Principles and Practice of Clinical Electrophysiology of Vision

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63

Retinitis Pigmentosa: Some Observations on the Course

Eliot L. Berson

Retinitis pigmentosa affects about 1 in 5,000 individuals worldwide.[1, 6, 19–22, 36, 38, 43] In the state of Maine in the United States, genetic types by family have been reported to be 19% autosomal dominant, 19% autosomal recessive, 8% X chromosome linked, 46% isolates, and 8% undetermined.[22] In England, the X-linked form has been reported to account for 16% of families and the autosomal recessive form for 7%.[38]

SYMPTOMS AND SIGNS

Patients with retinitis pigmentosa typically report abnormal adaptation, photophobia, night blindness, loss of midperipheral field, or some combination.[5, 25, 29, 34, 41] These symptoms usually appear by 20 years of age but can occur as late as 40 to 50 years of age. Patients usually lose their midperipheral visual field initially, then their far-peripheral field, and eventually, their central vision. As their fields become constricted, they report a tendency toward blue blindness. Some may compensate for field loss by moving their head or eyes and, for their night blindness, by avoiding scotopic conditions of illumination, thereby alleviating their symptoms so that a lack of symptoms does not exclude the possibility that an individual is affected.[9]

In the earliest stages, affected patients can have minimal if any changes on ophthalmoscopic examination. In more advanced stages, the characteristic fundus abnormalities include narrowed retinal vessels, depigmentation of the retinal pigment epithelium, intraretinal bone spicule pigment distributed around the midperipheral fundus, and waxy pallor of the optic discs. The bone spicule pigment is typically seen equidistant from the fovea in all quadrants in the midperipheral zone where rod photoreceptors are normally present in highest density. Some patients can have advanced disease with little if any pigment and will escape detection on ophthalmoscopic examination if the examiner does not observe retinal vessel attenuation. Other typical findings on routine ocular examination include pigmented cells in the vitreous,[44] posterior detachment of the vitreous,[44] and posterior subcapsular cataracts.[33] Hyaloid bodies of the optic nerve head[47] and cystoid macular changes[28] are seen in some cases, and refractive errors including astigmatism[14] and myopia[51] are common.

EARLY DETECTION WITH THE ELECTRORETINOGRAM

The initial reports of the electroretinogram (ERG) in primary retinitis pigmentosa revealed that affected patients had nondetectable or very small responses, but these patients had relatively advanced disease with attenuated retinal vessels and extensive pigmentary changes.[18, 39] More recent studies have shown that patients with early stages of retinitis pigmentosa could have subnormal ERGs to single flashes of light without computer averaging that were still large enough to separate into rod and cone components.[8, 11, 12, 30, 31] Some of these patients had minimal if any fundus abnormalities visible with the ophthalmoscope. Rod responses to blue light under dark-adapted conditions (Fig 63–1, left column) were reduced in all genetic types and, when detect-

