Diagnostic Clinical Findings of a New Syndrome With Night Blindness, Maculopathy, and Enhanced S Cone Sensitivity

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We studied eight patients who had night blindness, maculopathy (often cystoid), degenerative changes in the region of the vascular arcades, relatively mild visual field loss, and an unusual but characteristic electroretinogram. The dark-adapted electroretinogram showed no response to low-intensity stimuli that normally activate the rods, but large, slow responses to high-intensity stimuli. These large, slow waveforms persisted without change under light adaptation, and showed a striking mismatch to photopically balanced short and long wavelength stimuli (with sensitivity much greater to short than long wavelengths). Since there is evidence from other studies that the electroretinogram and psychophysical responses represent hypersensitivity of short wavelength-sensitive (S or blue) cones, we propose that this disorder be called the enhanced S cone syndrome. There can be different degrees of severity in this syndrome, and progression appears to be slow.

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A RETINAL DISEASE associated with night blindness, maculopathy (often cystoid), and an unusual pattern of electroretinographic findings in which scotopic and photopic waveforms look similar has been reported.[1-6] Psychophysical, electroretinogram, and fundus reflectometric analyses of photoreceptor-mediated dysfunction in three patients with this disorder indicated that there was severe rod sensitivity loss throughout the retina, no measurable rhodopsin, midspectral cone system abnormalities, and enhanced sensitivity of the short wavelength-sensitive (S or blue) cone system.[7]

The previous reports of this syndrome have described isolated patients, under different diagnostic categories, and have not recognized the unifying clinical features. We have studied eight patients, showing the spectrum of ophthalmoscopic findings that are associated with this disease and defining the diagnostic set of electroretinogram responses that distinguish it from other retinal disorders.

Patients and Methods

We studied eight patients. Patients with large-amplitude electroretinograms (> 300 μV) to conventional high-intensity stimuli are listed first in the Table (Cases 1 through 5), followed by those with smaller electroretinogram amplitudes (Cases 6 through 8). All of the patients were in good general health. Although the patients were studied in different laboratories, the electroretinogram recording techniques were similar in principle.[8-11] Contact lens electrodes were used, and either a ganzfeld stimulator dome (United States) or a Henkes diffuser electrode (Germany) was used to produce a full-field stimulus.

Results

The common symptom among these patients was night blindness, which all patients reported they had had for as long as they could remember. There were no complaints of color or side vision loss except for the oldest patient (Case 8), who had some peripheral vision disturbances. The family history was noncontributory in all patients except one (Case 4), who had a brother with similar symptoms. None of the families were aware of parental consanguinity. Visual acuity was reduced for many patients, but the onset and severity were variable. There was no characteristic refractive error.

The fundus appearance in this syndrome (Figs. 1 to 4) was symmetric between the two eyes and characterized by degenerative changes in the region of the vascular arcades. The lesions ranged from yellow flecks that sometimes resembled drusen to pigment epithelial atrophy and a deposition of black pigment spots. The far periphery was normal or showed only mild granularity. The central macula was abnormal in all cases, ranging from loss of the foveal reflex in some patients (Fig. 1) to cystoid degeneration of the fovea in others (Figs. 2, 3, and 4). However, angiograms done on five of the patients showed no leakage of dye associated with the cystoid changes (Figs. 3 and 4). One patient (Case 5) developed subretinal neovascularization in one eye. The optic disks were normal; the vessels were of normal caliber or only slightly narrowed.

Four patients (Cases 3, 4, 6, and 7) have been followed up for a minimum of four (and as long as 12) years, during which time two patients lost visual acuity (Cases 4 and 5) and the pigmentary changes in the arcade region became more prominent but not much more extensive. There was some intensification of the degenerative lesions over time, but little increase in the area of involvement (Fig. 3). The electrophysiologic measures have not shown a clear pattern of progression over time, and the electroretinogram b-wave amplitudes were mostly stable in these patients.

Dark adaptation was universally impaired among these patients. Conventional dark adaptation curves showed a normal initial cone limb, but little or no rod adaptation beyond the cone threshold (Fig. 5). Three patients (Cases 1, 2, and 8) demonstrated a small amount of slow, additional recovery of sensitivity (0.5 to 0.7 log unit over 60 to 90 minutes).[7]

The visual fields showed varying degrees of midperipheral scotomas (Fig. 6). Patients with only drusenlike or flecklike arcade lesions generally had normal kinetic fields (for example, with a Goldmann perimeter), whereas those with more advanced degenerative changes had relative ring scotomas.

