THE NEGATIVE ERG IS NOT SYNONYMOUS WITH NIGHTBLINDNESS*

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ABSTRACT

Purpose: To provide electroretinographic differentiation between 4 genetically distinct conditions associated with a negative, Schubert-Bornschein type electroretinogram (ERG): Complete congenital stationary night blindness (cCSNB), incomplete CSNB (incCSNB), Duchenne muscular dystrophy, and a family with an autosomal dominantly inherited negative ERG.

Methods: ERGs were recorded in all subjects according to the ISCEV standards. Additionally, a long-duration flash was used under photopic testing conditions to separate depolarizing (ON) and hyperpolarizing (OFF) bipolar cell contributions. Dark adaptometry was obtained in cooperative adult subjects.

Results: We were unable to differentiate between these 4 genetically distinct conditions using the scotopic ERG response to the bright white flash only. The photopic, cone-derived ERG to both short- and long-duration flashes was more informative in making distinctions between these 4 disorders and understanding the possible mechanisms behind the abnormal ERG.

Conclusion: None of these disorders are progressive or a result of abnormal photoreceptor phototransduction. We suggest that they each represent a signal transmission error at the photoreceptor to depolarizing bipolar cell synapse that affects both rod and cone output. We propose that vision is spared in the latter 2 conditions because of timing errors in transmission as opposed to a complete signaling block, as seen in cCSNB.

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INTRODUCTION

At the onset of light, photoreceptors hyperpolarize and glutamate is reduced at the synapse where photoreceptors, bipolar cells, and horizontal cells make their contact.[1] This subsequent glutamate uptake causes bipolar cells to either depolarize or hyperpolarize depending on their specific receptor subtypes.[2] The electroretinogram (ERG) records this activity: hyperpolarization of photoreceptors results in the negative-going a wave, and the subsequent activity of the postsynaptic second-order neurons, primarily depolarizing, on ON bipolar cells results in the ERG b wave.[3-7]

The negative ERG described by Schubert and Bornschein[8] refers to the response recorded to a bright white stimulus under scotopic testing conditions in the dark-adapted subject. The resulting waveform is made up of a large, photoreceptor-derived a wave followed by a subnormal, postsynaptic b wave. The investigators assigned the description to the ERG seen in complete congenital stationary night blindness (cCSNB), and the Schubert-Bornschein eponym became synonymous for both the negative ERG phenotype and cCSNB.

In time, a number of conditions other than cCSNB were identified that were also associated with a negative ERG (Table I). The mechanisms behind these disorders are varied. Some conditions are stationary, while others are associated with progressive vision loss. Thus, the Schubert-Bornschein eponym became lost for disease categorization but not for the negative ERG, which retained its association with night blindness.

In this article, we describe 4 genetically distinct disorders all indistinguishable on the basis of their negative ERG alone. All 4 are stationary disorders, and 2 are not associated with clinically measurable visual deficits. Expanding our ERG protocol to include long-duration photopic stimuli allowed us to understand the phenotypic differences in the ERG between these 4 disorders.

METHODS

SUBJECTS

Clinical patients were identified through the department of ophthalmology at The Children's Mercy Hospital, Kansas City, Missouri, and referred to the Vision Science Laboratory for an ERG. Subjects included 11 boys with cCSNB, 6 boys with incomplete CSNB (incCSNB), 51 boys with Duchenne muscular dystrophy (DMD), and 3 girls and

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TABLE I: OCULAR DISORDERS ASSOCIATED WITH A NEGATIVE ELECTRORETINOGRAM

Genetic
Complete and incomplete CSNB
X-linked retinoschisis
Early retinitis pigmentosa
Oguchi disease
Duchenne muscular dystrophy
Vascular
Ischemic central vein occlusion
Central retinal artery occlusion
Drug toxicity
Quinine[23]
Vincristine
Systemic
Cancer-associated retinopathy
Melanoma-associated retinopathy
Degenerative myopia

CSNB, congenital stationary night blindness.

1 boy with an autosomal dominant negative ERG (ADNE). Some subjects were part of a clinical investigation and were recruited for participation in the study following the tenets of the Declaration of Helsinki after obtaining Internal Review Board approval and informed consent. Children who could not cooperate with the ERG were sedated with oral chloral hydrate syrup, 50 mg/kg. The ERGs were compared to the data of age-matched pooled normal subjects. The ERG data are contained in a normative database compiled and updated continuously for 17 years.