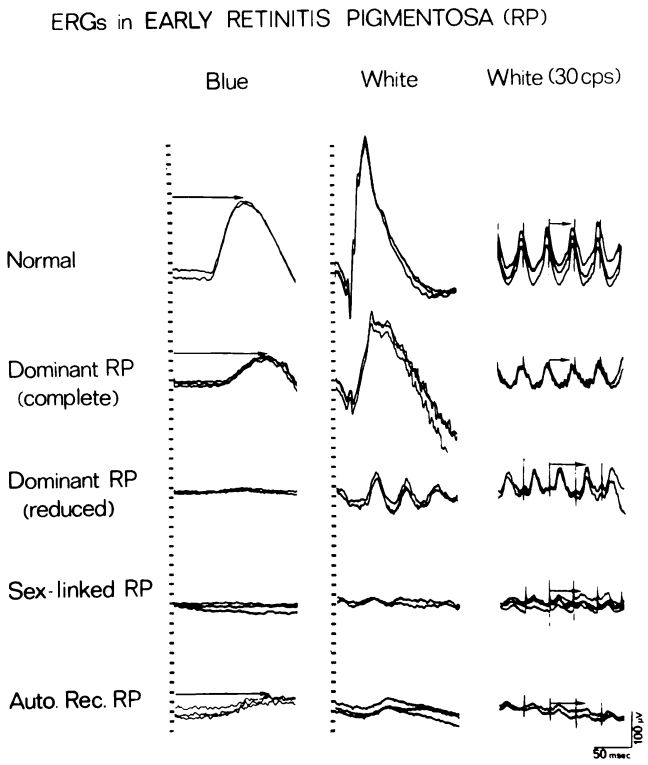

FIG 63–1.
Full-field ERG responses for a normal subject and four patients with retinitis pigmentosa (aged 13, 14, 14, and 9 years). Responses were obtained after 45 minutes of dark adaptation to single flashes of blue light *(left column)* and white light *(middle column)*. Responses *(right column)* were obtained to 30-cps (or 30-Hz) white flickering light. Cornea positivity is upward deflection. The calibration symbol *(lower right corner)* signifies 50 ms horizontally and 100 μV vertically. Rod b-wave implicit times in column 1 and cone implicit times in column 3 are designated with *arrows*. Normal ranges for peak-to-peak amplitude for patients 6 to 60 years of age with 6 or fewer diopters of myopia, clear media, and fully dilated pupils are blue, 100 to 275 μV; white, 350 to 700 μV; and white flicker, 50 to 125 μV. Normal rod b-wave implicit times range from 71 to 108 ms and normal cone b-wave implicit times from 25 to 32 ms. (From Berson EL: *Trans Am Acad Ophthalmol Otolaryngol* 1976; 81:659. Used by permission.)

able, were delayed in b-wave implicit time as designated by arrows. Cone responses to 30-Hz white flickering light (Fig 63–1, right column) were normal or reduced in amplitude with normal or delayed b-wave implicit times. In patients with the dominant form with reduced penetrance or the X-linked or autosomal recessive forms, cone b-wave implicit times, displayed by arrows in the right column, were so delayed that a phase shift occurred between the stimulus artifacts (designated by the vertical lines) and the response peaks; each flash elicited the next-plus-one response in contrast to the normal. In mixed cone-rod responses to single flashes of white light under dark-adapted conditions (Fig 63–1, middle column), the cornea-negative a-wave generated by the photoreceptors was reduced in amplitude in all types, thus pointing to involvement of the photoreceptors in the early stages. Isolate cases with a negative family history showed ERG waveforms comparable to those seen in siblings with autosomal recessive disease.[8]

In contrast to the subnormal responses with delayed b-wave implicit times seen in early stages of widespread progressive forms of retinitis pigmentosa, subnormal responses with normal b-wave implicit times have been observed in self-limited sector retinitis pigmentosa (Fig 63–2).[8, 13] For example, a

