Principles and Practice of Clinical Electrophysiology of Vision

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Choroideremia

John R. Heckenlively

Choroideremia was first identified as a separate entity from "typical" retinitis pigmentosa (RP) by Mauthner in 1871,[6] who reported two male patients with pigmentary changes in the fundus, night blindness, and constricted visual fields. However, Mauthner noted features different from typical RP: atrophy of the choroid, normal retinal vessels, and an absence of optic atrophy. Noting a similarity to choroidal coloboma, he described his patients as having "choroideremia." Subsequent reports by Zorn in 1920, who found six cases in three generations,[14] and Schutzbach in 1938, who reported 13 cases in four generations,[3] established the X-linked recessive nature of choroideremia.

Establishing the hereditary pattern was not without some confusion, for as earlier cases were seen, the distinctive scalloped pattern of tissue loss was seen and confused with cases of gyrate atrophy, which is inherited in an autosomal recessive fashion. In 1942, however, Goedbloed[2] and Waardenberg[12] independently suggested a sex-linked inheritance for the condition, which was confirmed by McCulloch and McCulloch in 1948,[7] who presented 86 cases of choroideremia in two families, one of which had over 600 members. They demonstrated that the disease follows X-linked Mendelian inheritance patterns and that females may have a less aggressive form of the disease (carrier states were less well understood in 1948).

The finding of elevated plasma ornithine levels in association with gyrate atrophy by Kirsten Takki in 1974[11] as well as a second article[10] in which she reported that choroideremia patients had normal ornithine levels gave a definitive method to separating gyrate atrophy from choroideremia in those cases in which the pattern of retinal degeneration or the inheritance pattern is not clear.

Choroideremia is characterized by diffuse progressive degeneration of the retinal pigment epithelium (RPE) and choriocapillaris. The degeneration is first manifested as mottled areas of pigmentation in the anterior equatorial region and macula (Fig 86–1); the anterior areas degenerate to confluent scalloped areas with a loss of RPE and choriocapillaris and preservation of larger choroidal vessels. The fluorescein angiographic changes are even more marked, with the scalloped areas of missing choriocapillaris appearing hypofluorescent next to brightly hyperfluorescent patent choriocapillaris (see Chapter 62).

Choroideremia meets all the standard definitions of RP. Patients are night-blind from an early age and have progressive visual field loss leading to tunnel vision; when the electroretinogram (ERG) is recordable, a rod-cone degenerative pattern is seen (Table 86–1). Inheritance is well established to be X-linked recessive. The reason that this group of patients has often been considered to be separate from those with RP is their distinctive retinal changes. Since the term *retinitis pigmentosa* is an umbrella term for a large number of different hereditary pigmentary retinal degenerations, it is reasonable to include choroideremia as one of the types of RP. Now that there

