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The Electroretinographic Diagnosis of the Incomplete Form of Congenital Stationary Night Blindness

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Fifteen patients with the incomplete form of congenital stationary night blindness (iCSNB) were reviewed to better characterize their electroretinographic (ERG) findings in view of differential diagnosis with other retinal conditions also presenting with negative bright-flash ERG responses. In all 15 patients, in dark-adapted conditions, the bright-flash ERG response had a normal *a*-wave followed by a subnormal *b*-wave. Oscillatory potentials (OPs) observed on the ascending limb of the *b*-wave, although delayed in implicit time, were of large amplitude. The response to a long-wavelength stimulus showed cone-related components and some well-delineated OPs. On the other hand, the photopically elicited cone responses were strongly abnormal, with a subnormal *a*-wave followed by a barely recordable *b*-wave. No OPs could be elicited under photopic conditions. The cone related components and the OP characteristics clearly distinguish iCSNB from the complete form of CSNB and other retinal conditions presenting with minimal fundus abnormalities but with negative bright-flash ERG responses, such as found in Duchenne muscular dystrophy and Åland Island eye disease. The severely abnormal post-synaptic components in the photopic recordings contrast with the well-differentiated cone activity evoked in scotopic conditions. We propose a cone system that does not respond optimally under the normal operating range (photopic) but rather under mesopic or scotopic conditions. In spite of the severe cone-ERG deficits, visual acuity was only slightly reduced. We propose that the defect, which interferes marginally with the neuronal flow of information, lies in the structures responsible for the building of the *b*-wave.

Electroretinogram Incomplete congenital stationary night blindness Complete congenital stationary night blindness Electronegative response Retina Cone Nyctalopia Nystagmus Amblyopia

INTRODUCTION

Congenital stationary night blindness (CSNB) is described as a set of inherited, non-progressive retinal conditions in which the rod pathway is primarily affected, resulting in an elevation of the dark adaptation threshold and night blindness (Carr, 1991; Keunen, Meel & Norren, 1988; Young, Price & Harrison, 1986; Ripps, 1982; Auerbach, Godel & Rowe, 1969; Riggs, 1954; Schubert & Bornschein, 1952). In spite of normal looking fundi, myopia, reduced visual acuity, nystagmus, strabismus and constricted scotopic visual field have also been found to be associated in a non-specific manner with this condition (Pearce, Reedyk & Coupland, 1990; Price, Juddisch & Thompson, 1988; Heckenlively, Martin & Rosenbaum, 1983; Merin, Rose, Auerbach, 1970). Because of the variability of the clinical presentation, only a high index of suspicion will lead the clinician to order electroretinography, which has become an invaluable diagnostic tool in CSNB.

Electroretinograms (ERGs) in CSNB show essentially two patterns with very characteristic features. The Riggs type, which is infrequent, presents with attenuated *a*- and *b*-waves in both photopic and scotopic conditions (Riggs, 1954). The Schubert–Bornschein type, on the other hand, can be recognized by a severely reduced rod-related activity and by a negative ERG to a bright flash scotopic stimulus: namely, the *a*-wave is of normal amplitude while the *b*-wave is subnormal (Schubert & Bornschein, 1952). In a review of 64 cases, Miyake, Yagasaki, Horiguchi, Kawase and Kanda (1986) distinguished two forms of Schubert-Bornschein type of CSNB. In 35 patients with the complete form (cCSNB), the rod-related activity is non-recordable; a severe night vision deficit is observed. The cone-related portion of the ERG signal is also affected. The *a*- and *b*-waves have normal or near-normal amplitude but the absence of

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early oscillatory potentials (OPs) gives to the waveform a particular truncated appearance (Heckenlively *et al.*, 1983; Lachapelle, Little & Polomens, 1983; Hill, Arbel & Berson, 1974; Krill & Martin, 1971). This could be caused by a defect in the depolarizing bipolar cells (Alexander, Fishman, Peachey, Marchese & Tso, 1992). In 20 other patients, an electronegative bright-flash ERG is also found but the rod-related activity is less profoundly reduced and the cone-related ERG is often almost unrecordable. The night vision deficit is minimal. This was classified as an incomplete form (iCSNB). The complete and incomplete forms of CSNB overlap considerably in their clinical presentation (Miyake, 1991; Miyake *et al.*, 1986).

The ERG findings in iCSNB must be differentiated from several new retinal conditions that also share the negative bright-flash dark-adapted response as their prominent ERG characteristics (Cibis, Fitzgerald, Harris, Rothberg & Rupani, 1993; De Becker, Riddell, Dooley & Tremblay, 1994; Kellner & Foester, 1993; Perlman, Leibu & Barth, 1993; Pillers *et al.*, 1993a, b; Weleber, Tongue, Kennaway, Budden & Buist, 1984). For instance, it is not yet clear if the retinal conditions described for Oregon eye disease (OED); (Pillers *et al.*, 1993a) and Duchenne muscular dystrophy (DMD); (DeBecker *et al.*, 1994; Cibis *et al.*, 1993; Pillers *et al.*, 1993b) are similar to either cCSNB or iCSNB or if they deserve a specific definition. In order to help clarify this situation, we reviewed 15 patients with iCSNB and analysed their ERG characteristics with the hope of a better definition of what iCSNB is and how it can be differentiated from other conditions also presenting with somewhat similar retinal phenotypes.