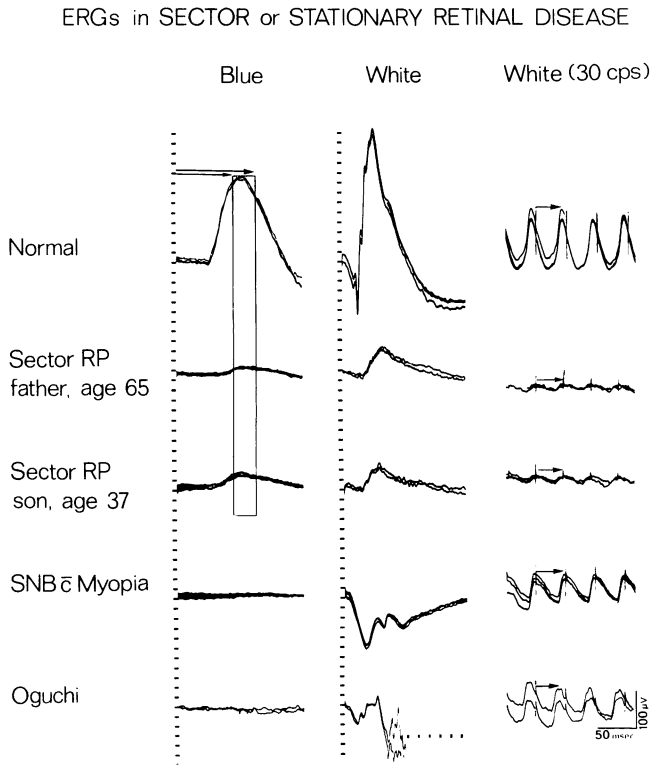

FIG 63–2.
Full-field ERG responses from a normal subject and four patients with sector or stationary retinal disease. *Horizontal arrows* (column 1) designate the range of normal rod b-wave implicit times, and a *vertical bar* defining this range (mean ± standard deviation) has been extended through the responses of patients with sector retinitis pigmentosa. Responses *(middle column)* from a patient with Oguchi's disease are interrupted by reflex blinking, so the latter part cannot be illustrated. Cone implicit times in column 3 are designated with *arrows*. (From Berson EL: *Trans Am Acad Ophthalmol Otolaryngol* 1976; 81:659. Used by permission.)

father and son with dominantly inherited sector retinitis pigmentosa who were separated in age by almost 30 years had comparably reduced amplitudes and normal b-wave implicit times. Specifically, rod b-wave implicit times were within the normal range designated by the vertical bars, and cone b-wave implicit times were within the normal range as each stimulus elicited the succeeding response. ERGs from a patient with stationary night blindness, myopia, and a defect in intraretinal rod signal transmission and from a patient with Oguchi's disease with a defect in rod neural adaptation also showed normal cone b-wave implicit times.

These findings, now substantiated in many patients evaluated over the past 20 years, have indicated that rod and cone b-wave implicit times can be used as an aid in establishing long-term visual prognoses since patients with self-limited sector retinitis pigmentosa or stationary night blindness have typically shown normal b-wave implicit times while patients with widespread progressive forms of retinitis pigmentosa have shown delayed b-wave implicit times.[6–8, 13, 16] Furthermore, at this time, no patient 6 years old or over has been observed with normal cone and rod amplitudes and normal cone and rod b-wave implicit times who later developed widespread retinitis pigmentosa.[6, 9, 10]

SPECIALIZED ELECTRORETINOGRAPHIC RECORDING TECHNIQUES

The earliest studies of the ERG in patients with retinitis pigmentosa were performed with electronic filters that passed responses unattenuated over a frequency bandwidth of several hundred hertz; under these test conditions, most patients had responses that were indistinguishable from noise (i.e., less than 10 μV).[18, 39] Narrow-band electronic filters that passed frequencies over a few hertz allowed the separation of retinal responses from noise in some patients who had apparently nondetectable ERGs recorded with wide-band filters.[35] Furthermore, summation of responses with computer averaging and wide-band filters made it possible to quantitate responses as small as 1 μV from patients with retinitis pigmentosa within a few minutes of testing.[2] With narrow-band filtering combined with computer averaging, the lower limit of detectability could be extended to 0.05 μV (a 20-fold increase in the signal-to-noise ratio) so that 90% of an outpatient population with retinitis pigmentosa and visual field diameters greater than 8 degrees had detectable responses.[15]

