses have been reported as severely abnormal in all of the affected males with X-linked cone dystrophy, whereas the rod ERG has ranged from normal to mildly abnormal. Carrier manifestations were documented in most but not all of the heterozygous females who were studied in three of the four reported families and included decreased visual acuity, myopia, and subnormal cone ERGs.[3, 8, 9] A carrier woman who showed the tapetal sheen in the macula had cone ERG responses intermediate in amplitude between affected males and normals (Fig 105–3).[3]

Electro-oculograms (EOGs)[3, 9, 10] have ranged from mildly subnormal (1.51 to 1.73) to supernormal (3.03 to 3.63), with most studies within the normal range. The younger patients were more likely to have normal or supernormal EOGs than were those patients over 50 years of age. An EOG in a 13-year-old boy was high normal in the right eye (light-to-dark ratio, 2.94; normal, 1.85 to 3.00) and supernormal in the left eye (ratio, 3.17). The supernormal ratio was due to a normal light-induced rise or slow oscillation of the standing potential coupled with a mildly subnormal dark trough amplitude (Fig 105–4). Fast oscillations of the EOG were normal in this patient.

CLINICAL DESCRIPTION AND NATURAL HISTORY

Because of the relatively small numbers of affected males, the entire range of expression of the gene at different ages is not fully known. A 9-year-old[9] had visual acuities of 20/50 OU, but a 13-year-old boy[3] in another family had a best-corrected visual acuity of 20/30± in each eye. Often the visual acuity deteriorates to approximately 20/100 in the

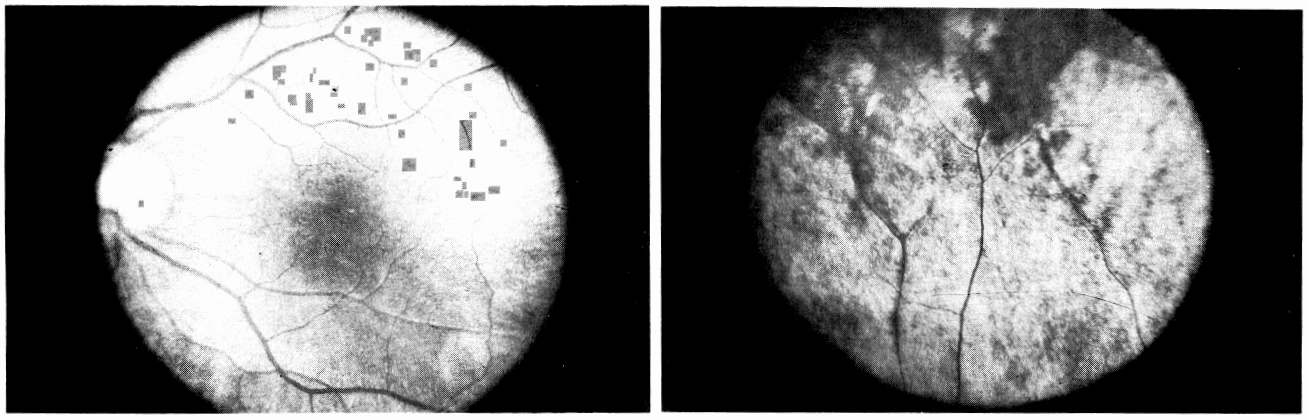

FIG 105–1.
The posterior pole **(A)** and inferior fundus **(B)** of the right eye of a 13-year-old boy with X-linked cone dystrophy show a yellow tapetal-like reflex. (From Heckenlively JR, Weleber RG: *Arch Ophthalmol* 1986; 104:1322–1328. Used by permission.) **(See also Color Plate 26.)**

