Principles and Practice of Clinical Electrophysiology of Vision

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Fundus Albipunctatus

Michael F. Marmor

Fundus albipunctatus is a hereditary stationary retinal disorder with abnormally slow visual pigment regeneration; typically this condition is associated with symptoms of night blindness and punctate, white dots in the posterior and midperipheral fundus.[6, 14, 17] The fundus appearance may be similar to that in a progressive retinal dystrophy, retinitis punctata albescens.[14] Some authors[1, 10, 25] believe that these two entities fall at ends of a continuum of disorders, but others[2, 6, 8, 16, 17, 22] treat fundus albipunctatus as quite distinct from retinitis punctata albescens, and for purposes of this chapter a clear separation will be made. Individuals with narrowed vessels, pigmented lesions, visual field constriction, a permanent dark adaptation threshold elevation, or a permanently subnormal electroretinogram (ERG), i.e., with evidence of a progressive degenerative condition, will *not* be considered in this description of fundus albipunctatus.

CLINICAL FINDINGS

Virtually all of the reported cases of fundus albipunctatus have been isolated individuals, but the remarkably high incidence of consanguinity among the parents of affected patients[9, 16–18, 22] strongly suggests autosomal recessive inheritance. One family has been described with a parent and child involved,[12] and another with apparent dominant transmission showed symptomatic improvement in the night blindness over time,[11] so a different physiological defect may be involved.

The characteristic fundus findings are small, sharply demarcated, whitish dots (Figs 99–1 and 99–2, Plates 20 and 21) at the level of the retinal pigment epithelium (RPE).[18] These may be scattered in the posterior pole but typically spare the central macular area. They may extend through and beyond the vascular arcade region, often in a striking pattern of rows that radiate out from the macula. In the midperiphery the pattern is more variable and may involve white dots or indistinct larger flecks that can be extensive and coalescent and are somewhat reminiscent of the flecks in fundus flavimaculatus. Some of these cases with flecklike appearance have been described as a separate entity,[16, 22] but individuals have been seen in which both manifestations are present.[18]

Several cases in the older literature have been described with follow-up between 25 and 49 years.[9, 12, 23] Symptoms were stable, and the fundi showed no narrowing of the vessels or pigmentary deposits, although the number of white dots was anecdotally noted to increase in one family.[12] Fundus photography from two patients followed for 13 to 14 years[19] shows not only that the punctate lesions increase in number within the macula but also that the extramacular fundus evolves from ill-defined flecks in youth to radiating punctate dots in adulthood (Fig 99–2). Although a rare punctate lesion may fade, most seem to be permanent, and the pattern of dots is remarkably constant over the years.[18, 19]

The central macula may be mildly abnormal and show a reduced foveal reflex and ill-defined pigmen-