Figure 63–3 illustrates full-field cone ERGs to

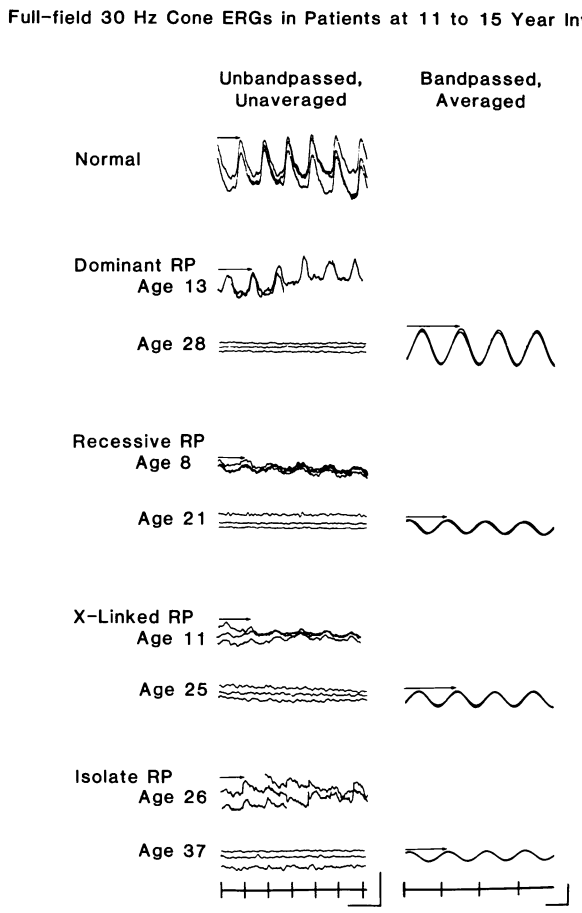

FIG 63–3.
Full-field 30-Hz cone ERGs from a normal subject and four patients with retinitis pigmentosa tested at an 11- to 15-year interval. Stimulus onset is shown by *vertical markers;* the calibration symbol *(left column, lower right)* designates 100 μV vertically for the normal subject and top three patients, 40 μV vertically for the *bottom* tracing, and 50 ms horizontally for all tracings. Calibration *(right column, lower right)* is 2 μV vertically for the dominant, X-linked, and isolate patients, 0.3 μV for the recessive patient, and 20 ms horizontally for all traces. b-Wave implicit times are designated by *arrows.* (*RP* = retinitis pigmentosa). (From Andréasson SOL, Sandberg MA, Berson EL: *Am J Ophthalmol* 1988; 105:503. Used by permission.)

30-Hz white light from four patients with retinitis pigmentosa who were tested initially and 11 to 15 years later without narrow-band–pass filtering and without computer averaging (left column) and also tested at the later time with narrow-band filtering and computer averaging (right column). Responses that were nondetectable (less than 10 μV) in the left column were now easily quantified with filtering and averaging (right column). Implicit times were comparable over time for each patient when comparing non–band-passed, unaveraged responses to

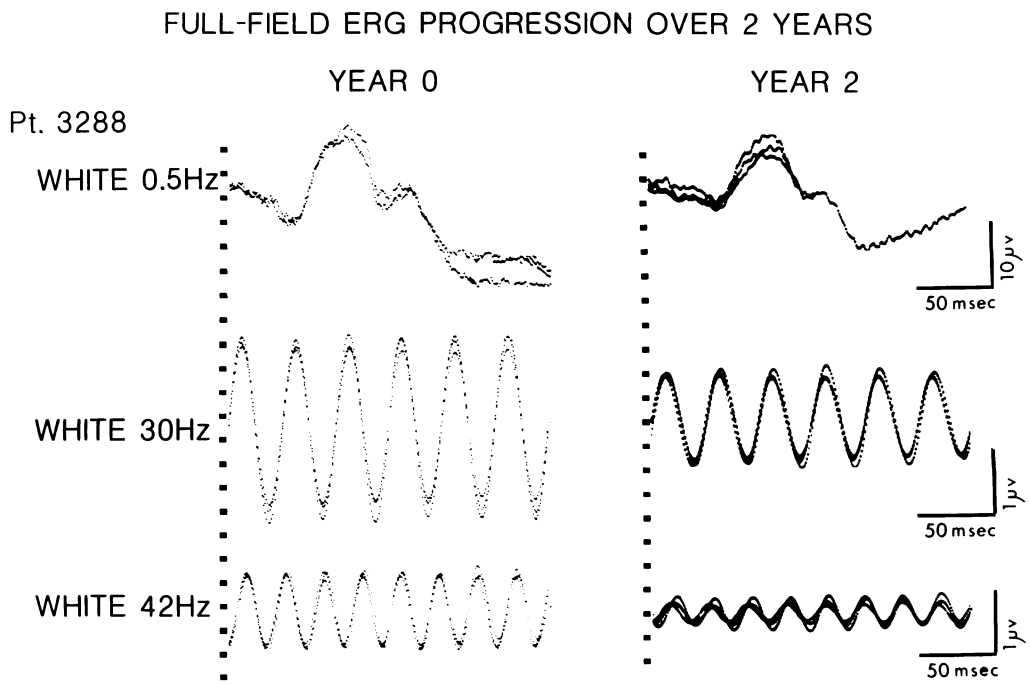

FIG 63–4.
Computer-averaged full-field ERGs from a 26-year-old man with X-linked retinitis pigmentosa that were obtained in response to 10-μs flashes of white light at 16,000 ft·lamberts presented at 0.5 Hz (n = 64), 30 Hz (n = 256), and 42 Hz (n = 256) at baseline *(Year 0)* and a 2-year follow-up *(Year 2)*. Three consecutive response averages are superimposed in each case. *Vertical broken lines* are normal flash onset for the 0.5-Hz condition and the onset of one of a train of flashes for 30-Hz and 42-Hz conditions. (From Berson, EL, Sandberg, MA, Rosner B, Birch DG, Hanson AH: *Am J Ophthalmol* 1985; 99:240. Used by permission.)