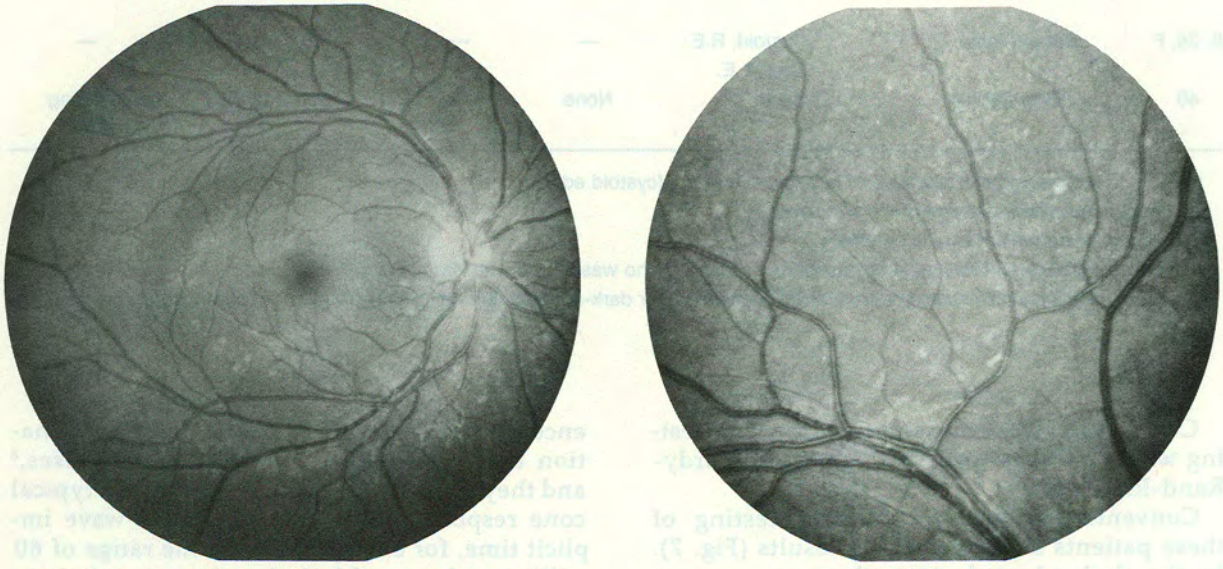

Fig. 1 (Marmor and associates). Case 1, the youngest in our series, had the mildest fundus lesions and the largest electroretinogram responses. Left, Wide-angle photograph showing faint yellow spots scattered in a ring in the vascular arcade region. The macula is dull. Right, Superotemporal arcade of the same eye, showing the faint yellow lesions.

TABLE
CLINICAL CHARACTERISTICS OF EIGHT PATIENTS

PATIENT NO., AGE (YRS), SEX	ARCADE REGION	FOVEA	FLUORESCEIN LEAKAGE*	REFRACTIVE ERROR†	VISUAL ACUITY R.E.	VISUAL ACUITY L.E.	VISUAL FIELDS‡
1, 10, F	Yellow flecks	Dull	—	−0.50	20/25	20/20	Full
2, 28, M	Pigmentary degeneration	Cystoid	None	+1.50	20/60	20/200	Relative ring scotoma
3, 12, M	Flecks	Dull	—	+4.00	20/30	20/25	Full
16	Same	Same	—	+4.00	20/30	20/60	Same
4, 23, M	Flecks	Cystoid	None	0	20/200	20/200	Central scotoma
28	Pigmented flecks	Same	—	0	20/200	20/200	Same
5, 23, M	Depigmented flecks	Scar, R.E. Cystoid, L.E.	—	+2.50	20/200	20/200	Central scotoma
25	Same	Same	—	+2.50	20/200	20/200	Same
6, 7, M	Pigmentary degeneration	Dull	—	0	20/30	20/25	—
15	Same	Same	None	−0.25	20/50	20/30	Relative ring scotoma
19	Same	Same	—	−1.75	20/30	20/25	Same
7, 9, F	Yellow flecks	Dull	—	+0.75	20/20	20/20	—
12	Flecks and gray depigmentation	Cystoid	—	−0.50	20/40	20/40	—
17	Pigmentary degeneration	Cystoid with hole	None	−0.50	20/40	20/40	Relative ring scotoma
19	Same	Same	—	−0.75	20/50	20/60	Same
8, 28, F	Not available	Cystoid, R.E. Scar, L.E.	—	—	20/20	20/200	—
40	Yellow flecks	Same	None	+4.50	20/50	20/200	Relative ring scotoma

*Refers to the presence or absence of late foveal leakage (cystoid edema).
†Spherical equivalent, average of the two eyes.
‡Goldmann or equivalent kinetic perimetry.
§Farnsworth D-15 test for all patients except one (Case 7), who was tested with Hardy-Rand-Rittler plates.
‖In response to the conventional high-intensity stimulus under dark-adapted (scotopic) or light-adapted (photopic) conditions.

Color vision was consistently normal by testing with the Farnsworth D-15 panel or Hardy-Rand-Rittler plates.

Conventional electroretinogram testing of these patients showed striking results (Fig. 7). In the dark-adapted state, there was no response to dim stimuli but a substantial response to brighter stimuli. The scotopic waveforms showed little diminution or change in the presence of routine levels of background illumination that are used to isolate cone responses,[8] and they were strikingly different from a typical cone response. The light-adapted b-wave implicit time, for example, was in the range of 60 milliseconds, roughly twice the normal time. The response in these patients was characterized by an unusually large and prolonged initial negativity (a-wave), especially at high stim-

TABLE (Continued)
CLINICAL CHARACTERISTICS OF EIGHT PATIENTS

COLOR[§]	ELECTRO-OCULOGRAM	ELECTRORETINOGRAM B-WAVE (μV)[‖] SCOTOPIC	PHOTOPIC
Normal	1.8	475	475
Normal	—	350	300
Normal	1.1	420	380
—	—	420	380
—	1.5	345	230
—	—	345	230
Normal	1.15	400	315
—	—	400	315
Unreliable	—	150	75
Normal	—	100	50
—	—	150	100
—	—	273	127
—	—	208	164
Normal	1.15	210	154
Normal	—	183	139
—	—	—	—
Normal	—	100	80

ulus intensities. The response to 30-Hz flicker was reduced in all patients, ranging from 60 μV (Case 1) to nonrecordable. Oscillatory potentials were recordable in only a few patients (Cases 1 and 2).