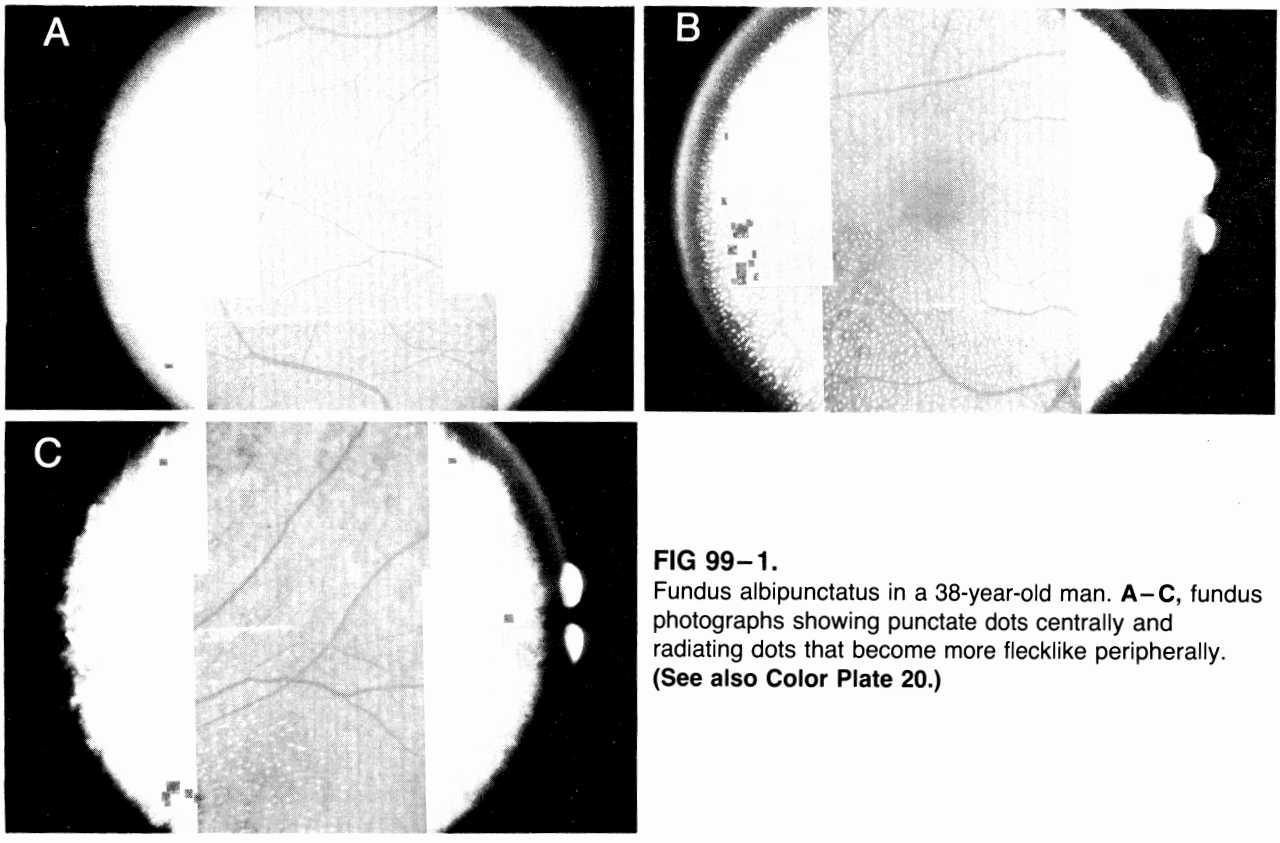

FIG 99–1.
Fundus albipunctatus in a 38-year-old man. **A–C,** fundus photographs showing punctate dots centrally and radiating dots that become more flecklike peripherally. **(See also Color Plate 20.)**

tary changes. However, one does not see gross atrophy or macular degeneration. The retinal vessels characteristically have normal caliber, and there are no bone spicule or clumped pigment figures in the periphery such as characterize retinitis pigmentosa or some patients with retinitis punctata albescens. Fluorescein angiography (Fig 99–1) shows normal vasculature but a diffuse, mild loss of pigmentation in the RPE.[2, 5, 18] The punctate or flecklike fundus lesions are, for the most part, invisible. On careful study, a few may be identified to block fluorescence to a mild degree. There is no leakage of dye from retinal vessels or through the RPE on angiography[5, 18] or with vitreous fluorophotometry.[21]

Visual acuity is typically normal. The major and definitive symptom of the disease is night blindness, although its severity depends on the degree of pigment regeneration delay (see below). Complaints range from minimal awareness of an adaptation problem[12, 24] to virtual blindness in the dark (until a very long period of adaptation has taken place[6, 18]): one of my patients told me he couldn't find a seat when he entered a movie theater, . . . but he could see as well as anyone after a double feature.