MATERIALS AND METHODS

Patients

Fifteen patients with iCSNB were identified from a retrospective chart review. All were males with reduced visual acuity and negative bright-flash ERGs. Age ranged from 10 months to 32 yr (median age: 7 yr). All patients were thoroughly examined by one of us (IDB or RGLR; refer to Table 1). Visual acuity was measured by Allen or Snellen charts and the refractions performed under cycloplegic conditions. For diagnostic comparison purposes, the ERGs of 10 patients with a diagnosis of cCSNB (median age: 6 yr) were reviewed. The cCSNB diagnosis was established from the characteristic ERGs, the presence of night blindness and the reduced visual acuity. Dark adaptation was performed on the older children but were found to be unreliable on retest; consequently, data were not used as a diagnostic criteria and are not included in this study.

TABLE 1. Clinical presentation

Case	Age*	Initial visit	Refraction	Visual acuity†	Fundi	Optic disk	Macula	Nystagmus	Others
1	11	Difficulty with reading	−6.25 + 2.00 × 120 −5.50 + 2.00 × 80	0.3 0.3	Light pigmentation	Pale	Normal	Latent	400′ Titmus
2	32	Low V.A.	NA	NA	NA	NA	NA	NA	NA
3	4	F. Hx. (case 4)		0.25 0.25	Normal	Pale	NA	No	
4	7	Optic disk pallor	NA	0.25 0.4	Normal	Pale	NA		
5	8	F. Hx. (case 6)	−12.00 + 3.25 × 100 −12.00 + 2.75 × 75	0.7 0.7	Light choroidal pigmentation	Elongated but normal coloration	No foveal reflex	No	100′ Titmus
6	4	Optic disk pallor	1.25 + 2.25 × 120 1.00 + 2.25 × 65	0.3 0.3	Light choroidal pigmentation	Tilted disk & temp. hypoplasia		No	60′ Titmus
7	7	Low V.A. ? Optic atrophy	1.25 + 2.25 × 100 1.00 + 2.25 × 90	0.4 0.4	Normal	Very pale	Normal	Horizontal	100′ Titmus VEP
8	10m	abN visual dev. Leber's	−2.000.U.	0.25 0.25	Peppered	Temporal pallor chorio-retina	Normal		Upbeat
9	4	F. Hx (case 8)	Hyperopia O.U.	0.3 0.4	Normal	Bilateral O.N. hypoplasia	Normal	No	VEP
10	6	Photodysphoria reduced V.A.	NA	0.5 0.5	Blond 6/12	Pale	Normal	Latent	N. D15
11	4	F.Hx (case 10) Photodysphoria	1.25 + 1.25 × 120 1.00 + 1.75 × 65	0.3 0.3	Normal	0.3 cupping	Normal	No	
12	9	Reduced V.A. amblyopia	−1.25 + 2.50 × 100 −1.25 + 2.50 × 90	0.8 0.5	Normal	Pale	Normal	Small vertical	VEP 100 Hues
13	13	Nystagmus exc. fixation	NA	0.7 0.5	Normal	Temporal pallor	Normal	Cyclorotatory	
14	5	Reduced V.A.	NA	0.6 0.3	Normal	Normal?	Normal	No	VEP Normal D15
15	3	Nystagmus	NA	0.5 0.3	Blond	Normal	Normal	Horizontal	VEP

NA, not available.
*Age when first seen.
†Best corrected visual acuity.

Electrophysiological recordings

The electrophysiological protocol included an initial period of dark adaptation under controlled dim red illumination (30 min) during which time the procedures were explained to the patient. Cutaneous gold electrodes were fixed to the forehead (reference) and right earlobe (ground) after skin preparation. After pupil dilatation and topical corneal anaesthesia, a contact lens (Lovac type, Medical Workshop, The Netherlands) was set on the cornea. A Ganzfeld stimulator (Nicolet GS2000, Madison, Wis.) produced a series of short (Kodak Wratten # 47,a, b, Rochester, N.Y.) and long (Kodak Wratten # 27) wavelength stimulation in scotopic condition, in order to characterize the dark-adapted rod and cone components. Bright white-flash stimulation ($1.0\,cd \cdot m^{-2} \cdot sec$) was also used to estimate the total retinal output. Single white-flash stimulation ($10.1\,cd \cdot m^{-2} \cdot sec$) under photopic condition ($34\,cd \cdot m^{-2}$) and 33.3 Hz flicker stimulation were delivered after a minimum of 5 min of light adaptation to provide an estimate of the cone activity. The amplifier's bandpass was set at 1 Hz–1 kHz in a first channel to record the standard ERG, and to 100 Hz–1 kHz in a parallel channel to allow the simultaneous recording of the oscillatory potentials. An artifact-rejection device eliminated data contamination from eye movements and an averager (Nicolet Pathfinder II) cumulated and stored the raw data. This protocol was in agreement with the minimum requirements stated by the International Society for Clinical Electrophysiology of Vision's Standardization Committee (Marmor, Arden, Nilsson & Zrenner, 1989).

A modified version of this protocol was also used in three patients who were seen on subsequent occasions. In this protocol, the photopic portion of the ERG was tested first, after at least 20 min spent in a controlled photopic environment [$20\,cd \cdot m^{-2}$ for 15 min (room illumination) and $34\,cd \cdot m^{-2}$ for 5 min (Ganzfeld background illumination)]. The scotopic portion of the ERG was then recorded after 25 min of dark adaptation; short and long wavelength stimuli as well as bright flash stimulation were generated with the same parameters as in the other protocol. Following this, photopic conditions were reset and every 2 min flashes were given to quantify the light adaptation dynamic. This protocol was given in order to test the hypothesis of an exaggerated suppression of the cone response by the dark-adapted rods (as hypothetized by Myake, Huriguchi, Ota & Shiroyama, 1987).