These patients comprised two groups. In the first group (Cases 1 through 5), the maximal electroretinogram responses were large, falling within or close to the normal range of scotopic

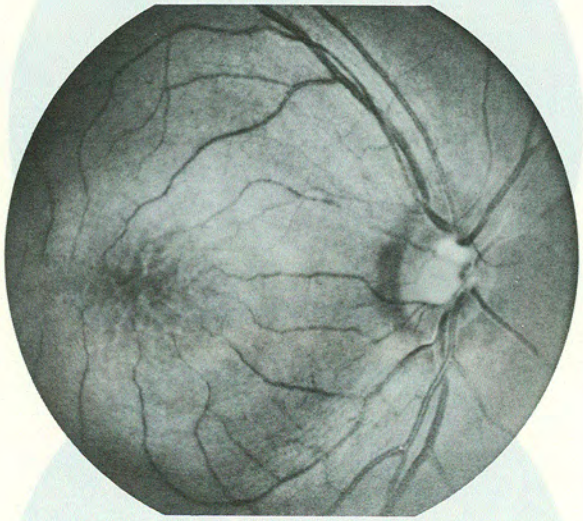

Fig. 2 (Marmor and associates). Case 2, central macula exhibiting prominent cystoid degeneration. There was no leakage on fluorescein angiography.

electroretinogram amplitudes. These patients showed extraordinarily large electroretinograms under light-adapted conditions. In the second group (Cases 6 through 8), scotopic electroretinogram amplitudes were reduced but the photopic signals were still homologous and remarkable for their slow waveform if not for their amplitude.

The electroretinogram responses to stimuli of increasing intensity had several unique characteristics. In a typical series of recordings with normal responses for comparison, the responses of the patients developed a large broad a-wave and remained virtually constant with respect to b-wave timing under both photopic and scotopic conditions, whereas normal scotopic responses showed a decrease in b-wave implicit time with increasing stimulus intensity (Fig. 8).

The relationship between electroretinogram response amplitude and stimulus intensity is shown graphically in Figure 9. All of the curves (a- and b-waves, dark- and light-adapted) rise more steeply than normal, and the a- and b-waves are similar. The scotopic electroretinogram of our patients was insensitive to dim light stimuli that normally elicit a rod response, but increased to a large amplitude when higher-intensity stimuli were used. The photopic V-log I curves are similar to those from normal patients at lower intensities, but at higher intensities the amplitudes are larger and the function is steeper. In contrast to normal eyes, none

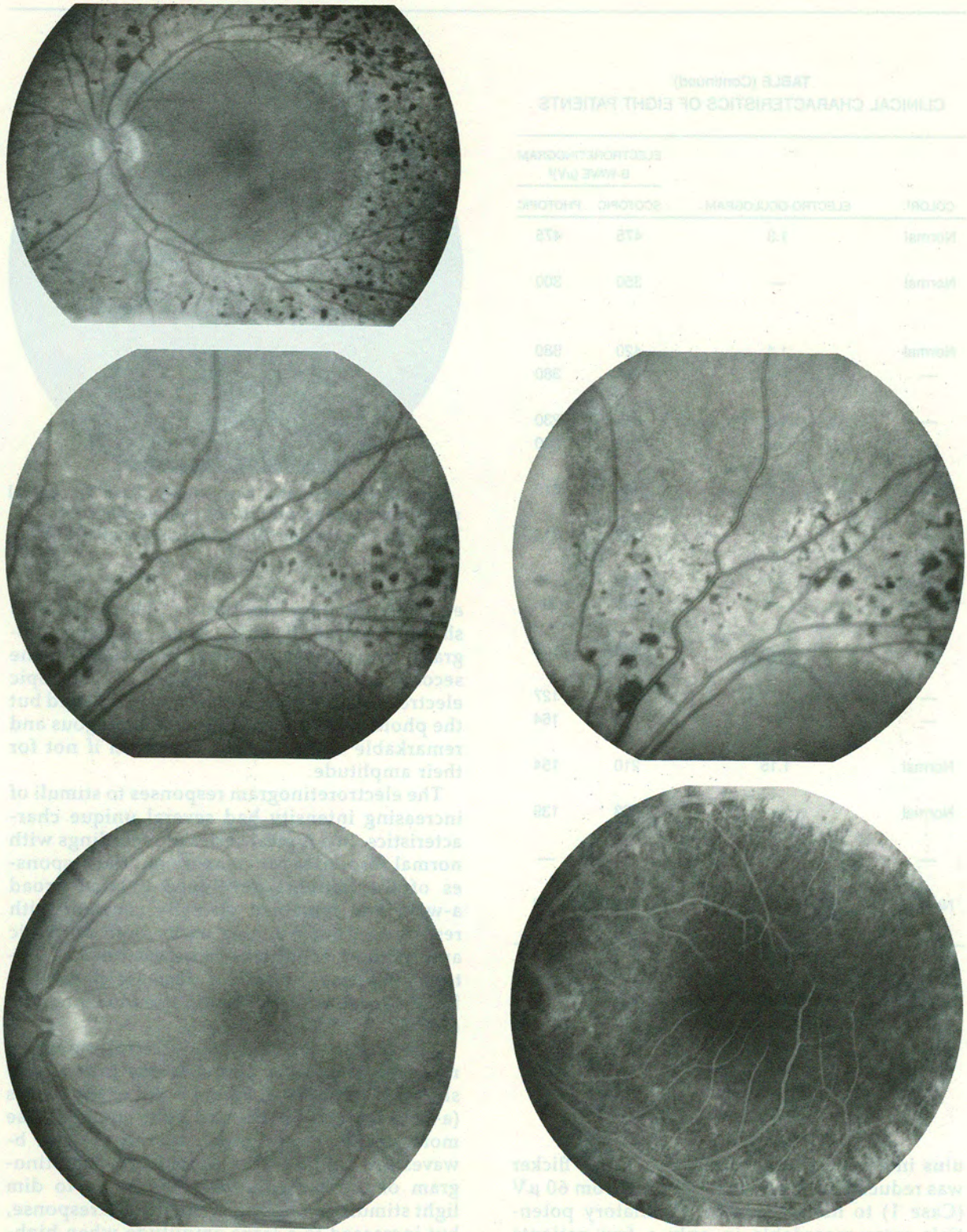

Fig. 3 (Marmor and associates). Case 6. Top left, Wide-angle photograph at age 19 years, showing a prominent ring of retinal degenerative changes in the vascular arcade region. Middle left, Superotemporal arcade of the same eye at 7 years. Middle right, The same arcade region at 15 years, showing little progression over the eight-year period. Bottom left, The central macula at age 15 years lacked foveal reflexes and showed suggestive cystoid changes. Bottom right, Late-phase fluorescein angiogram taken at the same time, showing no leakage.