Fundus albipunctatus was described as one of the "flecked retina" diseases by Krill and Klien.[13] This description no longer seems appropriate since fundus albipunctatus is clearly distinguishable by symptoms and physiological test results from disorders such as drusen, retinitis punctata albescens, and fundus flavimaculatus. The differential diagnosis must also include certain acquired conditions. Yellowish dots in the retinal periphery can occur in chronic vitamin A deficiency,[15, 25, 26] but patients with fundus albipunctatus have normal vitamin A levels and do not show corneal xerosis or other signs of systemic vitamin A deficiency.[4, 18] Scattered white dots are also seen in crystalline retinopathies. Oxalosis can develop on a congenital basis[20] or because of renal toxicity such as from methoxyflurane anesthesia,[3] but serum oxalate levels are normal in fundus albipunctatus,[4] and there is no evidence of renal damage. Bietti's crystalline retinopathy[27] is a dystrophic disease with progressive symptoms and retinal damage. All of these disorders differ with respect to history (they are not both stationary and hereditary), and they lack the striking delay in visual pigment regeneration that provides the true physiological definition of this disease. The only known condition that delays dark adaptation to a similar degree is Oguchi's disease,[7] but there are no white fundus lesions, and the adaptation delay is neural rather than

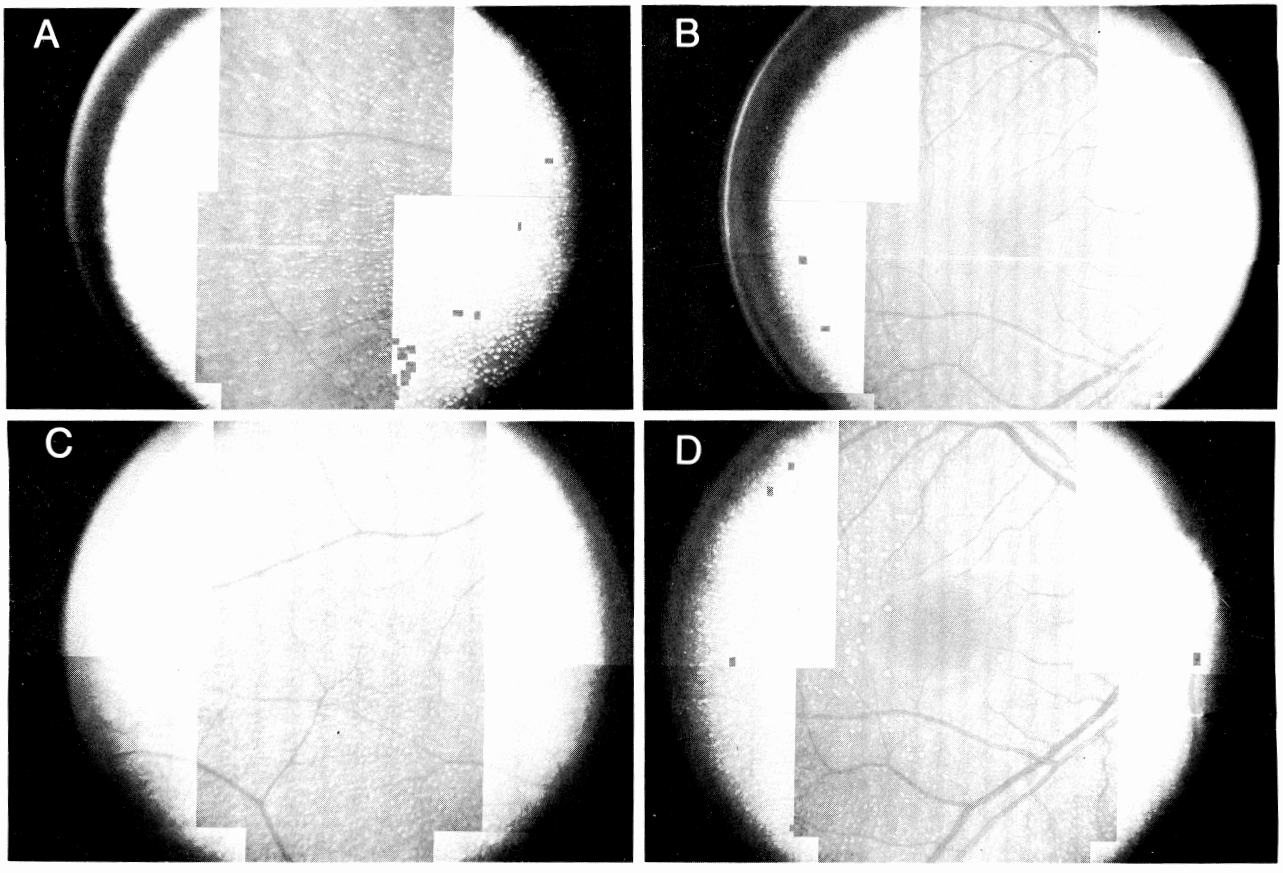

FIG 99–2.
Fundus albipunctatus, age 8 **(A** and **B)** and age 21 years **(C** and **D).** Note the increase in macular dots and the conversion of many peripheral flecks to dots. **(See also Color Plate 21.)**

chemical (i.e., the visual pigment regenerates normally).