Measurements and statistical analysis

Electroretinogram normative data was obtained using the same protocol on a control group ($N = 20$; median age, 13 yr). Amplitude measurements were taken from the pre-stimulus baseline to the first trough for the *a*-wave and from the *a*-wave trough to the positive peak for the *b*-wave. Oscillatory potential amplitude was calculated according to the square caliper method (from a line joining the preceding and following throughs). Implicit time were measured from the stimulus artifact to the peak of the corresponding wave. All ERG parameters measured in either the normal and the patient groups were initially tested for fitness to a normal distribution (Kolmogorov–Smirnov two-sample test; $P < 0.05$). Subsequently, all measurements were tested through a paired *t*-test ($P < 0.05$). Comparison was performed between the iCSNB group and both the normal and the cCSNB groups.

RESULTS

The patients

Detailed case presentation and clinical findings are given in Table 1. Visual acuity and refractive errors were variable. Six patients demonstrated mild nystagmus with no particular pattern. A fundus examination did not reveal any definite characteristic. Ten patients had well-defined macular reflex and all but three did show partial (mostly temporal) or complete optic disk pallor. The initial complaints at the first visit were diversified: five because of subnormal vision, three with a previous diagnosis of optic nerve atrophy, two for nystagmus; another for mild photodysphoria; and finally, four were siblings of an affected patient. Patient 8, the youngest, had been initially diagnosed with Leber's amaurosis. None of these patients complained of night vision impairment.

The ERG recordings

The *photopic* cone ERGs of all patients are illustrated in Fig. 1. The quantitative data is in Table 2. Following the flash onset only a small negativity can be observed. This can be better visualized in the group-average ERGs (cf. AVE. iCSNB with AVE. NORMAL and AVE. cCSNB tracings). The initial negativity is well defined and, although slightly smaller in amplitude than the normal *a*-wave, its temporal decay is similar. Its peak time is longer due to the absence of a well-demarked *b*-wave onset. The *b*-wave peak time is prolonged and the amplitude is markedly reduced to the point it does not reach back to the baseline level thus giving the waveform an electronegative appearance. The right side of Fig. 1 depicts the OPs. No consistent pattern emerges from the OPs in iCSNB, even in the group-averaging. The average obtained for the cCSNB group shows the well delineated truncated *b*-wave and one OP (OP4). The flicker activity has also been recorded (not illustrated). In iCSNB, there is no activity that could be visualized on the raw recordings or after a fast Fourier transform. This is in contrast with cCSNB.

The *scotopic* cone ERG (Fig. 2, quantitative data in Table 3) is not suppressed, as one would have expected from the photopic recordings. The recordings were obtained with long-wavelength stimulation, after 30 min of dark adaptation. There is some early activity in the time-domain where the cone activity is expected in normal subjects. This activity is delayed and the *x*-wave is not well demarked. As many as three, and often four OPs are seen. The amplitude of the three first OPs is normal but they are delayed. Conversely, the rod *b*-wave