band-passed, averaged responses obtained 11 to 15 years later.[3]

Figure 63–4 shows full-field ERGs in a patient with X-linked retinitis pigmentosa over a 2-year period as monitored with computer averaging for mixed cone-rod responses to 0.5-Hz white light and with computer averaging and narrow–band-pass filtering for cone isolated responses to 30-Hz and 42-Hz white flickering light. Responses are significantly smaller at year 2 when compared with those recorded at baseline.[15]

NATURAL COURSE OF COMMON FORMS

A prospective study of 94 patients with retinitis pigmentosa, 1 per family, representing the autosomal dominant, autosomal recessive, X-linked, and isolate forms in approximately equal numbers was conducted to help define the natural course of the common forms of this condition over a 3-year interval.[15] Exclusion criteria included visual acuity less than 20/200 in both eyes, advanced cataracts that prevented visualization of the fundus, profound deafness, and age less than 6 years or greater than 49 years. Patients were evaluated with respect to Snellen visual acuity, Goldmann kinetic visual fields with a V-4_e white test light, dark adaptation thresholds to an 11-degree white test light, foveal ERGs to a 4-degree flickering white stimulus elicited with a stimulator-ophthalmoscope, full-field ERGs, and fundus appearance.

Some of these patients, randomly selected, were recalled within 2 months of a given visit to measure intervisit variability and develop criteria for what constitutes significant functional change (Table 63–1). For example, ERG amplitudes to 30-Hz flashes of white light would have had to decline by more than 44% to be certain with 99% confidence that change had actually occurred in any given patient. The visual field area would have had to decline by more than 22% to be certain at the $p < .01$ level of confidence that a patient had lost visual field.[15]

Changes in visual function in this study population are summarized in Table 63–2. By year 3, 77%

TABLE 63–1.

Threshold Criteria for Significant ($P < .01$) Change in Visual Function in a Study Population With Retinitis Pigmentosa*

			Change (%)†	
Test	*n*	ln Change	Loss	Improvement
Visual acuity	32	0.235	26	21
Visual field	28	0.252	22	29
Dark threshold	26	0.464	—	—
Foveal ERG	25	0.470	37	60
Full-field ERG				
0.5 Hz	27	0.369	31	45
30 Hz	29	0.575	44	78
37 or 42 Hz	27	0.617	46	85

*From Berson EL, Sandberg MA, Rosner B, Birch DG, Hanson AH: *Am J Ophthalmol* 1985; 99:240. Used by permission.
†Change relative to baseline.

had become worse or progressed, none had regressed, and 23% were unchanged on at least one full-field ERG test condition. The *P* value comparing number worse to number better was highly significant for all full-field ERG test conditions by year 2 and for the foveal ERG test condition by year 3. With respect to geometric means (Table 63–3), visual acuity changed on average over the 3-year interval from 20/39 to 20/40, and visual field area, expressed as equivalent circular diameter including all remaining islands of vision, decreased from a mean diameter of 66.5 degrees at baseline to a mean diameter of 61.9 degrees at year 3. Mean final dark-adapted thresholds remained comparable over this period. The mean full-field ERG amplitude to 0.5-Hz white light declined from 11.3 μV at baseline to 9.4 μV at year 1, 7.8 μV at year 2, and 6.7 μV at year 3; patients lost on average 16% of remaining amplitude per year. Full-field cone responses to 30-Hz flicker declined from 2.1 μV at year 0 to 1.1 μV at year 3; patients lost on average 18.5% of remaining full-field cone ERG amplitude per year. Over this 3-year interval, bone spicule pigment increased in 54% for whom comparisons could be made by inspection of fundus photographs, thus suggesting that this method of following the condition was not as sensitive as full-field ERG testing.[15, 49]

Caution must be exercised in applying these population results to predict longitudinal patterns in individual patients because standard deviations derived from standard errors indicated considerable variation about the mean for this population. However, these results provide a framework in which to consider risk factors that may be affecting the course of this condition, particularly as monitored by full-field ERG testing.[15]

TABLE 63–2.