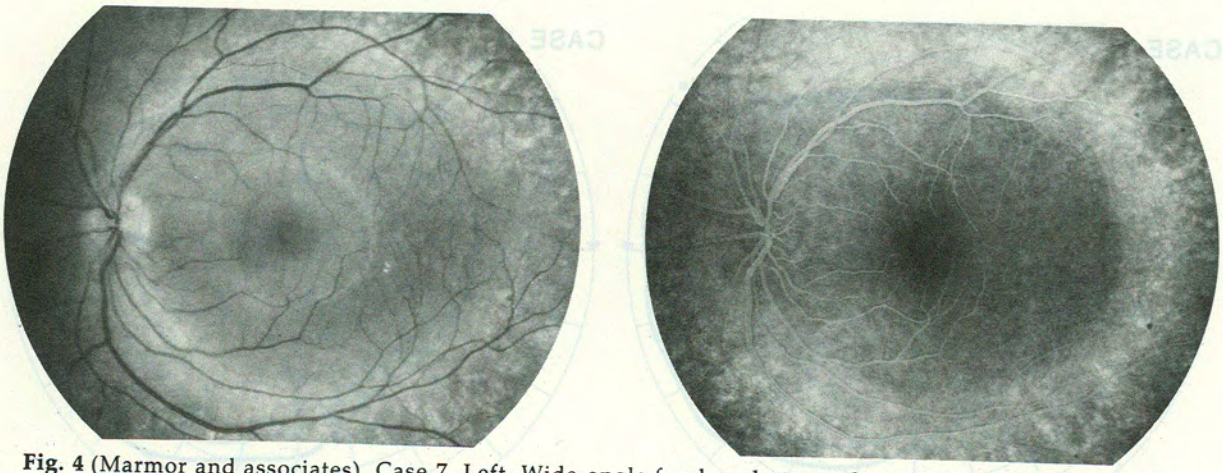

Fig. 4 (Marmor and associates). Case 7. Left, Wide-angle fundus photograph at 17 years, showing a holelike foveal lesion and pigmentary degeneration in the arcade region. Right, Fluorescein angiography shows hyperfluorescence in the degenerated regions, but no foveal leakage.

of the eyes in our series showed a plateau of b-wave amplitude at the highest conventional scotopic or photopic stimulus intensities. The results of presenting brighter stimuli to one patient (Case 6) are shown in Figure 10. Although this patient (Case 6) is in our low-amplitude group, the a-waves and b-waves rose to high amplitudes with bright stimuli that exceeded the intensities used in standard electroretinogram testing.[9] The b-wave eventually reached a plateau, but only at stimulus levels well above normal for both dark- and light-adapted signals. The a-wave did not show a plateau, and exceeded the b-wave in amplitude at the highest scotopic and photopic stimulus intensities.

We observed in four of our patients (Cases 1, 2, 6, and 7) that the single-flash photopic electroretinogram failed to augment during the first ten to 20 minutes of light adaptation, whereas normal cone responses grow substantially.[12] Increasing the background light intensity above 20 $cd \cdot m^{-2}$ in two patients (Cases 1 and 6) led to a diminution of the responses (as occurs with normal cones).

Long and short wavelength stimuli, balanced for photopic and scotopic signals, were presented to five of our patients (Cases 1, 2, 6, 7, and 8). The light-adapted responses showed a striking photopic mismatch that is an important diagnostic feature of this syndrome (Fig. 11). The photopic electroretinogram was more sen-

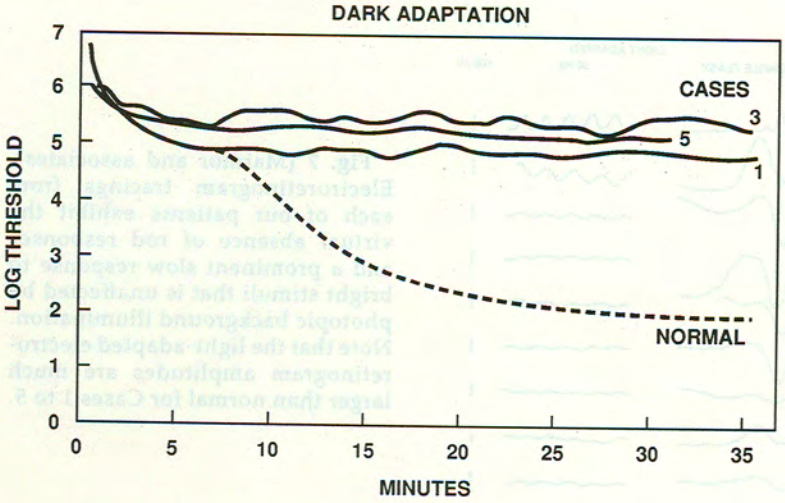

Fig. 5 (Marmor and associates). Representative dark-adaptation curves showing no evidence of rod function within the time frame of conventional dark-adaptation testing.