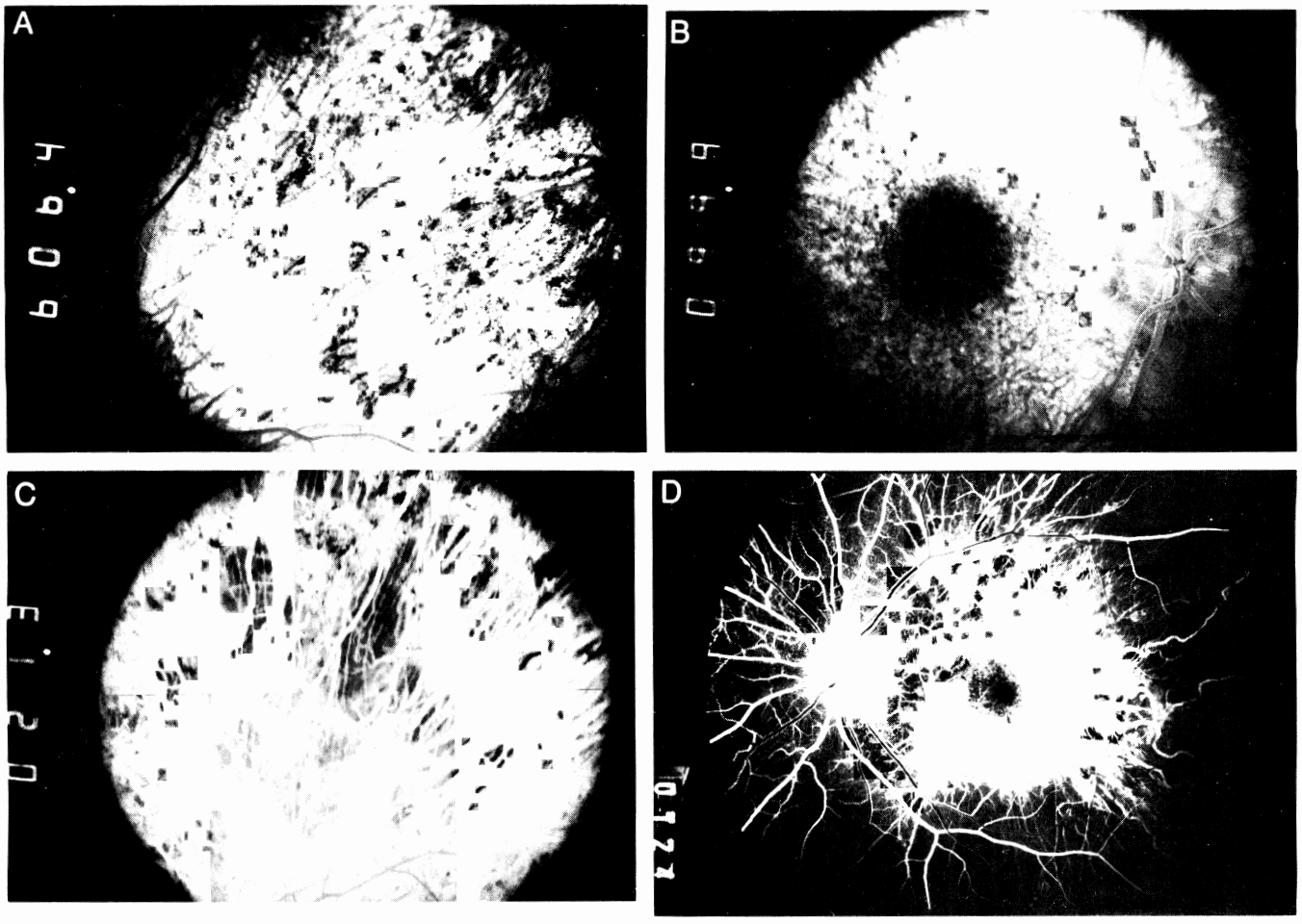

FIG 86–1.
Seven-year-old boy with choroideremia. Fluorescein angiography demonstrates on late frames granular changes of the RPE of the equatorial area **(A)** and posterior pole **(B)**. The macula is hypofluorescent. **C,** a transit frame similar in location to panel **A** demonstrates granular deposits and early scalloped loss of RPE and choriocapillaris. **D,** the posterior pole of the same patient at 9 years of age shows loss of choriocapillaris and RPE outside the macular area.

are better tools for distinguishing RP types, an artificial separation is unnecessary, and choroideremia can be regarded as one of the many RP types.

CLINICAL FINDINGS IN CHOROIDEREMIA

Hemizygotes (Males)

Choroideremia patients represent approximately 6% of patients with RP who are seen at UCLA. The average age for patients initially seen with choroideremia was 31 years, with on average a 21-year history of symptoms of night blindness and visual field loss. The mean visual acuity was 20/30, while the visual field with the IV-4 target averaged 24 degrees and ring scotomas and enlarged blind spots were common. Posterior subcapsular cataracts occurred in an average of 31% of patients.