Change in Visual Function in a Study Population With Retinitis Pigmentosa*

		Years 0–1				Years 0–2				Years 0–3			
Test	*n*	%–†	%+‡	%0§	*P*	%–	%+	%0	*P*	%–	%+	%0	*P*
Visual acuity	93	26	3	71	<.001	26	9	66	.007	23	11	67	NS
Visual field	92	21	16	63	NS	28	11	61	.012	33	14	53	.015
Dark adaptation threshold	75	21	15	64	NS	25	14	61	NS	23	19	59	NS
Foveal ERG	71	10	14	76	NS	13	14	72	NS	32	10	58	.005
Full-field ERG													
0.5 Hz	71	18	4	78	.021	49	4	46	<.001	62	0	27	<.001
30 Hz	82	13	4	83	NS	42	1	56	<.001	50	0	50	<.001
37 or 42 Hz	77	10	1	88	.039	37	1	62	<.001	44	0	56	<.001
Combined	86	24	6	70	.002	58	3	38	<.001	77	0	23	<.001

*From Berson EL, Sandberg MA, Rosner B, Birch DG, Hanson AH: *Am J Ophthalmol* 1985; 99:240. Used by permission.
†Percentage with disease progression.
‡Percentage with disease regression.
§Percentage with no change.

TABLE 63–3.
Mean Change in Visual Function Over 3 Years in a Study Population With Retinitis Pigmentosa*

Test	*n*	Geometric Mean				*P*			Annual Change (%)
		Year 0	Year 1	Year 2	Year 3	Years 0–1	Years 0–2	Years 0–3	
Visual acuity	91	20/39	20/45	20/44	20/40	<.001	<.001	NS	1.2
Visual field	90	3,463	3,395	3,197	3,011	NS	NS	.038	4.6
		66.5°	65.6°	63.8°	61.9°				
Foveal ERG (0.18 μV)†	67	0.15	0.16	0.15	0.13	NS	NS	.009	5.2
Full-field ERG									
0.5 Hz (350 μV)†	68	11.34	9.46	7.89	6.72	<.001	<.001	<.001	16.0
30 Hz (50 μV)†	76	2.16	1.76	1.28	1.17	<.001	<.001	<.001	18.5
37 or 42 Hz (44 μV)†	75	0.92	0.76	0.57	0.52	<.001	<.001	<.001	17.1

*From Berson EL, Sandberg MA, Rosner B, Birch DG, Hanson AH: *Am J Ophthalmol* 1985; 99:240. Used by permission.
†Lower norms.

RARE TREATABLE FORMS

One rare form of retinitis pigmentosa, potentially treatable if detected in an early stage, is that associated with hereditary abetalipoproteinemia (Bassen-Kornzweig syndrome).[4] These patients have fat malabsorption, generalized retinal degeneration, diffuse neuromuscular disease with ataxia, acanthocytosis, low serum cholesterol and triglyceride levels, and an absence of apolipoprotein B in their plasma.[37, 48] Untreated patients generally present with steatorrhea in childhood, ataxia in adolescence, and visual symptoms in early adult life.[50] Because they do not make chylomicrons, they cannot efficiently absorb fat and fat-soluble vitamins. Patients develop a deficiency of vitamins A and E in serum with consequent effects on retinal function and loss of photoreceptor cells.[24, 53] They also develop vitamin K deficiency and show excessive bleeding at surgery. Large doses of vitamin A have resulted in a return of the dark adaptation threshold and ERG responses to normal in the early stages, with a therapeutic effect