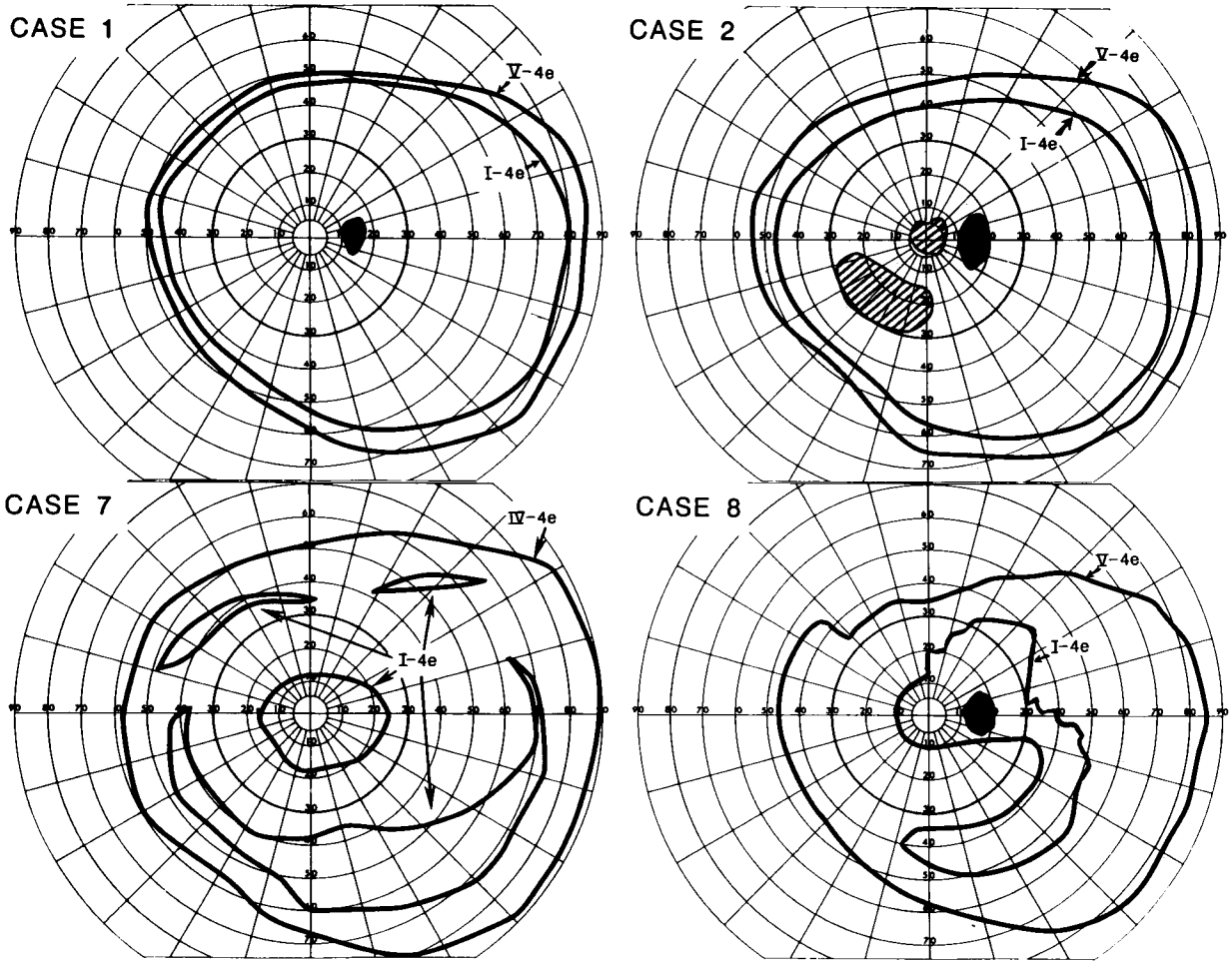

Fig. 6 (Marmor and associates). Representative Goldmann visual fields with defects ranging from none to relative ring scotomas.

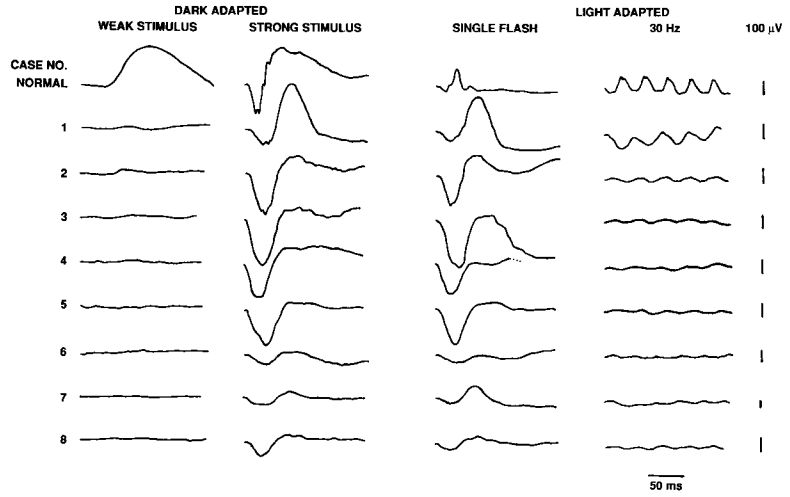

Fig. 7 (Marmor and associates). Electroretinogram tracings from each of our patients exhibit the virtual absence of rod responses and a prominent slow response to bright stimuli that is unaffected by photopic background illumination. Note that the light-adapted electroretinogram amplitudes are much larger than normal for Cases 1 to 5.