PHYSIOLOGICAL TEST FINDINGS

Psychophysical Test Results

Most reports have noted no functional abnormalities other than with dark adaptation. One of my own patients[18] has subtle foveal changes and a mild acquired color deficiency with tritan errors on the Farnsworth D-15 panel. Visual fields are full, and the presence of scotomas or constriction should lead one to question the diagnosis in favor of a progressive disorder.

Dark adaptometry shows marked prolongation of *both* the cone and rod phases of adaptation[6, 10, 12, 17, 26] (Fig 99–3). Whereas the cone/rod break normally occurs at 6 to 10 minutes after an adapting bleach, some patients with fundus albipunctatus require 1 to 2 hours before a stable cone threshold is reached and rod adaptation begins.[6, 17, 22] Final adaptation of the rods is also prolonged and may require an additional 1 to 2 hours. Some mild cases have been described in which cone and rod adaptation are only prolonged by minutes,[12, 16, 24] but the most prototypic cases require hours before normal thresholds are reached. The striking fact that distinguishes fundus albipunctatus from the more common kinds of congenital stationary night blindness (e.g., the Schubert-Bornschein type) (see Chapter 96) is that with sufficient time, sensitivity recovers to a completely normal level. Once full dark adaptation has been achieved, individuals with fundus albipunctatus function as well in the dark as do normals. The dark adaptation defect seems stable over many years subjectively,[9, 12, 23] and adaptometry thresholds have been shown to be constant over a period of 13 to 14 years.[19]

Fundus Reflectometry

The physiological defect of fundus albipunctatus has been defined most precisely by fundus reflecto-