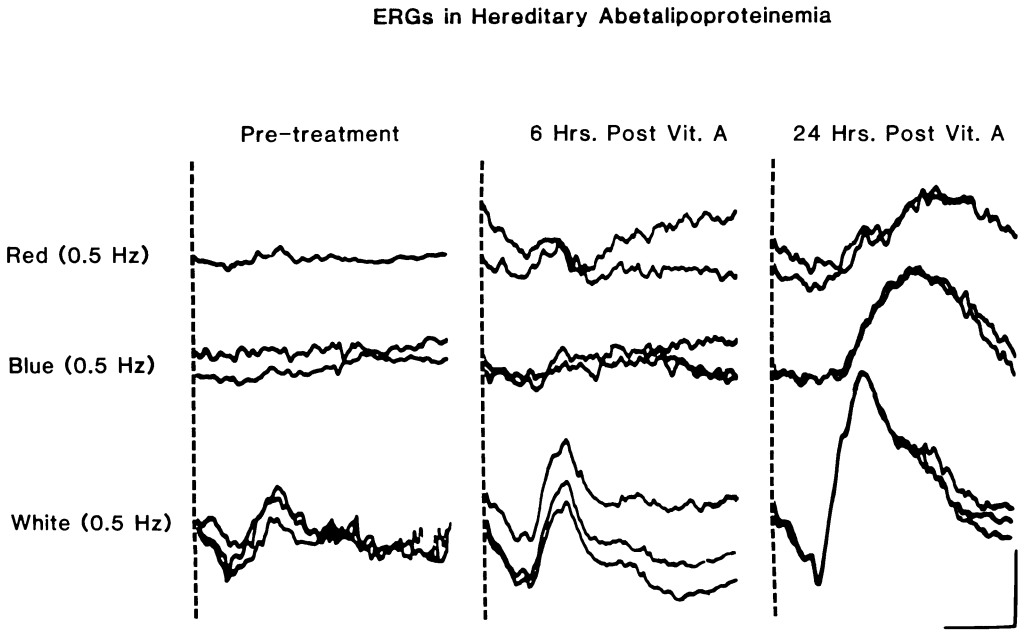

FIG 63–5.
Full-field ERGs to red *(top)* and blue *(middle)* light, equal for rod vision, and a brighter white stimulus *(bottom)* from a patient with hereditary abetalipoproteinemia (dark adapted). Responses in the *left column* were obtained before vitamin A therapy, those in the *middle column* at 6 hours, and those on *right* at 24 hours after vitamin A therapy. Two to three responses to the same stimulus are superimposed. Light stimulus begins with each trace. The calibration *(lower right)* signifies 0.06 mV vertically and 60 ms horizontally. (From Gouras P, Carr RE, Gunkel RD: *Invest Ophthalmol Vis Sci* 1971; 10:790. Used by permission.)

reported in one case within 24 hours after the administration of vitamin A (Fig 63–5).[23, 32] More advanced cases have not responded to treatment. Vitamin E has also been advocated to prevent the progression of this retinal degeneration.[17] The recommended treatment for this condition at present is fat restriction sufficient to minimize diarrhea and approximately 300 units/kg/day of vitamin A in water-soluble form, 100 units/kg/day of vitamin E, and 0.15 mg/kg/day of vitamin K.[50] Because these patients have a deficiency of essential fatty acids in their serum, omega-3 fatty acids (i.e., eicosapentanoic acid, and docosahexanoic acid) have also been recommended in the amount of 0.10 g/kg/day.[50] Serum levels of vitamin A should be monitored to avoid toxicity. The long-term effects of vitamin A and E and essential fatty acids in preserving retinal function in this condition remain to be established.

Another rare form of retinitis pigmentosa that is potentially treatable is that seen in association with Refsum's disease,[45] an inborn error of metabolism in which patients accumulate exogenous phytanic acid.[40] Findings include a peripheral neuropathy, ataxia, an increase in cerebrospinal fluid protein levels with a normal cell count, and retinitis pigmentosa. Some patients have a loss of smell, neurogenic impairment of hearing, electrocardiographic (ECG) abnormalities, and skin changes resembling ichthyosis. A defect exists in the conversion of phytanic acid to α-hydroxyphyanic acid.[26] The pathogenesis appears to involve an accumulation of phytanic acid in a variety of tissues including the pigment epithelium.[40, 52] Treatment consists of restricting not only animal fats and milk products (i.e., foods that contain phytanic acid) but also green leafy vegetables containing phytol.[27, 42] Success of treatment also depends on the patient maintaining body weight; if body weight becomes reduced, phytanic acid is released from tissue stores and results in an increase of phytanic acid in the serum and exacerbation of symptoms. Refsum has reported two patients whose serum phytanic acid levels were lowered to normal and who showed improvement in motor-nerve conduction velocity, some relief of ataxia, and return of cerebrospinal fluid protein levels to normal.[46] Moreover, the retinitis pigmentosa and hearing loss did not progress; one of his patients was followed for 10 years and the other for many years. A young adult with a mild form of this disorder has been reported to retain a stable ERG while maintained on a low-phytol, low–phytanic acid diet for 4 years (Fig 63–6).[6] The long-term effects of this diet on retinal function continue to be studied.