fourth decade of life, with further deterioration to 20/800 to counting fingers or hand motions in the fifth to sixth decade of life or later. A 54-year-old male had 20/70 visual acuity OU, but a 33-year-old half-brother had 20/200 OD and 20/80 OS.[3] Color vision defects of mixed red-green and blue-yellow types have been reported. Anomaloscope testing in several males has revealed strongly diminished red sensitivity with scotopization of responses similar to that seen with achromatopsia.[9] All affected males but one[9] (who was emmetropic) have been moderate to high myopes; most of the carrier women were also myopic. Older patients have developed marked atrophy of the retinal pigment epithelium and choriocapillaris in the macular region. Vision in older years may be reduced to hand motion or finger counting. Affected patients appear to be more susceptible to atrophic retinal holes and retinal detachment, so patients with this dystrophy should be evaluated periodically for retinal breaks. Two patients in their 40s had retinal detachments from atrophic holes, which appears to be a complication of the disease.

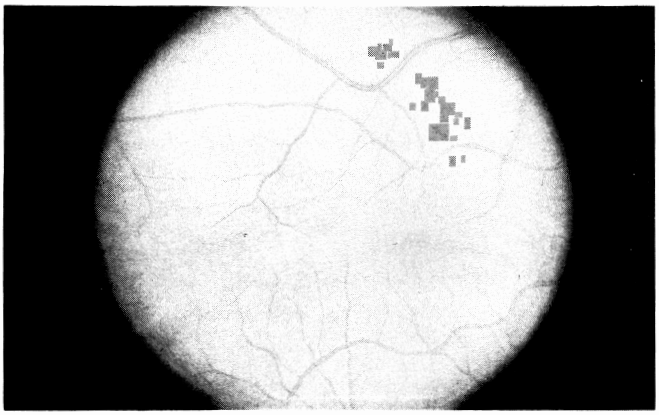

FIG 105–2.
The macular region of the left eye of the 40-year-old mother of the patient shown in Figure 105–1 shows a faint tapetal-like reflex in the macular region. (From Heckenlively JR, Weleber RG: *Arch Ophthalmol* 1986; 104:1322–1328. Used by permission.) **(See also Color Plate 27.)**

The tapetal-like fundus reflex reported by Heckenlively and Weleber was a glistening golden yellow to yellowish green iridescent sheen that was present both in the periphery and in the posterior pole. The sheen appeared more or less visible when viewed through the nasal or temporal halves of the pupil. This was most evident in comparing stereoscopic pairs of fundus photographs. Two patients demonstrated the Mizuo-Nakamura phenomenon, with fading of the sheen and return of a more normal fundus appearance after prolonged dark adaptation.[3]

Although there are sporadic reports of a tapetal-like sheen in cases of cone dystrophy,[2, 5, 6] only recently have pedigrees been published that are consistent with X-linked inheritance.

PATHOPHYSIOLOGY/HISTOPATHOLOGY/ BIOCHEMISTRY OF THE DISEASE

The disorder begins as a peripheral cone disease that progresses to a diffuse cone disease and eventually to a cone-rod disease. Uncommonly, carrier women will have what can be termed central cone