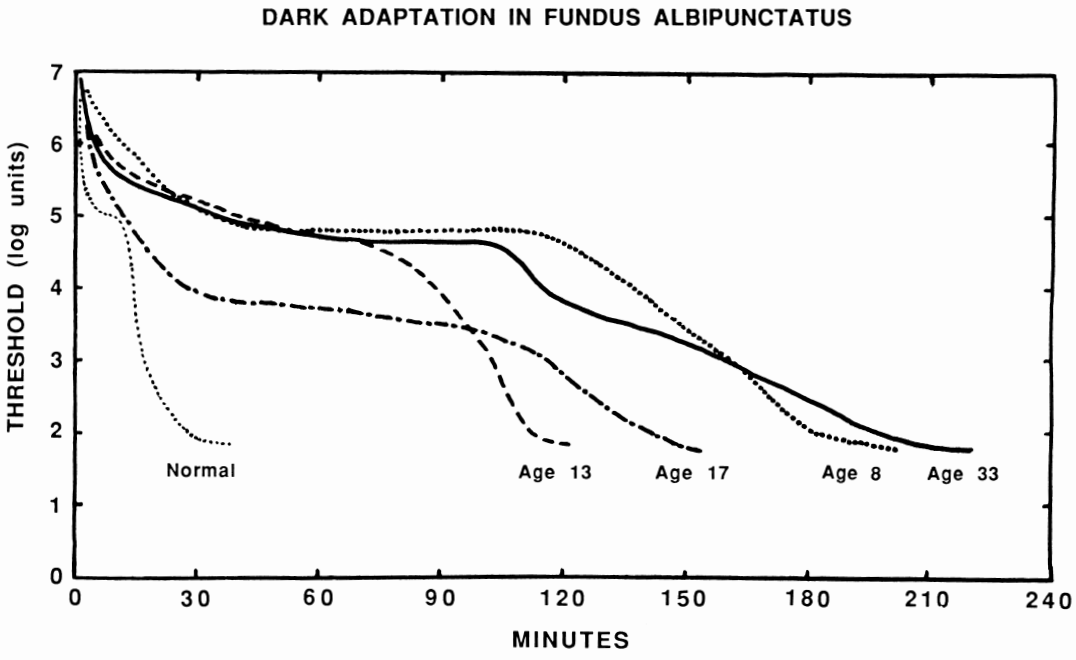

FIG 99–3.
Dark adaptation curves from four patients with fundus albipunctatus. Note that the time scale is in hours rather than minutes. The two longest curves are from the patients illustrated in Figures 99–1 and 99–2.

metry, which allows a measurement of visual pigment levels within the retina. The pioneering experiments by Carr, Ripps, and Siegel on various forms of stationary night blindness[4, 6] showed that visual pigment regeneration was normal in congenital stationary night blindness with normal fundi and in Oguchi's disease, thus proving that these disorders represent defects in transduction or in synaptic transmission. However, in fundus albipunctatus the amount of visual pigment in the retina correlates with retinal sensitivity, and regeneration after bleaching is extremely slow[4, 6] (Fig 99–4). This suggests that the physiological defect in this disease lies in the chemistry of the visual pigment regeneration cycle and very likely within the RPE. We do not know how the yellowish dots relate to this physiological defect; perhaps there is a local or functional vitamin A deficiency within the RPE since similar dots may appear in vitamin A deficiency.[15, 25, 26] In the latter disorder, however, the dots disappear with recovery, whereas fundus albipunctatus does not respond to treatment with vitamin A and zinc[17] and the dots are permanent.

Electroretinography

The ERG measured under conventional conditions is severely abnormal (Fig 99–5). The cone responses are usually normal[2, 17, 22] but may be minimally subnormal.[16] However, little or no rod response is present after the usual 15 to 30 minutes of dark adaptation.[6, 16, 17, 22] With routine testing, therefore, the ERG may appear similar to that in

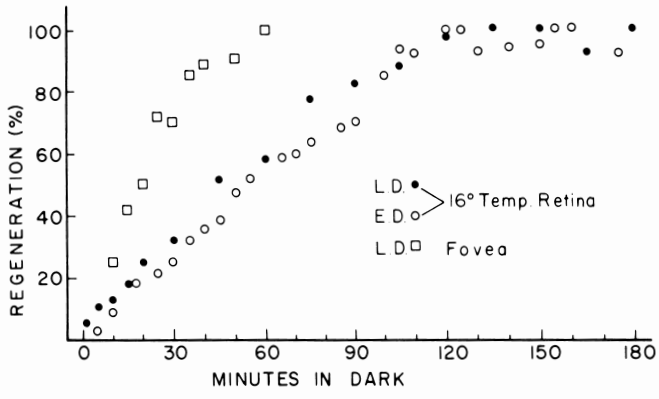

FIG 99–4.
Regeneration of visual pigments in fundus albipunctatus, as measured by fundus reflectometry. The foveal data represent cone pigments; the temporal retina data indicate rhodopsin. The regeneration of both pigments follows the time course of psychophysical dark adaptation and thus is markedly delayed in these patients. (From Carr RE, Ripps H, Siegel IM: *Doc Ophthalmol Proc Ser* 1974; 4:193–204. Used by permission.)