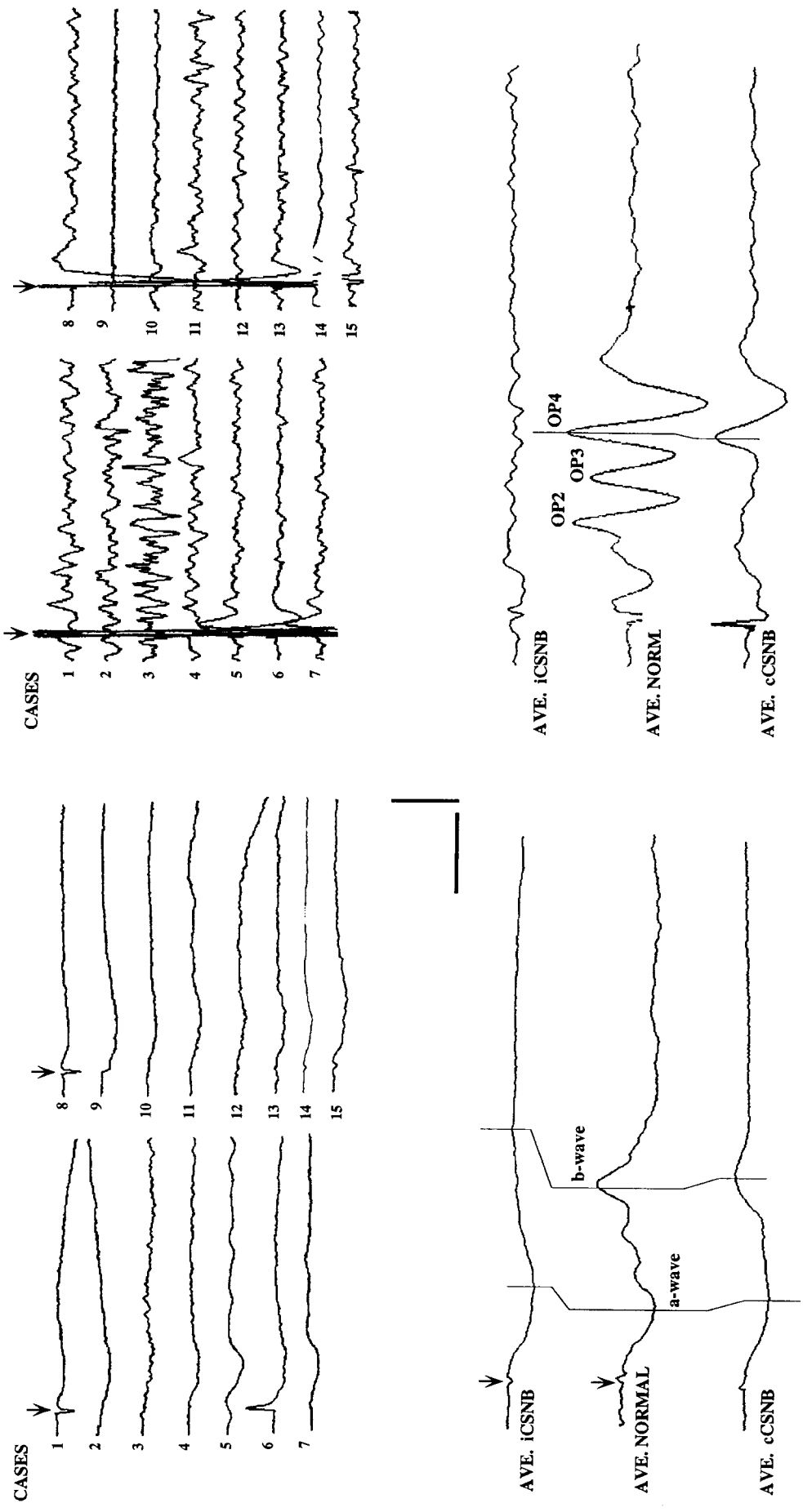

FIGURE 1. Electroretinographic recordings (left side, full bandwidth 1–1 kHz; right side, restricted bandwidth 100–1 kHz) obtained under photopic conditions in patients with iCSNB. Individual recordings are shown in the upper part of the figure (numbers refer to case No. in Table 1) while group average are presented in the bottom part along with group averages from normal and patients with cCSNB. Vertical lines are provided to help make the correspondence between identical components. Arrow: flash onset. Horizontal calibration: traces 1–15, 25 msec; averagings, 15 msec. Vertical calibration: traces 1–15, 500 μV for ERGs and 50 μV for OPs; averagings, 175 μV for ERGs and 15 μV for OPs.

has a normal implicit time but is severely attenuated in amplitude. In cCSNB only OP5 could be reliably identified; the wide-band ERG shows the absence of early cone activity but the presence of a well-delineated *x*-wave.

The *scotopic* bright flash (Fig. 3, quantitative data in Table 3) produces a slightly smaller *a*-wave in iCSNB. The slope of the *a*-wave is similar in both the patients and the normal subjects with the characteristic cone-notch corresponding to the presence of OP2 the implicit time of which was significantly delayed. The *b*-wave has a significantly reduced amplitude, which produces the characteristic electronegative waveform. The culmination time is also shorter. The OPs are of relatively large amplitude and the three first ones (OP2–OP4) are usually well defined. OP5 is often absent or extremely reduced in amplitude. In normals, OP3 is the largest OP and the one that increases the most during dark adaptation. In our patients, such an increase is not observed and causes OP3 and OP2 to remain equal. OP4 and OP5 are often present but generally severely reduced. All those OPs are delayed in their implicit time. In comparison, cCSNB reveals electronegative response that lacks the cone notch on the descending *a*-wave and shows no oscillation on the ascending limb of the *b*-wave. Quantitative data (Table 3) reveal that the *b*/*a* ratio is smaller than in iCSNB but that the *a*-wave amplitude is similar. Only OP5 can be reliably recorded. The pure rod-related activity is subnormal in iCSNB but of extremely low amplitude when recordable in cCSNB (not shown).

The effect of light adaptation on the *photopic* cone-related activity was also investigated in the most cooperative patients (Fig. 4). Cone ERGs were obtained after 2, 4, 8 and 10 min of light adaptation under Ganzfeld illumination of 34 cd/m^{-2} (enough to saturate the rod signal). The data from the *a*-wave measurements superimpose adequately with normal data. For the *b*-wave, which is much smaller in amplitude, no increase in the slope of the curve could be demonstrated to corroborate an exaggerated suppressive effect during dark adaptation.

DISCUSSION

The ERGs in this group of 15 patients with iCSNB are all very similar. The rod activity is severely reduced, reaching about 25% of the normal amplitude. This is in contrast with cCSNB where there is no detectable rod activity (Carr, 1991). In iCSNB, the electronegative bright-flash response presents with the typical cone-notch on the descending limb of the *a*-wave and several OPs (OP2–OP5 in Fig. 3) can be identified on the ascending limb of the *b*-wave. In cCSNB, the waveform shows only OP5. With a *scotopic* long-wavelength stimulation, iCSNB produces early oscillatory activity and a subnormal rod response. Isolated OPs are almost of normal amplitude, though they are delayed. In cCSNB, no such early activity can be detected; only the *a*- and *x*-waves are present, without rod-related components. On the other hand, the *photopic* cone activity is very abnormal in iCSNB, with a subnormal and delayed *a*-wave, a barely recordable *b*-wave and no single-sweep flicker activity. In cCSNB, the *b*-wave can be identified, having a very peculiar "square-wave appearance" due to the absence of early OPs (Lachapelle *et al.*, 1983; Heckenlively *et al.*, 1983). There is also a flicker activity. These differences in the electroretinographic recordings clearly distinguish the two entities which, otherwise, cannot be clearly separated by clinical findings alone (Miyake, 1991; Miyake *et al.*, 1986). Linkage analysis locates the gene for cCSNB at Xp11 but no information is yet available for iCSNB.