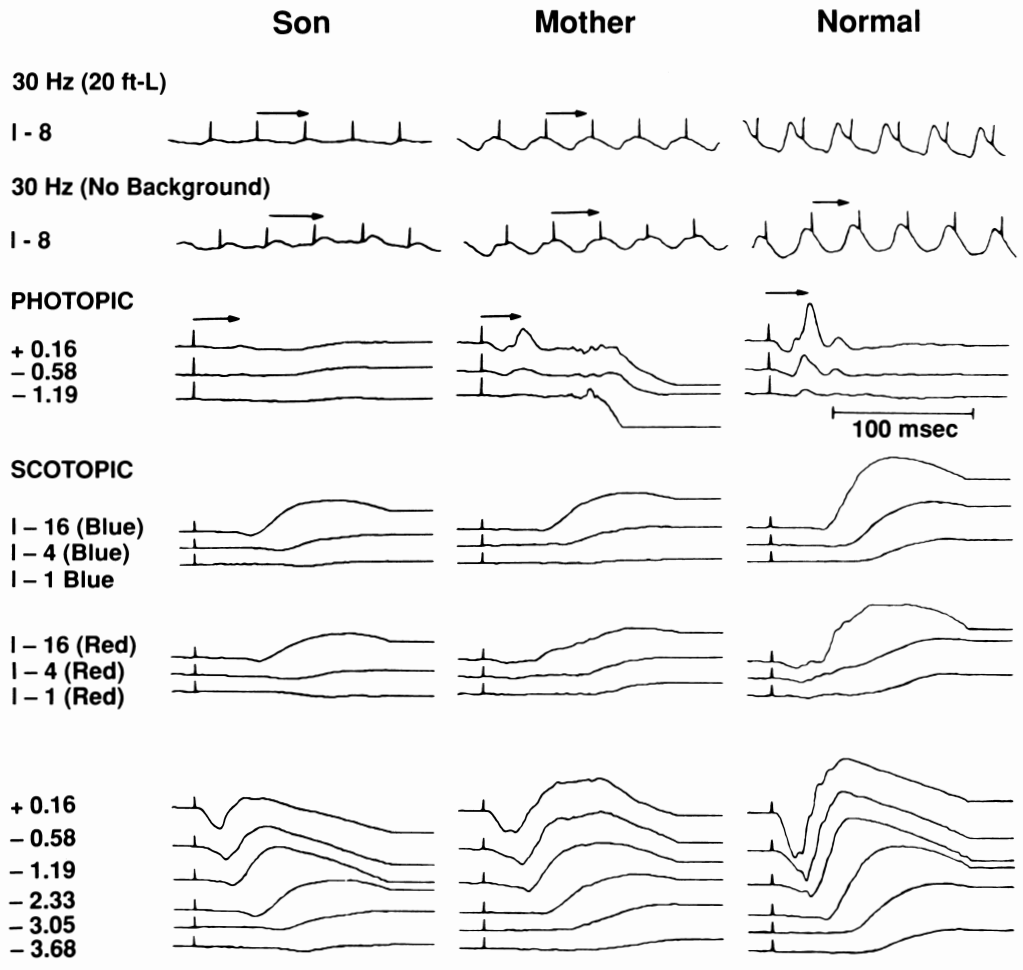

FIG 105–3.
Ganzfeld ERGs in a 13-year-old boy with X-linked cone dystrophy, his 40-year-old mother, and a normal for comparison. Note the mildly prolonged residual cone responses for the boy and the subnormality of photopic cone responses in the mother. Note also the subnormal dark-adapted cone-mediated x-wave response to red light under scotopic dark adaptation. The numbers to the left of the responses preceded by a plus or minus sign indicate the intensity of the stimulus in log foot-lambert-seconds. The numbers preceded by the letter *I* are the photostimulator intensity settings. The red ($\lambda > 600$ nm) and blue ($\lambda < 470$ nm) filters were scotopically balanced to produce equal-sized rod b-wave amplitudes in normals.[11] The stimulus spikes for the 30-Hz flicker, the photopic responses, and the scotopic series were set at 75, 75, and 100 μV as a visual calibration signal for amplitude of the peaks. (Adapted from Weleber RG, Eisner A: Cone degeneration ("bull's-eye dystrophies") and color vision defects, in Newsome DA (ed): *Retinal Dystrophies and Degenerations.* New York, Raven Press, 1988, pp 233–256.)

disease with isolated macular or foveal cone dysfunction (poor visual acuity and abnormal color vision) but normal cone ERG responses, which indicates that the great proportion of the cones are still functioning. The central cone disease in these women presumably results from lyonization. No cases of X-linked cone dystrophy have been studied histopathologically, biochemically, or with molecular genetics.