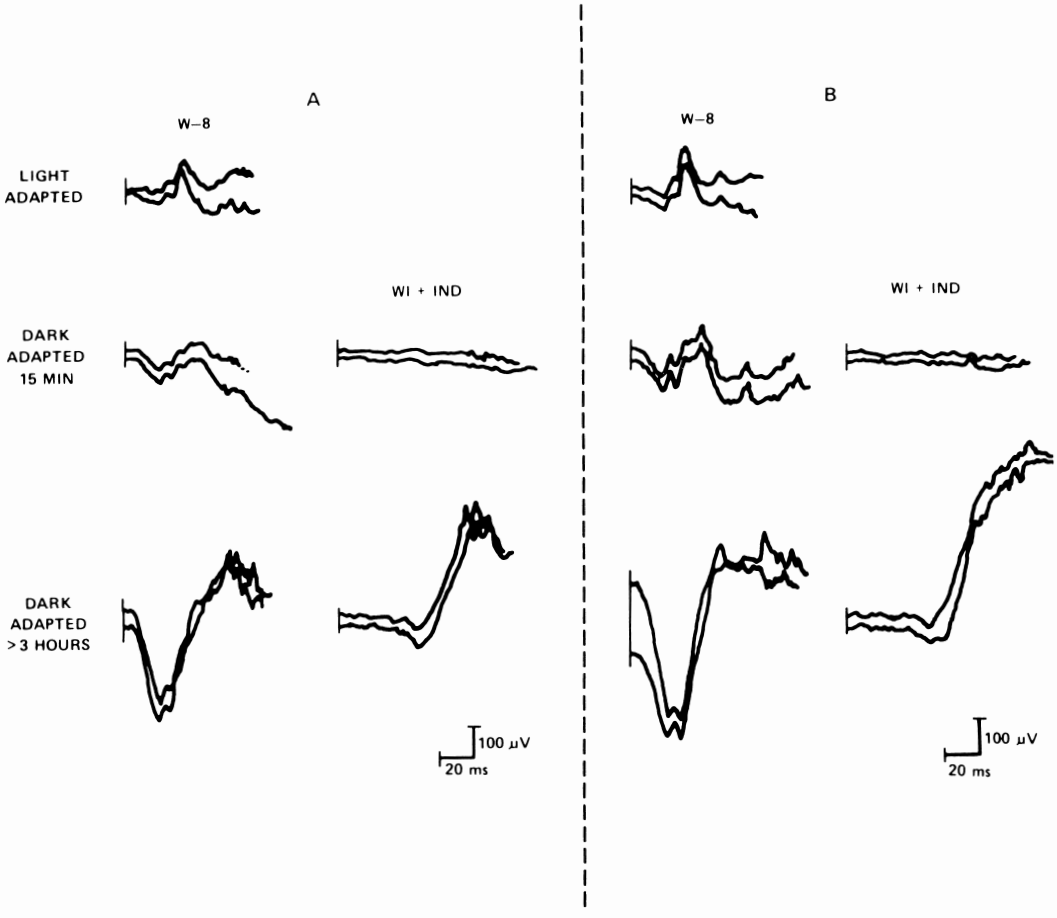

FIG 99–5.
ERG from two patients with fundus albipunctatus. **A,** the patient illustrated in Figure 99–1, aged 33 years; **B,** the patient illustrated in Figure 99–2, aged 8 years. Rod signals are absent in the conventional (15 minute) ERG but are normal after full dark adaptation. *W-8* is a bright white flash; *W-1 + IND* is roughly 2 log units attenuated. (From Marmor MF: *Doc Ophthalmol Proc Ser* 1977; 13:227–234. Used by permission.)

congenital stationary night blindness or even a rod dystrophy. The difference is that the scotopic ERG will recover to normal size if the patient is allowed to dark-adapt for a sufficient time to reach a normal psychophysical threshold (which may require several hours). The time course of ERG recovery follows that of visual pigment regeneration and psychophysical dark adaptation.[6, 17] Some of the variation in ERG size and waveform among early reports of fundus albipunctatus (before the ability to recover full sensitivity was understood) may be a result of recording at different levels of dark adaptation. ERG responses measured 13 to 14 years apart in two patients did not show any change.[19]

ERG recovery after prolonged dark adaptation is also observed in Oguchi's disease, but in some patients with that condition[4] the presentation of one or two brief light flashes can "reset" the defect in dark adaptation and return the patient to a state of reduced retinal sensitivity. In fundus albipunctatus, the dark-adapted state remains until enough light energy has been absorbed to bleach a significant proportion of the rhodopsin; for practical purposes, therefore, the ERG can be recorded with brief flashes without fear of light adaptation.