The differential diagnoses of the electronegative bright-flash ERG includes X-linked congenital retinoschisis (Peachey, Fishman, Derlacki & Brigell, 1987), paraneoplastic syndrome associated with melanoma (Milam, Saari, Jacobson, Lubinski, Feun & Alexander, 1993), central retinal vein occlusion (Johnson, 1991), quinine (Bacon, Spalton & Smith, 1988) and vincristine intoxications (Ripps, Carr, Siegal & Greenstein, 1984), Oguchi's disease (Kubota, 1965), infantile Refsum's disease (Weleber *et al.*, 1984) and optic

TABLE 2. Quantitative ERG data and statistical analysis in iCSNB, cCSNB and normal: photopic conditions

Variable	iCSNB mean ± 1 SD	Normal mean ± 1 SD	cCSNB mean ± 1 SD	iCSNB / Normal	iCSBB / cCSNB
Latency (msec)					
a-Wave	16.5 ± 1.4	13.2 ± 0.5	15.1 ± 1.0	*	*
b-Wave	40.9 ± 4.4	34.5 ± 1.8	37.7 ± 5.1	*	NS
OP2	— —	15.8 ± 0.4	— —	—	—
OP3	— —	23.3 ± 0.8	— —	—	—
OP4	— —	32.8 ± 1.5	31.7 ± 1.1	—	—
Flicker	— —	30.7 ± 2.3	32.1 ± 2.3	—	—
Amplitude (μV)					
a-Wave	50.8 ± 11.6	76.9 ± 15.6	72 ± 13.0	*	*
b-Wave	57.1 ± 15.8	178.2 ± 45.3	127 ± 20.0	*	*
OP2	— —	26.4 ± 5.9	— —	—	—
OP3	— —	25.3 ± 8.9	— —	—	—
OP4	— —	36.8 ± 11.2	26.6 ± 8.6	—	—
Flicker	— —	193.1 ± 41.0	118.2 ± 33.4	—	—

*Significant difference (paired *t*-test, $P < 0.05$).
NS, no significant difference.
—, components absent.

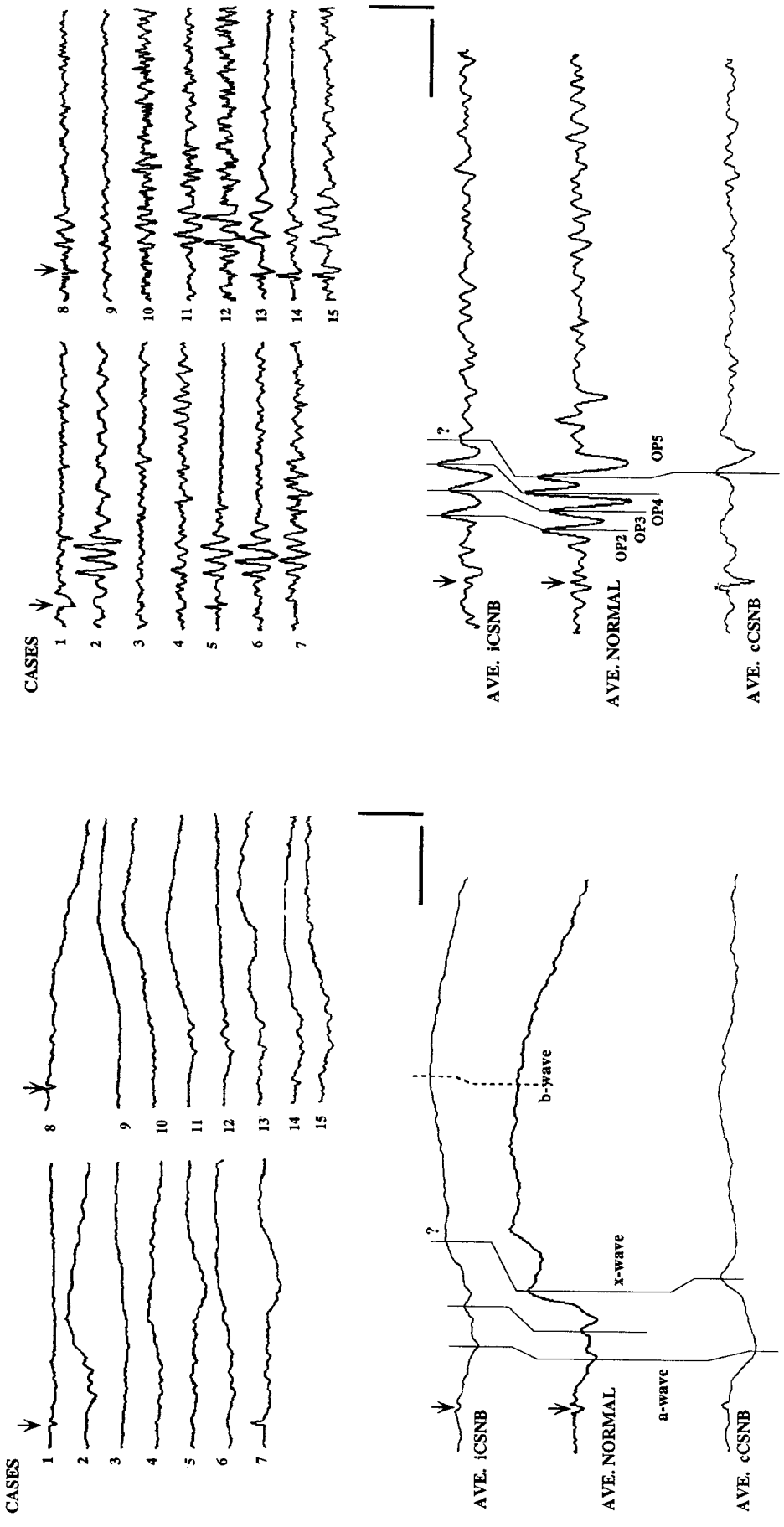

FIGURE 2. Electroretinographic recordings obtained under scotopic conditions with a long-wavelength stimulus in patients with iCSNB. Presentation as in Fig. 1. Horizontal calibration: traces 1 15, 50 msec; averagings, 30 msec. Vertical calibration: traces 1 15, 500 μV for ERGs and 50 μV for OPs; averagings, 175 μV for ERGs and 15 μV for OPs.

atrophy (Weleber & Miyake, 1992) (for a review see Heckenlively, Weleber & Arden, 1991). They can be differentiated from iCSNB on the basis of distinctive ERG findings or on characteristic clinical presentation.

