Principles and Practice of Clinical Electrophysiology of Vision

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Evaluation of the X-Linked Carrier State in Choroideremia

Paul A. Sieving

Choroideremia[12] is an X-linked recessive[3, 19] ocular disorder characterized by progressive loss of the choriocapillaris and the overlying retinal pigment epithelium (RPE) as demonstrated by histopathological studies of affected young males.[17, 18] Although the symptoms in males are similar to "retinitis pigmentosa," including progressive night blindness, peripheral visual loss, and ultimately central vision loss, choroideremia has ophthalmoscopic features characteristically different from X-linked retinitis pigmentosa (XLRP): the overlying retina appears preserved better, and the caliber of retinal vessels remains greater far longer in the course of disease than in XLRP. The optic nerve head is less gliotic until the late stages of choroideremia, and consequently in the early stages the "waxy pallor" is not as prominent as in XLRP. Retinal pigmentation typically forms clumps or remains loosely dispersed in a reticular pattern in choroideremia rather than forming the bone spicules that characterize XLRP.

Female carriers usually show only mild fundus changes, which can include patchy depigmentation of the RPE and coarse pigment granularity or even pigment clumps in the periphery (Fig 102–1,A and B, Plate 25). Pigmentary changes may follow the underlying radial distribution of the large choroidal vessels, and the pigmentary pattern in carriers is best appreciated with an indirect ophthalmoscope. A five-stage classification of female carriers was devised by Forsius et al.[2] according to fundus appearance: stage I shows no or minimal RPE granularity. Stage II shows patchy RPE atrophy and early choriocapillaris loss, as shown in Figure 102–1. Stage III includes peripapillary RPE atrophy and white dots in the midperiphery. Stage IV shows progression into the macula. Stage V is comparable to a male with all but the worst disease. Stage V is rarely seen.

Subjective vision is asymptomatic for most heterozygotes of choroideremia.[5, 6, 8, 13–16, 20] McCulloch and McCulloch[14] reported that most choroideremia carriers had normal vision despite the presence of patchy atrophy of the RPE in the periphery. In a follow-up study of the same families, McCulloch[13] reported no significant progression of vision abnormality in these carriers. Normal visual function in heterozygotes generally extends to normal peripheral visual fields, and color vision. Subjective symptoms of visual field abnormalities were experienced by only 7 of 52 carriers examined by Karna.[6] Final dark adaptation thresholds are generally normal, and the time course of dark adaptation is also generally normal even in visually symptomatic carriers,[15] which is consistent with patchy disease involvement allowing the females to use intact regions of retina.

Selected abnormalities of vision are reported in some females, usually in conjunction with marked fundus pigmentary abnormalities.[13] Individual cases with quite severe loss of visual function are reported.[8] Harris and Miller[4] studied a female carrier with the fundus appearance of advanced disease who showed marked peripheral visual field loss, prolonged dark adaptation, elevated final thresholds, and reduced light-adapted electroretinogram (ERG) responses. Only in severe cases is dark adap-