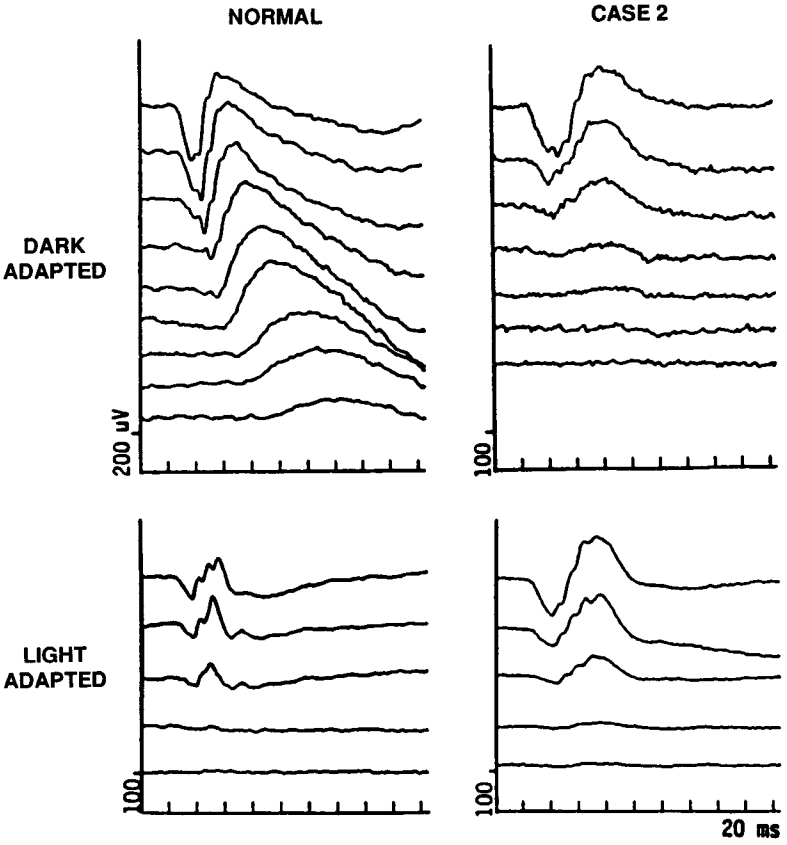

Fig. 8 (Marmor and associates). Case 2, electroretinogram responses arranged to illustrate the change in waveform with increasing stimulus intensity. All of our patients failed to show the normal shortening of the b-wave implicit time.

sitive to blue or green than to red or orange, in contrast to the behavior of normal midspectral cones. The scotopic matches were harder to evaluate and of less diagnostic value under conventional electroretinogram test conditions. Our routine scotopically balanced stimuli produced little response since our patients were insensitive to dim stimuli. The threshold signals were somewhat larger to red than to blue light, perhaps because we elicited a small midspectral cone response.[7]

Electro-oculography performed on several of our patients disclosed light/dark ratios that were reduced but not eliminated. The fast oscillations[13] of the electro-oculograms from two patients (Cases 1 and 7) were subnormal.

Discussion

This group of patients share an unusual but diagnostic set of clinical characteristics: long-standing night blindness and variably reduced visual acuity in association with dull or cystoid maculopathy; retinal degenerative changes in the region of the vascular arcades with relative ring scotomas; absent rod electroretinogram responses (to dim stimuli) but maximal dark-adapted responses that are large and slow, do not saturate with photopic background illumination, and do not reach a plateau of amplitude unless high stimulus intensities are used; and photopic electroretinogram responses that appear nearly identical with the scotopic ones, have an extremely long implicit time (relative to normal cone responses), show a mismatch to photopically balanced short and long wavelength stimuli, and do not augment with light adaptation.

The strikingly supernormal-appearing photopic responses in one subgroup of patients (Cases 1 to 5) are electrophysiologically distinct from those in any disorder of which we are aware. These large photopic signals may also be recognized in some patients who appear to have lower-amplitude responses (Fig. 7) by the use of unusually high-intensity stimuli. Although we are unaware of other conditions that show supernormal photopic responses homologous with scotopic responses, subnormal homologous responses may occur in diseases such

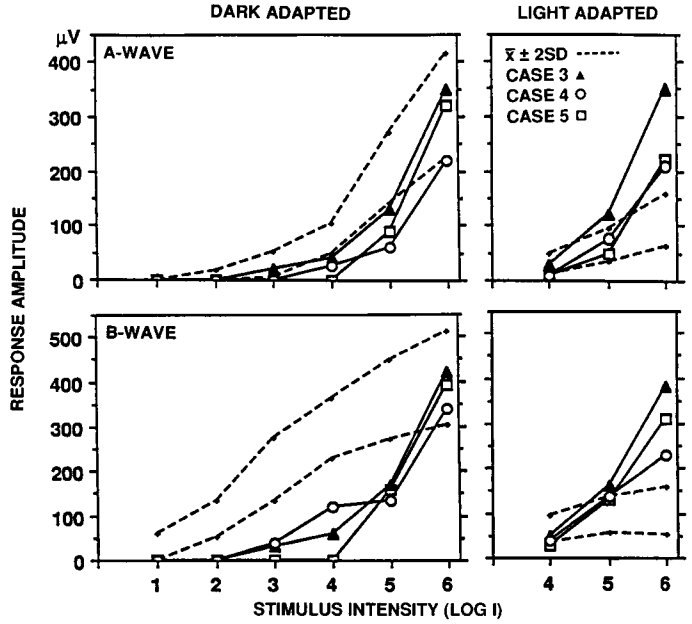

Fig. 9 (Marmor and associates). Representative stimulus-response curves for the a-wave and b-wave of the electroretinogram. Both responses are relatively insensitive to dim stimuli, but the curves rise more steeply than normal as stimulus intensity increases. Stimulus intensity 6 represents 7.8 cd·s·m^{-2}.