On funduscopy, patients have pink discs with a cup-to-disc ratio of 0.21 (normal, 0.35) and near-normal–sized retinal vessels. Temporal optic atrophy (missing tissue) was seen in 29% of patients and nerve fiber alterations in 47% (some patients had such blond fundi that it was impossible to discern nerve fiber loss). Analysis of fluorescein angiography in 25 patients showed temporal optic atrophy (missing tissue) in 29%, optic nerve head telangiectasia in 50%, macular edema in 0%, parapapillary edema in 8%, vascular arcade edema in 15%, macular window defect in 21%, and paramacular window defect in 0%. All patients demonstrated the characteristic scalloped loss of RPE and chorio-

TABLE 86–1.
Values in Four Case Examples of Choroideremia*

Case/Age (yr)	Eye	Photopic		Rod Mediated				Bright Flash Dark-Adapted			
		Aamp (μV)	AIT (ms)	Bamp (μV)	BIT (ms)	Bamp (μV)	BIT (ms)	Aamp (μV)	AIT (ms)	Bamp (μV)	BIT (ms)
1/10	OD	—	—	85	43	NR	NR	—	—	70	42
	OS	—	—	50	40	NR	NR	50	22	70	45
DA elevated 3.8 log units at 12 degrees and 4.0 at 30 degrees											
2/16	OD	30	16	70	37	20	86	40	22	80	58
	OS	30	14	50	38	20	84	30	22	70	58
DA elevated 2.5 log units at 12 degrees, 4.0 at 20 degrees, and 2.2 at 30 degrees											
3/7	OD	70	13	171	31	70	78	187	22	382	45
	OS	65	14	177	32	125	80	257	22	429	42
DA elevated 1.25 log units at 12 degrees and 1.3 at 30 degrees											
4/7 yrs	OD	20	16	40	88	40	20	70	38		
	OS	20	16	40	88	40	20	60	38		
DA elevated 2.5 log units at 12 degrees, 2.4 at 20 degrees, and 4.3 at 30 degrees											
Normal		86	13	144	31	346	68	240	14	469	46
±SD		16	1	60	1	54	4	81	1	104	3
DA normal 0.0 to 0.80 log units of elevation											

*Age = at time at testing; Aamp = a-wave amplitude; AIT = a-wave implicit time; Bamp = b-wave amplitude; BIT = b-wave implicit time; DA = final rod threshold after 40 minutes of dark adaptation with a 2-degree target on a Goldmann-Weekers dark adaptometer in log units of elevation.

capillaris in the equator and anterior retinal regions, leaving islands of intact macular tissue.

The typical history was that young patients in preschool years noted night blindness, but like many patients with RP, they assumed that everyone sees in the dark as they do. Visual field loss was usually found in the teenage years. The early funduscopic appearance in lightly pigmented individuals is a generalized loss of the RPE pigment that results in a blond fundus. Areas of fine granular subretinal pigment deposits are seen in the anterior and midequator regions. Fluorescein angiography shows a hypofluorescent macula (Fig 86–1,B), and localized confluent loss of RPE and choriocapillaris equatorial regions may be seen (Fig 86–1,C and D).[4] Some patients may have subtle changes without obvious loss on indirect ophthalmoscopy (Fig 86–2,A), but they will show typical changes on fluorescein angiography (Fig 86–2,B).