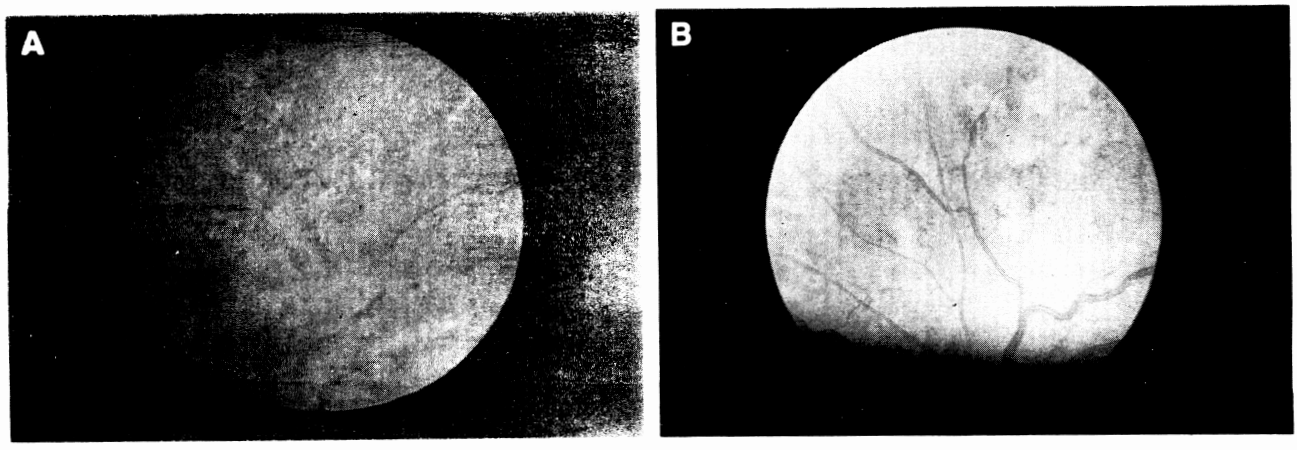

FIG 102–1.
A, 27-year-old woman with granular pigmented fundus changes who was referred to rule out retinitis pigmentosa; she tested normally, but her brother was found to have choroideremia. **B,** 54-year-old woman who has two sons with choroideremia with granular atrophic patches in the equatorial regions and posterior pole. **(See also Color Plate 25.)**

tation prolonged in carriers, with a predominant loss of the rod-mediated curve[4] that is comparable to the loss of rod function in affected males.[15] Severe disease in heterozygotes is believed, according to the Lyon hypothesis,[11] to result from extreme X chromosomal mosaicism causing a loss of visual function comparable to the males but occurring only in patches for females.

Psychophysical testing of 61 heterozygotes of choroideremia, not all of whom were obligate carriers, was reported by Kurstjens.[8] This showed the following: Color vision by AO-HRR plates and Farnsworth panel D-15 was normal for 29 and showed tritanopia for 3. Of 21 carriers tested on a Goldmann-Weekers Dark-Adaptometer, 14 showed normal dark adaptation curves. Seven others were reported to have abnormal photopic and scotopic sensitivity elevations of 1 to 3 log units in one or both eyes. However, from the single figure of actual results (Fig 19 in Kurstjens[8]), an alternative interpretation is that cone dark adaptation is prolonged rather than elevated. Of 23 tested on a Goldmann Perimeter, 16 had normal peripheral visual fields. Four showed minimal sensitivity reductions, and 3 had more extensive losses including perimeter reductions or midperipheral scotomas to the largest (V4e) white target. Heckenlively and Bird[5] described findings on 12 obligate carriers at UCLA. All 12 had normal color vision and normal or near-normal psychophysical dark-adapted final thresholds.

ERG abnormalities occur only infrequently in heterozygotes of choroideremia. Pameijer and associates[16] were the first to suggest that scotopic ERG function might be reduced. Most reports, however, emphasized the relatively normal ERG responses in carriers, such as that of Kurstjens,[8] who reported normal ERG responses in 12 heterozygotes. Three others had normal photopic but subnormal scotopic responses, and a further 3 showed more advanced ERG reductions. Ohba[15] described five carriers who were identifiable ophthalmoscopically by patchy atrophy of the RPE, but psychophysical and electrophysiological results were negative in all cases except one in which the peripheral fields were constricted and the ERG amplitudes reduced. Harris and Miller[4] and Krill[7] reported abnormal ERGs only in the most severely affected carriers.

In an ERG study of 26 obligate female carriers of choroideremia, only 4 (15%) had ERG abnormalities[20] despite ophthalmoscopically evident disease in the majority of these carriers (25 of 26). Only 1 carrier had reduced rod ERG function to single flashes of dim blue light in the dark-adapted state. Three other carriers had delayed cone implicit times on 30-Hz flicker. However, no carrier had abnormalities on all three ERG test conditions (rod-isolated responses to blue flash, dark-adapted; dark-adapted responses to a single white flash; and cone-isolated responses to white 30-Hz flicker stimuli). The remaining 22 carriers had normal rod and cone ERG responses to these test conditions.

The electro-oculogram (EOG) has been studied infrequently in female carriers, but generally it remains normal despite fundus pigmentary changes.[15] Five obligate carriers tested at UCLA showed normal light peak/dark trough (LP/DT) ratios.[5] Kurstjens[8] found a normal EOG LP/DT ratio in 18 carriers, but 2 carriers with ophthalmoscopic evidence of severe

disease had no increase in the standing potential during light adaptation. Since choroideremia causes a dissolution of the RPE, it is not surprising that EOG abnormalities occur frequently in affected males.[8, 15]

Photopic oscillatory potentials (OPs) may show selective abnormalities in choroideremia heterozygotes. In a study of 11 carriers, 7 had diminished or absent OP_4 responses when recorded immediately following a period of dark adaptation.[10] Since OP_4 responses in normals were modified only during light readaptation,[9] the abnormalities of OP_4 in choroideremia carriers may indicate an abnormal light adaptation process.