Patients with DMD (deletion at Xp21.3) have recently been described as having an electronegative *scotopic* bright-flash ERG (De Becker *et al.*, 1994; Pillers *et al.*, 1993b; Cibis *et al.*, 1993). The muscular atrophy in DMD indeed distinguishes the two entities but it may be absent in young subjects (Bushby, 1992). The electroretinographic difference between DMD and iCSNB resides in the normalcy of the cone-related responses in DMD which contrasts with the severely attenuated *b*-wave and absence of OPs in iCSNB. Patients with DMD also have normal ophthalmological findings and, in particular, visual acuity of 6/6 or better (DeBecker *et al.*, 1994).

Åland Island eye disease (AIED) and complex glycerol kinase deficiency [(CGKD) or OED] are also reported with a negative bright-flash ERG along with a reduced rod-related activity and a subnormal cone-related response. CGKD/OED results from defects in the dystrophin gene, which resides in Xp21, whereas the gene or genes involved in AIED and iCSNB probably both reside in the Xp11 region (Schwartz & Rosenberg, 1991; Pillers *et al.*, 1993a). Patients with AIED and CGKD may have ocular hypopigmentation, an ocular characteristic that helps in differentiating them from iCSNB. However, from an ERG point of view, the distinction can be difficult and it is conceivable that the ERG phenotypes in AIED and iCSNB could be expressed similarly from two different gene locations.

Finally, three male patients with progressive cone dystrophy, progressive loss of vision, colour discrimination impairment, central scotoma and macular pigmentary changes and with electronegative bright-flash ERG, have been described by Kellner and Foerster

TABLE 3. Quantitative ERG data and statistical analysis in iCSNB, cCSNB and normal: scotopic conditions

Variable	iCSNB mean ± 1 SD	Normal mean ± 1 SD	cCSNB mean ± 1 SD	iCSNB / Normal	iCSBB / cCSNB
Short wavelength					
Latency (msec)					
b-Wave	64.5 ± 6.3	55.8 ± 2.9	56.6 ± 6.3	*	*
Amplitude (μV)					
b-Wave	99.0 ± 58.5	406.5 ± 75.3	48 ± 24.0	*	*
Long wavelength					
Latency (msec)					
a-Wave	21.8 ± 2.2	17.3 ± 0.6	19.3 ± 1.7	*	*
x-Wave	52.4 ± 7.4	44.6 ± 1.8	45.3 ± 1.9	*	*
b-Wave	94.8 ± 7.0	92.3 ± 3.2	— —	NS	—
OP2	24.6 ± 1.2	19.9 ± 1.0	— —	*	—
OP3	33.5 ± 1.7	26.6 ± 1.1	— —	*	—
OP4	43.1 ± 2.5	34.2 ± 1.8	— —	*	—
OP5	51.4 ± 3.4	40.2 ± 1.9	41.2 ± 1.4	*	*
Amplitude (μV)					
a-Wave	34.0 ± 15.1	43.8 ± 11.0	43.2 ± 14.0	*	*
x-Wave	48.1 ± 36.3	207.4 ± 50.3	55.5 ± 19.9	*	NS
b-Wave	109.2 ± 42.6	215.5 ± 43.1	— —	*	—
OP2	12.6 ± 6.4	16.3 ± 4.0	— —	NS	—
OP3	13.9 ± 7.9	23.5 ± 10.4	— —	NS	—
OP4	14.8 ± 9.2	26.7 ± 13.5	— —	NS	—
OP5	13.4 ± 4.3	26.9 ± 11.2	10.5 ± 5.0	*	NS
Sum of OPs	64.7 ± 33.1	123.9 ± 45.2	10.5 ± 5.0	*	*
Bright flash					
Latency (msec)					
a-Wave	25.4 ± 1.7	22.7 ± 0.6	22.3 ± 1.0	*	*
b-Wave	41.4 ± 2.8	45.1 ± 1.8	43.7 ± 3.9	*	NS
OP2	21.4 ± 2.1	18.1 ± 0.5		*	—
OP3	29.5 ± 1.8	25.1 ± 0.5	— —	*	—
OP4	37.7 ± 2.4	31.5 ± 0.7	— —	*	—
OP5	49.3 ± 3.3	38.5 ± 1.1	42.7 ± 2.7	*	*
Amplitude (μV)					
a-Wave	197.8 ± 29.7	261.5 ± 46.9	204.1 ± 37.0	*	NS
b-Wave	160.9 ± 57.1	416.7 ± 100.1	132.3 ± 30.0	*	NS
b/a Ratio	0.8 ± 0.2	2.0 ± 0.3	0.6 ± 0.1	*	*
OP2	19.9 ± 10.3	29.7 ± 5.9		*	—
OP3	65.6 ± 34.5	130.5 ± 49.4	— —	*	—
OP4	19.1 ± 9.9	38.6 ± 20.3	— —	*	—
OP5	12.0 ± 5.3	23.6 ± 11.7	11.0 ± 7.7	*	NS
Sum of OPs	110.2 ± 43.9	222.5 ± 81.4	29.3 ± 12.5	*	*

*Significant difference (paired *t*-test, $P < 0.05$).
NS, no significant difference.
—, components absent.