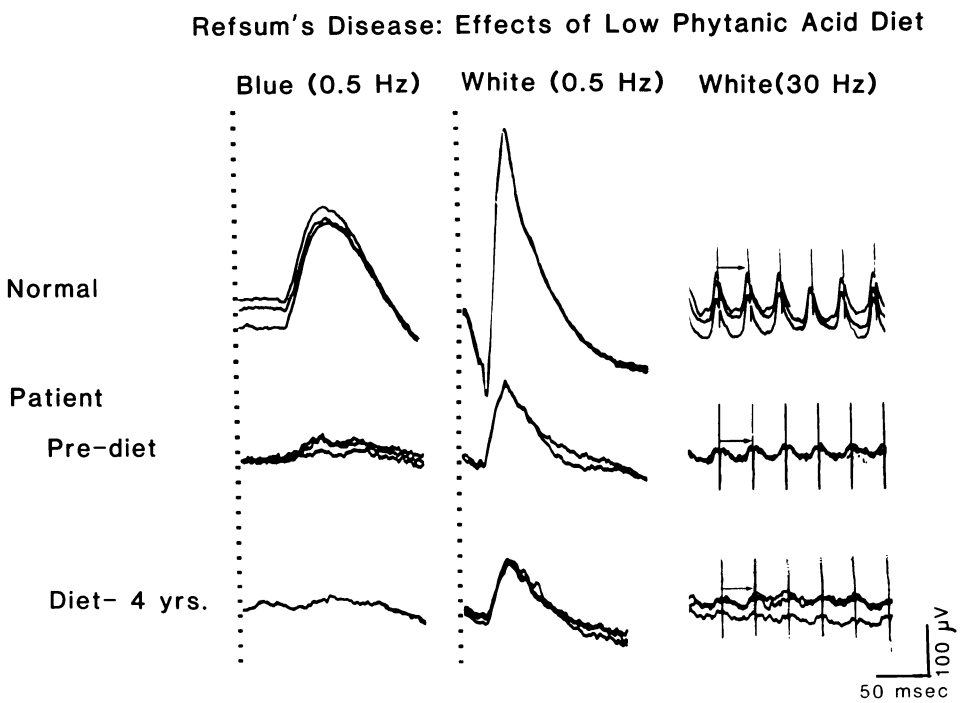

FIG 63–6.
Full-field ERGs from a normal subject and a patient with a mild form of Refsum's disease prior to and 4 years after treatment with a low-phytol, low–phytanic acid diet. Pretreatment responses were recorded at 31 years of age. (From Berson EL: *Jpn J Ophthalmol* 1987; 31:344. Used by permission.)

SUMMARY

Some progress has been made in defining the natural course of the common forms of retinitis pigmentosa on a year-to-year basis. Affected individuals can be identified in early life, even at a time when changes visible with an ophthalmoscope are minimal or absent, by demonstrating reduced ERGs with delayed temporal characteristics. Specialized recording techniques making use of both computer averaging and narrow-band–pass filtering have allowed quantification of retinal function in most patients. In a prospective study of an outpatient population, affected individuals aged 6 to 49 years lost on average 16% to 18.5% of remaining full-field ERG amplitude per year. It remains to be established to what extent these rates can be used to establish the course for individual patients.

Further study of the course of the condition prospectively in well-defined populations may reveal potential ameliorating or aggravating factors in the common forms. Two rare forms of retinitis pigmentosa, namely, those associated with abetalipoproteinemia and Refsum's disease, have yielded to specific treatments in selected patients once the biochemical defects were understood. Discovery of biochemical abnormalities in the common forms may set the stage for rational therapeutic trials for the majority of patients for whom no treatments are yet known.

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