It is not known whether the patients reported by Pinckers et al.[9, 10] who did not show the tapetal-like fundus reflex represent the same genetic entity as reported by Heckenlively and Weleber[3] and Jacobson et al.[4] Heterogeneity exists; in addition, features of X-linked incomplete congenital stationary night blindness could be confused as an X-linked cone dystrophy.

RELEVANT TESTING AND DIFFERENTIAL DIAGNOSIS

The most important tests for diagnosing this X-linked cone dystrophy are an ERG demonstrating

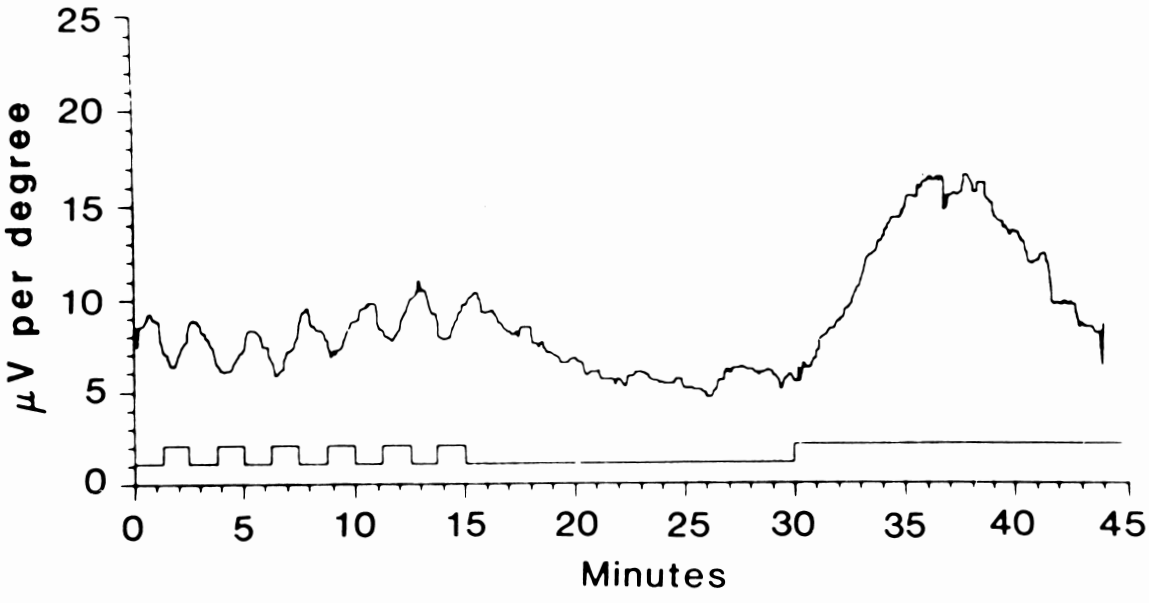

FIG 105–4.
Ganzfeld EOG in a 13-year-old male with X-linked cone dystrophy. Fast oscillations measured during the first 15 minutes of testing were normal. The slow oscillation, as measured by the light-to-dark ratio, was supernormal because of the mildly subnormal amplitude of the dark trough (5 μV/degree; normal, 6 to 27 μV/degree). (From Weleber RG, Eisner A: Cone degeneration ("bull's-eye dystrophies") and color vision defects, in Newsome DA (ed): *Retinal Dystrophies and Degenerations.* New York, Raven Press, 1988, pp 233–256. Used by permission.)