From the preceding descriptions of the relatively modest vision abnormalities found for most female carriers of choroideremia, it must be recognized that discussing progressive pathology applies to relatively few heterozygotes. In his 20-year follow-up study of families with choroideremia, McCulloch[13] believed that fundus pigmentary abnormalities changed at most only minimally with time. However, the impression is that older carriers show more severe fundus changes and that abnormalities in visual fields and dark adaptation are also more severe,[6] from which it may be inferred that carriers experience progressive pathology. Progression of fundus pigmentary abnormalities was documented photographically in a few carriers over a 3 ½-year period by Krill.[7]

Changes with time are reported for choroideremia carriers by ERG testing. Two obligate carriers showed a reduction in ERG amplitudes over a 10-year interval (35% to 41% loss, $P < .01$) to dark-adapted single white flashes (Fig 102–2), which demonstrates that the course of disease is progressive in carrier females as well as in affected males.[20] Thus the ERG may provide a means for identifying progressive retinal dysfunction in these carriers.

Ophthalmoscopy remains the best way to identify heterozygote female carriers of choroideremia. Obligate carriers may demonstrate patchy depigmentation of the RPE and coarse granularity or clumped pigmentation in the periphery.[8, 14] Sieving et al.[20] found that 25 of 26 carriers (96%) showed abnormal fundus pigmentation. The pigmentary distribution is characteristically radial, possibly due to the radial distribution of the large choroidal vessels. The pattern of pigmentary change is different from the more regionalized atrophy found in carriers of X-linked recessive retinitis pigmentosa. Even the youngest carrier of choroideremia examined by McCulloch and McCulloch[14] at age 4½ months showed peripheral RPE pigmentary changes consistent with the carrier state.

A greater percentage of obligate choroideremia carriers (25 of 26 tested; 96%) showed ophthalmoscopic changes[20] than did obligate carriers of X-linked recessive retinitis pigmentosa (61%).[1] By comparison, the ERG was less sensitive in detecting

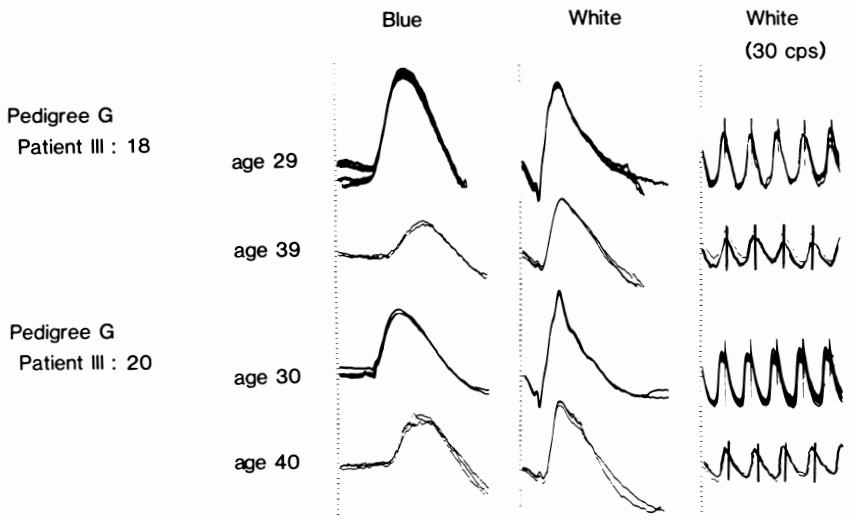

FIG 102–2.
ERG responses from two obligate heterozygotes of choroideremia over a 10-year interval (calibration bar, 100 μV for *blue* and *30 cps;* 200 μV for *white;* all at 50 ms except 55 ms for *30 cps* on first examinations. (From Sieving PA, Niffenegger JH, Berson EL: *Am J Ophthalmol* 1986; 101:361–367. Used by permission.)

these same choroideremia carriers (4 of 26; 15%)[20] and more sensitive for the carriers of XLRP (22 of 23 tested; 96%).[1]

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