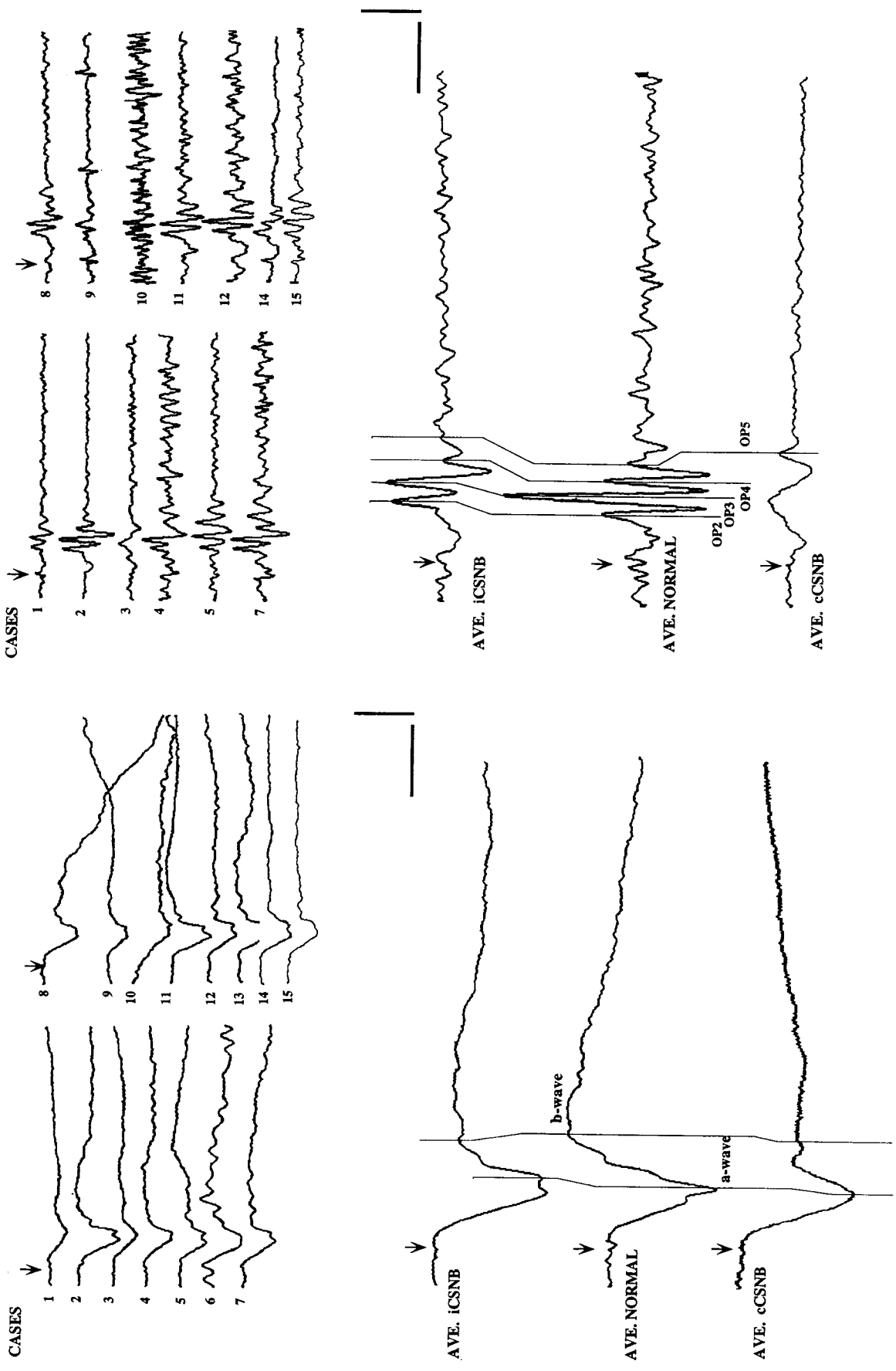

FIGURE 3. Electroretinographic recordings obtained under scotopic conditions with a bright white stimulus in patients with iCSNB. Presentation as in Fig. 1. Horizontal calibration: traces 1–15, 50 msec; averagings, 30 msec. Vertical calibration: traces 1–15, 500 μV for ERGs and 100 μV for OPs; averagings, 175 μV for ERGs and 30 μV for OPs.

(1993). The cone-related ERGs are severely attenuated (mostly the *b*-wave) and the negative bright-flash response has oscillatory potentials on the ascending *b*-wave limb. The brother of their case 3 presented with normal visual function but had the same abnormal ERG pattern as observed in our group; this raises some concerns whether this patient truly has a progressive cone dysfunction or if he has iCSNB. Do the cases described by Kellner and Foerster (1993) have a progressive complication so far unreported in patients with iCSNB? Only long term follow-up will tell us if iCSNB patients are more susceptible to develop macular problems.