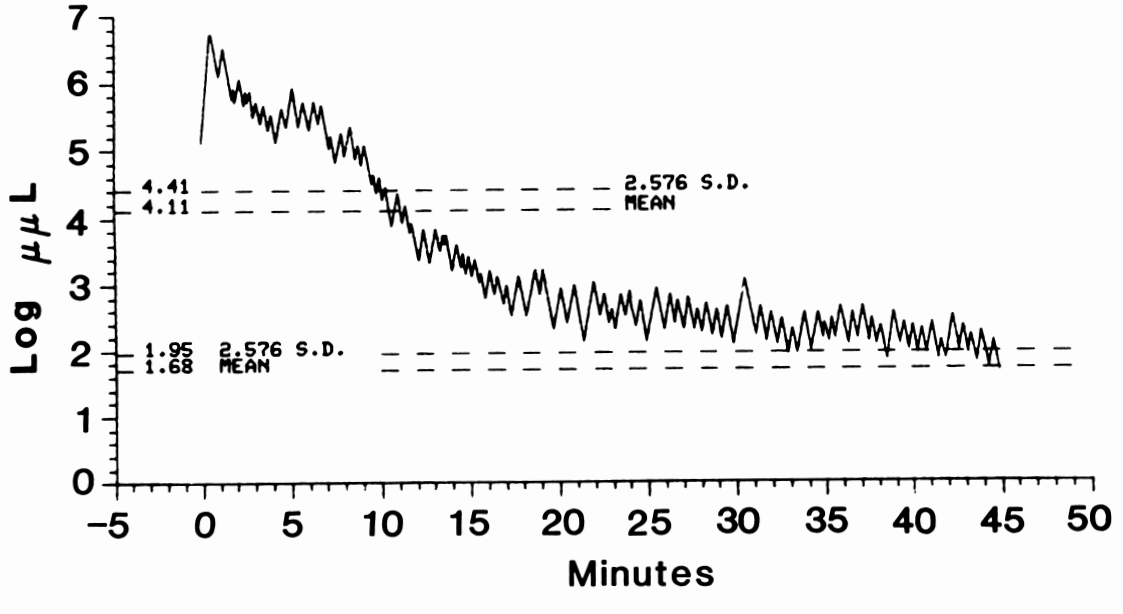

FIG 105–5.
Goldmann-Weekers dark adaptometry in a 13-year-old male with X-linked cone dystrophy demonstrates a markedly elevated cone segment of curve with a final 45-minute dark-adapted rod threshold near the upper range of normal (patient 1 in Heckenlively and Weleber[3]). The test target subtended 11 degrees and was centered 10 degrees above fixation. (From Weleber RG, Eisner A: Cone degeneration ("bull's-eye dystrophies") and color vision defects, in Newsome DA (ed): *Retinal Dystrophies and Degenerations.* New York, Raven Press, 1988, pp 233–256. Used by permission.)

cone dysfunction with normal to abnormal rod dysfunction and a fundus examination showing the tapetal-like retinal sheen; a family history consistent with X-linked inheritance is confirmatory. Visual fields should be full, although scotomatous areas will be present. Rod psychophysical thresholds may be mildly to moderately elevated.[3] The cone segment of the full dark adaptation curve was more elevated than the rod threshold in one affected male (Fig 105–5).[12]

The differential diagnosis for cone dystrophy includes the various forms of congenital achromatopsia. Both will show decreased or absent cone ERG responses with normal or mildly subnormal rod ERG responses. The history of poor vision since infancy strongly supports the diagnosis of congenital achromatopsia, just as the history of progressive visual loss and maculopathy support a cone dystrophy. Complete achromatopsia is autosomal recessive. At least one form of partial congenital achromatopsia, blue cone monochromatism, is X-linked. If intact blue cone function can be demonstrated in a patient with major ERG cone dysfunction, these findings support the diagnosis of blue cone monochromatism. In order to make the diagnosis of cone dystrophy, one must show progressive loss of cone function by either longitudinal studies of the patient or by evaluation of older affected family members who presumably have the same disorder. Fleischman and O'Donnell presented two X-linked families with incomplete achromatopsia with progressive cone dysfunction and macular changes.[1] Unfortunately, the affected males were not tested for intact remaining blue cone function. The authors suggested that X-linked incomplete achromatopsia may itself be a slowly progressive disorder. However, Pinckers and Deutman[8] believe that the cases reported by Fleischman and O'Donnell more likely represent X-linked cone dystrophy.

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