as rod-cone dystrophy in which a lack of rod function results in only the cone signal being detectable under both dark- and light-adapted conditions. Differentiation can be made most directly by comparing the light-adapted responses to photopically balanced stimuli. Our patients show a characteristic mismatch. Some cases previously reported as rod-cone dystrophy with foveal retinoschisis[3] or Goldmann-Favre disease[14] may represent this new syndrome. More severe dystrophies such as retinitis pigmentosa will be distinguished on

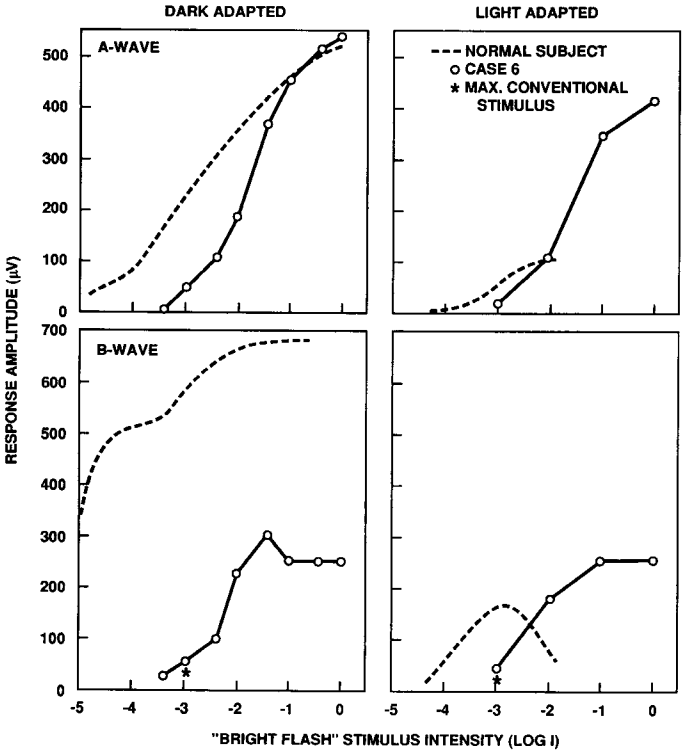

Fig. 10 (Marmor and associates). Case 6, Stimulus-response curves. These responses were generated with a photoflash unit designed to generate bright-flash electroretinograms through opaque media. Our standard maximal stimulus[9] of 3.0 cd·s·m^{-2} is indicated by the asterisk. The a-wave rose continuously with increasing stimulus intensity, but the b-wave reached a plateau about 1.5 log units below the maximal stimulus intensity. Note that the normal photopic b-wave diminishes at high stimulus intensities.

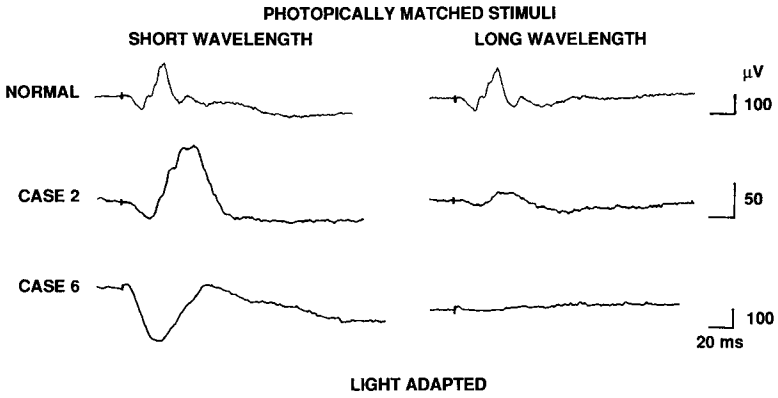

Fig. 11 (Marmor and associates). Examples of the light-adapted electroretinogram response to photopically balanced stimuli. Our patients showed a severe mismatch, with sensitivity biased markedly toward the short-wavelength stimulus. This finding is a critical diagnostic criterion for the syndrome.

the basis of symptoms, pigmentary changes, vascular narrowing, visual field loss, and loss of the electroretinogram under all conditions.

Our patients appear symptomatically similar to patients with congenital stationary night blindness, because they have poor night vision, mild to moderate loss of visual acuity, and they lack severe peripheral vision abnormalities. However, patients with congenital stationary night blindness do not have pigmentary degeneration in the arcade region or cystoid maculopathy, the scotopic electroretinogram shows a small or absent b-wave, and the cone electroretinogram is only mildly abnormal. Krill and Martin[15] described a few patients with congenital stationary night blindness and prolonged cone electroretinograms, which might represent unrecognized examples of this new syndrome (other clinical data are not available to allow a decision). The patients described by Keunen, Van Meel, and Van Norren,[5] which were shown to lack rhodopsin, also may represent examples of this disorder.

Our study does not allow a firm conclusion as to whether these patients have a stationary night blinding disorder with variable degrees (or evolution) of maculopathy or a slowly progressive dystrophy in which they are at some risk to lose peripheral visual field as well as central vision. The advanced degenerative changes in the arcade region and ring scotoma in our oldest patient (Case 8) suggest that this disorder may be progressive. There was considerable variability in expression, however, and there was no direct relationship of electroretinogram and visual field loss to age in our patients. Some of the older patients had large electroretinograms and normal visual fields, whereas younger ones had reduced-amplitude signals and scotomas. Even patients with low amplitudes may have the potential to generate large signals, such as in Case 6. The patients who have been followed up for more than four years showed variable degrees of visual acuity loss, but little or no change in the electroretinogram and little change in the area covered by retinal degenerative changes (although the pigmentation sometimes became more prominent).