The fluorescein angiographic findings are the hall-

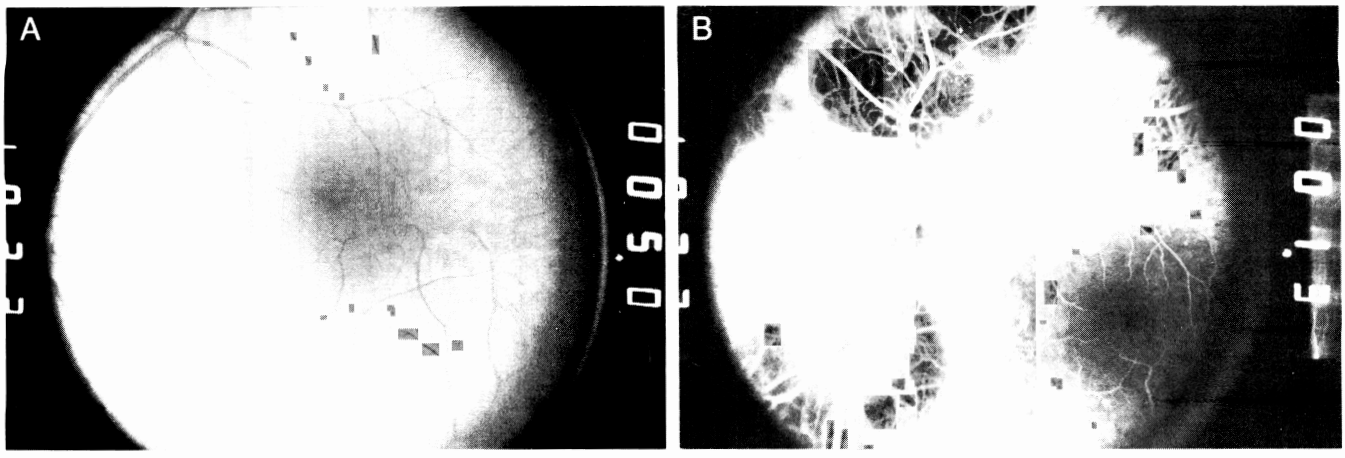

FIG 86–2.
Patient with choroideremia, age 52 years, with **(A)** no obvious changes on red-free photographs. **B,** on late transit frames on the fluorescein angiogram generalized hyperfluorescent RPE is demonstrated, and obvious scalloped loss of choriocapillaris and RPE can be seen superiorly.

mark of the disease. The scalloped areas of RPE atrophy with choriocapillaris loss are hypofluorescent except for the prominent hyperfluorescent larger choroidal vessels that cross the area of missing tissue. The remaining RPE is granular appearing and is hyperfluorescent; the edge of remaining RPE and choriocapillaris is usually stained on later frames of the angiogram.[5]

Visual fields early in the disease reveal multiple scotomatous areas corresponding to the scalloped tissue loss seen on funduscopy. As the disease progresses, ring scotomas usually develop, and typical RP-type visual field loss is seen along with preserved central fields that often have temporal islands of vision.[5] The anterior retina often has some preservation of function.

ERG testing of patients with choroideremia usually demonstrates a nonrecordable ERG, or if recordable, it is abnormal with a rod-cone pattern of degeneration (Table 86–1). Sieving and colleagues reviewed the ERG findings in 47 hemizygotic and 26 heterozygotic cases. They found that rod responses were markedly reduced while cone responses, even if in the normal range, had increased implicit times.[9] The ERG responses in the female carriers of choroideremia were mainly normal.

The ERG was recordable only in children in a rod-cone pattern. The mean dark adaptation final rod threshold was 4.1 log units of elevation.

Heterozygotes For Choroideremia (Carriers)

The retinal changes in carrier of choroideremia are probably the easiest to see and the most frequently found among the various X-linked recessive ophthalmological diseases. In fact, many choroideremia carriers with marked fundus changes will be referred with the diagnosis of RP, but on testing they generally are found to have normal ERGs and visual fields. Other carriers may have more subtle changes with lightly scattered pigment deposits that might be considered a normal variant except for the family history of choroideremia. The fundus changes appear to be age related such that as carriers age they may show areas of retinal degeneration, which occasionally may be quite marked with functional loss.

The clinical findings in the choroideremia carrier state are usually found because an affected male has been seen and female members of the family are examined to confirm the diagnosis or to answer, for genetic counseling reasons, which female members of the family are at risk for affected offspring. A few carriers, mainly in later years, will have symptoms of night blindness, photophobia, and occasionally visual field loss. In looking at a dozen obligate carriers at UCLA, we found that there was a bimodal distribution for refractive error, with half the carriers showing marked hypermetropia averaging +3.10, while the others averaged plano. No correlation was seen between the amount of refractive error and ERG or other clinical findings. Further studies may clarify the bimodal refractive error distribution.

Electrophysiological and psychophysical testing in a dozen obligate carriers was performed at UCLA (Table 86–2). Patients' ages ranged from 23 to 71, with a mean of 45 years. The final rod threshold mean value at 40 minutes was 0.56 log units elevated, which is a borderline-abnormal value (normal is 0.0 to 0.3). However, two patients were more severely affected and had elevations of the final rod threshold of 1.2 and 2.0 log units. Mean electro-oculogram values (light peak to dark trough) in five carriers were 213%. Color vision was normal.

Asymmetry of normal values between eyes was common for all tests, which is unusual since most patients typically have symmetrical test values between eyes.

The ERG findings are particularly interesting because carriers had abnormal values, sometimes below normal, but also at times greater when compared with age-matched normal controls, which is reflected in the higher standard deviations. (see Table 86–2).