Electro-oculography

Reports on the electro-oculogram (EOG) are variable in fundus albipunctatus. Most of this variability relates to the time of testing since the EOG does not show a normal response until the patient has become sufficiently dark-adapted that the rods (which account for much of the EOG response[7]) have reasonable sensitivity (Fig 99–6). Patients who have been tested in the state of full dark adaptation show

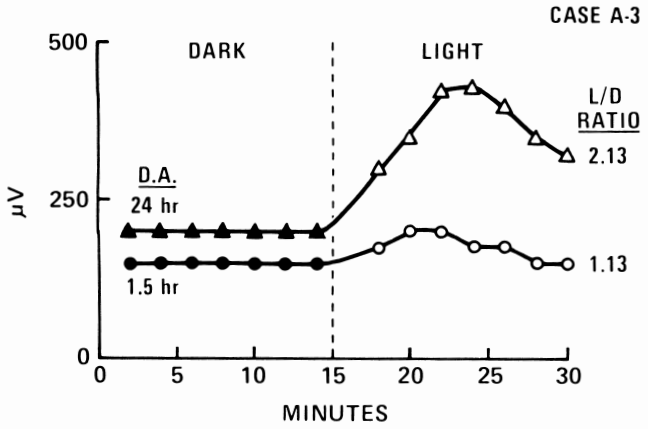

FIG 99–6.
EOG from the patient in Figure 99–1. The two eyes were dark adapted *(D.A.)* for different periods of time before light exposure; the light/dark *(L/D)* ratio was pathologically low after 90 minutes of dark adaptation but normal after 24 hours. (From Marmor MF: *Doc Ophthalmol Proc Ser* 1977; 13:227–234. Used by permission.)

a normal EOG,[6, 18] whereas EOG recordings made in the routine manner after only 12 to 15 minutes of dark adaptation show a very subnormal light/dark ratio.[2, 6, 18, 24] The EOG does not appear to give any information about the state of the RPE relative to the pathophysiology of this disease.

In theory, the physiological status of the RPE may be more specifically documented by nonphotic standing potential responses that do not depend upon visual pigment or photoreception. In a brief report, Yonemura and colleagues[28] noted that the acetazolamide (Diamox) response was normal in fundus albipunctatus, but half of their patients showed an abnormal hyperosmolarity response. However, this finding is difficult to interpret because the patients were not described with respect to fundus changes or dark adaptation defects.

SUMMARY

Fundus albipunctatus is a recessively inherited disorder characterized by white dots in the posterior fundus and abnormally slow visual pigment regeneration during dark adaptation. Electrophysiological tests follow the status of the visual pigments, so ERG testing within a conventional time frame shows borderline cone and absent rod function, but testing after several hours (when full visual pigment recovery has occurred) is entirely normal. The nonphotic hyperosmolarity response has been reported to be abnormal. Fundus albipunctatus must be distinguished from other forms of stationary night blindness in which scotopic function never recovers with time and from progressive dystrophies in which there may be degeneration of photoreceptor elements, vascular narrowing, and field loss.