From a clinical point of view, the paucity of visual complaints contrasts with the severity of the abnormality of the cone-related ERGs in patients with iCSNB. We think that in this condition, it is essentially the expression of the ERG signal that is affected, with only marginal consequences for the visual processing. This hypothesis has also been recently proposed for patients with DMD where in spite of an electronegative bright-flash ERG and attenuated rod-related activity, no visual dysfunction could be demonstrated (De Becker *et al.*, 1994; Pillers *et al.*, 1993b; Cibis *et al.*, 1993). This has also been proposed for patients with enhanced S cone sensitivity syndrome (Kellner, Zrenner, Sadowski & Foerster, 1993) where in spite of severely reduced L (long wavelength sensitive, red) and M (medium wavelength sensitive, green) cone ERG responses, the spectral sensitivity is normal, thus suggesting the normal function of the cone systems. Some altered membrane properties of the glial cells, or alternatively, some abnormalities in the thickness of the interphotoreceptor matrix have been proposed to explain how a severely disturbed cone-ERG response, which is driven by potassium ions movement in the extracellular space of the retina, could be associated with the mild alterations in the vision, which is driven by the neuronal activity associated with the cone system (Schnapf, Nunn, Meister & Baylor, 1990; Kellner *et al.*, 1993). Discrepancies between ERGs and visual function have also recently been reported in cases of night blindness by Perlman and colleagues (Perlman *et al.*, 1993). They presented four patients with night blindness corroborated by a severe attenuation of the rod-related ERGs, which was well supported by history and dark adaptometry. However, their cone-related ERGs were found to be seriously abnormal with delayed *b*-wave implicit time, subnormal response at low stimuli intensity, steeper response–intensity relationship and absence of OPs. These findings were found not to be compatible with the normal visual acuity, normal color vision and absence of photophobia.

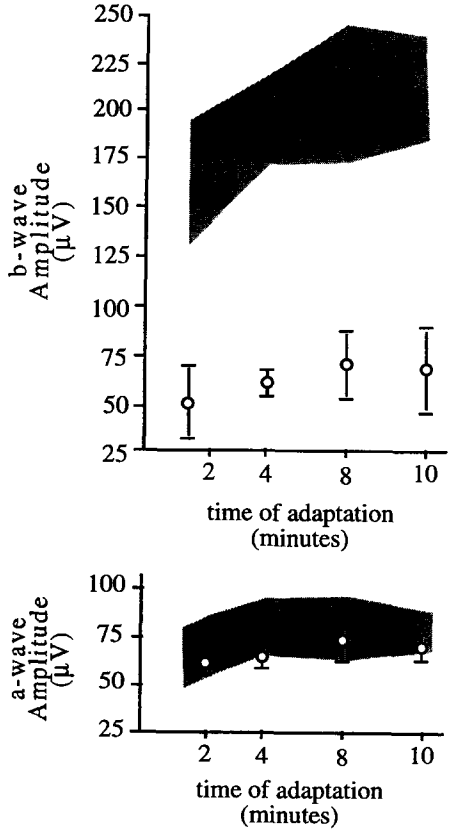

FIGURE 4. Effect of light adaptation (34 cd·m^{-2}) on the amplitude of the *a*- and *b*-waves in patients with iCSNB. Gray zones are the variations obtained in normals, ±1 SD ($n = 20$).

With regard to our patients' cone activity, no OPs could be recorded in *photopic* conditions while some large amplitude OPs could be detected with either a bright or a red flash in *scotopic* conditions. This would suggest that the cone system does not respond optimally under the normal operating range (photopic) but rather has its best responses under mesopic or scotopic conditions. Of particular interest is the presence of OP2 in *scotopic* conditions; this OP has been related to the cone activity (Lachapelle, Benoit, Blain, Guité & Roy, 1990). This may in some ways contradict the idea expressed by Miyake *et al.* (1987) that the cone activity is exaggeratedly suppressed during dark adaptation. Under the condition of their experiment, the mean amplitude increase of the flicker response after 30 min of dark adaptation was 60% in normal and 294% in iCSNB patients. Measurements were made during a continuous flicker stimulation (64 averagings), from a flash 16 times brighter than the one used in single-sweep recordings. Under our conditions (no response averaging and flash intensity equivalent to our single-flash stimulation), the flicker response could not be distinguished from the background noise. Moreover, in three subjects (Fig. 4), the single sweep cone activity was recorded after a period of dark adaptation. The relative growth in the *b*-wave amplitude in these patients paralleled the growth shown with the normal individuals. In our few cases where the cone ERGs were recorded before dark adaptation, the cone *b*-wave was no larger than the one recorded after dark adaptation. These differences in the cone behavior resulting from the two studies could not be explained any other way than by methodological considerations.

Four out of 15 patients were seen only for genetic counseling, because one sibling had iCSNB. None of these four were seen prior to their sibling having ERGs performed, thus suggesting that, otherwise, the paucity

of their symptoms would have precluded further investigation and appropriate diagnosis. This leads us to consider the possibility that iCSNB might be much more common in the general male population. Also, the lack of consistent clinical features at presentation (ERGs excepted) may prevent this entity to be correctly identified. Based on our experience, it would be advisable to further investigate through ERG testing any male presenting with slight temporal pallor of the optic disk along with non correctable visual acuity loss. The elevation of the dark-adapted threshold (Miyake *et al.*, 1987) is not a major complaint.

Finally, we have reservations about the use of the terms iCSNB to describe a retinal condition in which night blindness is not a major complaint. In fact, Miyake (1991) already suggested that the term iCSNB may not be appropriate. For the moment, the term is used simply to avoid further confusion in the terminology of the retinal conditions presenting with electronegative bright-flash responses.

In conclusion, iCSNB is a distinct X-linked retinal condition with often a benign clinical presentation. Hallmarks include unexplained reduced visual acuity, temporal optic disk pallor and in some patients, nystagmus. A high index of suspicion on the part of the clinician will lead to an electrophysiological investigation. The combination of a negative bright-flash ERG response with large OPs, a reduced but still recordable isolated rod response, with a severely attenuated *photopic* cone *b*-wave (without OPs) are characteristic of the condition.

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