Funduscopy revealed variable findings. The more severely affected carriers demonstrated focal areas of RPE loss and/or extensive subretinal granular pigment deposits (Fig 86–3). Affected carriers have

TABLE 86–2.

Comparison of ERG Parameters in Choroideremia

Parameter	Normal (12), Age Matched	Carriers (12)
Photopic ERG		
a-wave amplitude (μV)	58.9 ± 10.4*	67.6 ± 19.6
a-wave implicit time (ms)	12.3 ± 1.2	13.8 ± 1.2
b-wave amplitude (μV)	156.0 ± 29.6	164.0 ± 46.0
b-wave implicit time (ms)	32.3 ± 2.3	32.5 ± 2.2
Scotopic ERG		
b-wave amplitude (μV)	287.5 ± 74.9	313.4 ± 73.7
b-wave implicit time (ms)	70.7 ± 3.8	70.7 ± 5.5
Bright-flash dark-adapted ERG		
a-wave amplitude (μV)	230.0 ± 14.1	241.9 ± 60.6
a-wave implicit time (ms)	15.0 ± 1.8	16.6 ± 2.0
b-wave amplitude (μV)	428.7 ± 74.3	468.0 ± 98.5
b-wave implicit time (ms)	48.2 ± 3.1	48.9 ± 3.2

*Values are ±1 SD.

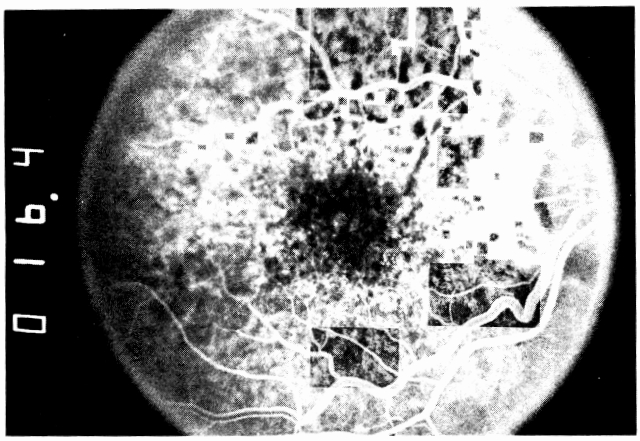

FIG 86–3.
Choroideremia carrier, 62 years of age, with a transit fluorescein angiogram showing granular hyperfluorescent deposits in the posterior pole.

been reported.[1, 3] A few carriers had minimal pigmentary changes; one notable case was a mother of a patient with choroideremia who had an identical twin sister. The mother had minimal pigmentary changes, and her twin sister had no changes on funduscopy, but focal pigmentary changes were found on fluorescein angiography.

DIFFERENTIAL DIAGNOSIS

The disease that is most similar to choroideremia is gyrate atrophy. The major difference between the two is the inheritance pattern, with choroideremia patients having X-linked and gyrate atrophy patients having autosomal recessive inheritance. Another difference generally present is hyperpigmentation of the RPE in gyrate atrophy, while patients with choroideremia tend to have a generalized depigmentation of the RPE. While both groups of patients tend to be myopic, patients with gyrate atrophy tend toward high myopia and are more likely to develop significant cataracts at an earlier age. If there is any question about the clinical diagnosis, a plasma ornithine or a skin sample for ornithine aminotransferase activity will answer the question of whether gyrate atrophy is present.

Some patients with severe myopia will present with a scalloped loss of the RPE under the vascular arcades into the equator region; no inheritance pattern is usually established in these patients, and the course of the disorder is quite different from patients with choroideremia. The onset of the myopic retinal degeneration occurs in later adulthood, and there is usually a history of progressive myopia.

Patients with Bietti's crystalline retinal dystrophy demonstrate a scalloped confluent loss of RPE in the paramacular-posterior pole, and the fluorescein angiographic pattern in this area looks like that seen in choroideremia, but the crystalline deposits throughout the retina (and sometimes limbal cornea), the lack of equatorial involvement in the RPE-choriocapillaris atrophy, and the lack of an X-linked inheritance pattern are clues that choroideremia is not present.[13]

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