REFERENCES

1. Aouchichi M, Boyer R, Zetchi A: De la difficulté du diagnostic entre la retinopathie ponctuée albescente et le fundus albipunctatus cum hemeralopia. *Bull Mem Soc Fr Ophthalmol* 1969; 82:573–585.
2. Bartl G, Koudelka A, Benedikt O: Elektrophysiologische und fluoreszenzangiographische Untersuchungen bei einem Fall von Fundus albipunctatus cum Hemeralopia congenita. *Klin Monatsbl Augenheilkd* 1977; 171:587–591.
3. Bullock JD, Albert DM: Flecked retina appearance secondary to oxalate crystals from methoxyflurane anesthesia. *Arch Ophthalmol* 1975; 93:26–31.
4. Carr RE: Congenital stationary nightblindness. *Trans Am Ophthalmol Soc* 1974; 72:448–487.
5. Carr RE, Margolis S, Siegel IM: Fluorescein angiography and vitamin A and oxalate levels in fundus albipunctatus. *Am J Ophthalmol* 1976; 82:549–558.
6. Carr RE, Ripps H, Siegel IM: Visual pigment kinetics and adaptation in fundus albipunctatus. *Doc Ophthalmol Proc Ser* 1974; 4:193–204.
7. Elenius V, Aantaa E: Light-induced increase in amplitude of electro-oculogram. *Arch Ophthalmol* 1973; 90:60–63.
8. Ellis DS, Heckenlively JR: Retinitis punctata albescens. Fundus appearance and functional abnormalities. *Retina* 1983; 3:27–31.
9. Franceschetti A, Chome-Bercioux N: Fundus albipunctatus cum hemeralopia. *Ophthalmologica* 1951; 121:185–193.
10. Franceschetti A, Dieterle P, Ammann F, Marty F: Une nouvelle forme de fundus albipunctatus cum hemeralopia. *Ophthalmologica* 1963; 145:403–410.
11. Kranias G, Augsburger JJ, Raymond LA: Resolution of night blindness in fundus albipunctatus. *Ann Ophthalmol* 1981; 13:871–874.
12. Krill AE, Folk MR: Retinitis punctata albescens: A functional evaluation of an unusual case. *Am J Ophthalmol* 1962; 53:450–455.
13. Krill AE, Klien BA: Flecked retina syndrome. *Arch Ophthalmol* 1965; 74:496–508.
14. Lauber H: Die sogenannte Retinitis punctata albescens. *Klin Monatsbl Augenheilkd* 1910; 48:133–148.
15. Levy NS, Toskes PP: Fundus albipunctatus and vitamin A deficiency. *Am J Ophthalmol* 1974; 78:926–929.
16. Margolis S, Siegel IM, Ripps H: Variable expressivity in fundus albipunctatus. *Ophthalmology* 1987; 94:1416–1422.
17. Marmor MF: Defining fundus albipunctatus. XIV ISCERG Symposium, 1976. *Doc Ophthalmol Proc Ser* 1977; 13:227–234.
18. Marmor MF: Fundus albipunctatus: A clinical study of the fundus lesions, the physiologic deficit, and the vitamin A metabolism. *Doc Ophthalmol* 1977; 43:277–302.

19. Marmor MF: Long term follow-up of the physiologic abnormalities and fundus changes in fundus albipunctatus. *Ophthalmology* 1990; 97:380–384.
20. Meredith TA, Wright JD, Gammon JA, Fellner SK, Warshaw BL, Maio M: Ocular involvement in primary hyperoxaluria. *Arch Ophthalmol* 1984; 102:584–587.
21. Miyake Y, Gto S, Ando F, Ichikawa H: Vitreous fluorophotomeotry in congenital stationary nightblindness. *Arch Ophthalmol* 1983; 101:574–576.
22. Miyake Y, Harada K: Familial fleck retina with night blindness. *Ann Ophthalmol* 1982; 14:836–841.
23. Nettleship E: A note on the progress of some cases of retinitis pigmentosa sine pigmento and of retinitis punctata albescens. *R Lond Ophthalmic Hosp Rep* 1914; 19:123–129.
24. Smith BF, Ripps H, Goodman G: Retinitis punctata albescens. *Arch Ophthalmol* 1959; 61:93–101.
25. Teng KH: Further contributions to the fundus xerophthalmicus. *Ophthalmologica* 1965; 150:219–238.
26. Uyemura M: Ueber eine merkwurdige Augenhintergrundveranderung bei zwei Fallen von idiopathischer Hemeralopie. *Klin Monatsbl Augenheilkd* 1928; 81:471–473.
27. Wilson DJ, Weleber RG, Klein ML, Welch RB, Green WR: Bietti's crystalline dystrophy. A clinicopathologic correlative study. *Arch Ophthalmol* 1989; 107:213–221.
28. Yonemura D, Kawasaki K, Madachi-Yamamoto S: Hyperosmolarity response of ocular standing potential as a clinical test for retinal pigment epithelium activity. Chorioretinal dystrophies. *Doc Ophthalmol* 1984; 57:163–173.