Gouras and associates[4] described patients with electroretinogram characteristics similar to our patients. Their spectral electroretinogram recordings showed that the slow photopic responses were unusually sensitive to short-wavelength light, which led them to speculate that the response may be rod-mediated, although the mechanism by which rods could be insensitive to dim illumination yet fail to saturate under photopic conditions was unclear. One of us (M.F.M.) described previously[1] the extraordinarily large rodlike photopic electroretinograms in Case 1 and speculated that insensitive but nonsaturable rods might be involved, although the scotopic b-wave failed to decrease normally in implicit time with increasing stimulus intensity. Fishman and Peachey[6] described one patient with scotopic-photopic homology and lower-amplitude electroretinogram signals and stated once again that the photopic signals were rod-mediated.

The earlier descriptions all concluded that the large slow photopic responses represented signals from the rods. However, spectral sensitivity studies on three of our patients (Cases 1, 2, and 8) disclosed that they had no measurable rhodopsin and the large photopic electroretinogram responses were derived from short wavelength–sensitive cells (420 to 460 nm) that had the spectral properties of the S cones.[7] S cone sensitivity cannot be confirmed directly by conventional electroretinogram procedures, but the finding of large slow light-adapted respons-

es that are more sensitive to blue than red light is virtually pathognomonic.

The electroretinogram waveforms of our patients resemble the S cone responses that have been recorded with specialized techniques.[15] For example, S cone responses have a long implicit time, are insensitive to dim stimuli, persist over a photopic background, fail to saturate, maintain a constant implicit time with increasing stimulus intensity, and, of course, react unequally to photopically balanced stimuli.[16] Thus, we call this newly recognized disorder the enhanced S cone syndrome. The presence of an enhanced S cone response does not by itself indicate a loss of either midspectral cones or rods, or prove the cellular origin of the electroretinogram signals. Although the rod system is extremely insensitive in these patients, we do not know whether they lack rhodopsin in structurally normal rods, have rods that contain a short wavelength-sensitive photopigment instead of rhodopsin, have few rods with an excess of structural S cones, or derive some of their apparent S cone hypersensitivity from alterations of postreceptoral circuitry.

References

1. Marmor, M. F.: Large rod-like photopic signals in a possible new form of congenital night blindness. Doc. Ophthalmol. 71:265, 1989.

2. Marmor, M. F., and Jacobson, S. G.: A new form of night blindness with rod-like ERGs under photopic conditions. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1989, p. 45.

3. Noble, K. G., Carr, R. E., and Siegel, I. M.: Familial foveal retinoschisis associated with a rod-cone dystrophy. Am. J. Ophthalmol. 85:551, 1978.

4. Gouras, P., MacKay, C., Evers, H., and Eggers, H.: Computer assisted spectral electroretinography (case). A tool for examining hereditary retinal degenerations. In LaVail, M. M., Hollyfield, J. G., and Anderson, R. E. (eds.): Retinal Degeneration. Experimental and Clinical Studies. New York, Alan R. Liss, Inc., 1985, pp. 115–130.

5. Keunen, J. E. E., Van Meel, G. J., and Van Norren, D.: Rod densitometry in night blindness. A review and two puzzling cases. Doc. Ophthalmol. 68:375, 1988.

6. Fishman, G. A., and Peachey, N. S.: Rod-cone dystrophy associated with a rod system electroretinogram obtained under photopic conditions. Ophthalmology 96:913, 1989.

7. Jacobson, S. G., Marmor, M. F., Kemp, C. M., and Knighton, R. W.: SWS (blue) cone hypersensitivity in a newly identified retinal degeneration. Invest. Ophthalmol. Vis. Sci. 31:827, 1990.

8. Marmor, M. F., Arden, G. B., Nilsson, S. E., and Zrenner, E.: Standard for clinical electroretinography. Arch. Ophthalmol. 107:816, 1989.

9. Jacobson, S. G., Yagasaki, K., Feuer, W. J., and Roman, A. J.: Interocular asymmetry of visual function in heterozygotes of X-linked retinitis pigmentosa. Exp. Eye Res. 48:679, 1989.

10. Foerster, M. H., Kellner, U., and Wessing, A.: Cone-dystrophy and supernormal dark-adapted b-waves in the electroretinogram. Graefes Arch. Clin. Exp. Ophthalmol. In press.

11. Weleber, R. G., and Eisner, A.: Retinal function and physiological studies. In Newsome, D. A. (ed.): Retinal Dystrophies and Degenerations. New York, Raven Press, 1988, pp. 21–69.

12. Gouras, P., and MacKay, C. J.: Growth in amplitude of the human cone electroretinogram with light adaptation. Invest. Ophthalmol. Vis. Sci. 30:625, 1989.

13. Weleber, R. G.: Fast and slow oscillations of the electro-oculogram in Best's macular dystrophy and retinitis pigmentosa. Arch. Ophthalmol. 107:530, 1989.

14. Fishman, G. A., Jampol, L. M., and Goldberg, M. F.: Diagnostic features of the Favre-Goldmann syndrome. Br. J. Ophthalmol. 60:345, 1976.

15. Krill, A. E., and Martin, D.: Photopic abnormalities in congenital stationary nightblindness. Invest. Ophthalmol. Vis. Sci. 10:625, 1971.

16. Sawusch, M., Pokorny, J., and Smith, V. C.: Clinical electroretinography for short wavelength sensitive cones. Invest. Ophthalmol. Vis. Sci. 28:966, 1987.