ERG

The methods for recording clinical ERGs and long-duration photopic ERGs have been described in previous publications. Under scotopic testing conditions, a dim blue flash (-1.00 log cd-sec/m^2) and bright white flash (2.0 log cd-sec/m^2) were delivered. Under photopic testing conditions, the following stimuli were used: a brief white flash on a steady Ganzfeld background (2.0 log cd-sec/m^2 flash with a 1.5 log cd/m^2 background), 30-Hz flicker (0.5 log cd-sec/m^2 with 0.5 log cd/m^2 background), and a long-duration photopic stimulus (3.0 log cd-sec/m^2 with 2.0 log cd/m^2 background). The long-duration stimulus remained on for 200 msec and off for 100 msec and was recorded in a 300 msec window.

DARK ADAPTOMETRY

The pupils were dilated with 1.0% cyclopentolate hydrochloride and 2.5% phenylephrine hydrochloride drops. Following 5 minutes of adaptation to a 2.8 log cd/m^2 full-field stimulus, absolute threshold was tested for 40 minutes using the Goldmann-Weekers dark adaptometer. The test light was 11 degrees in diameter and centered at 10 degrees from foveal fixation, and the intensity ranged from -8.5 to -1.5 log cd/m^2. Results were compared to age- and sex-matched control subjects.

RESULTS

COMPLETE CONGENITAL STATIONARY NIGHT BLINDNESS (CCSNB, CSNB1, MIM310500)

X-linked cCSNB is associated with moderate to high myopia, nystagmus, and elevated cone threshold during dark-adaptometry testing with no rod contribution to the response (Fig 1). Under scotopic testing conditions, the ERG shows an absence of rod-derived b waves, a negative response to a bright white stimulus, and an abnormal cone-derived response with a square a wave followed by a positive peak (Fig 2). Use of a long-duration flash under scotopic testing conditions shows that the photopic ON response is blocked and the response consists only of a cone photoreceptor-derived a wave, a hyperpolarizing trough (probably generated by the hyperpolarization of horizontal and hyperpolarizing bipolar cells at the onset of light), followed by a positive-going response at the offset of light, the d wave (Fig 2). Therefore, the positive peak seen in the response to the short photopic flash is not the b wave but is the OFF response, or the d wave. The gene for cCSNB, designated *NYX*, encodes a leucine-rich repeat protein of 481 amino acids and is found in the inner segments of photoreceptors, outer and inner nuclear layers, and the ganglion cell layer of human retinal sections.[9]

INCOMPLETE CONGENITAL STATIONARY NIGHT BLINDNESS (INCCSNB, CSNB2, MIM300071)

IncCSNB is an X-linked nonprogressive disorder associated with elevated rod threshold of 1.0 to 1.5 log units (Fig 1), reduced visual acuity, and moderate hyperopia or myopia.[10] The ERG differs from the complete form (Fig 2). The rod-derived b waves are diminished but recordable, the response to the bright flash is negative, and cone-derived responses are nearly abolished. Use of the long-duration photopic flash highlights the differences between the 2 stationary disorders. In incCSNB, the ON response is reduced but not absent. There are prolonged oscillations with a small depolarization lasting approximately 50 msec imbedded in the hyperpolarizing trough. The OFF response is present but also prolonged. It is lacking the steep, rapid depolarization seen in both normal and cCSNB subjects. Therefore, cone signaling to both depolarizing and hyperpolarizing bipolar cells is altered. Mutations in the calcium-channel a1-subunit gene, CACNA1F, are responsible for incCSNB.[11]

DUCHENNE MUSCULAR DYSTROPHY (DMD, MIM310200)

DMD affects 1 in 3,500 live male births, resulting in a

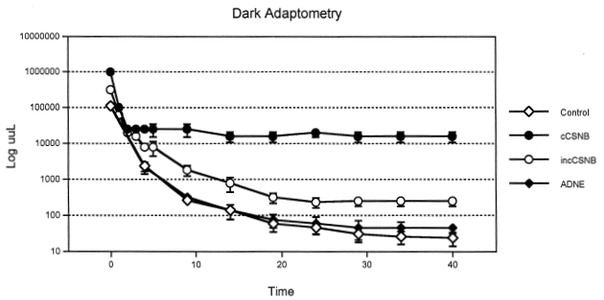

FIGURE 1

Goldmann-Weekers dark adaptometry in 3 groups of subjects with negative electroretinograms (ERGs): complete congenital stationary night blindness (cCSNB), incomplete congenital stationary night blindness (incCSNB), and autosomal dominant negative ERG (ADNE). Subjects were age-matched with control subjects. Subjects with cCSNB show elevated cone threshold and no rod function. Subjects with incCSNB show elevated rod threshold of approximately 1 log unit. Subjects with ADNE do not differ from control subjects.

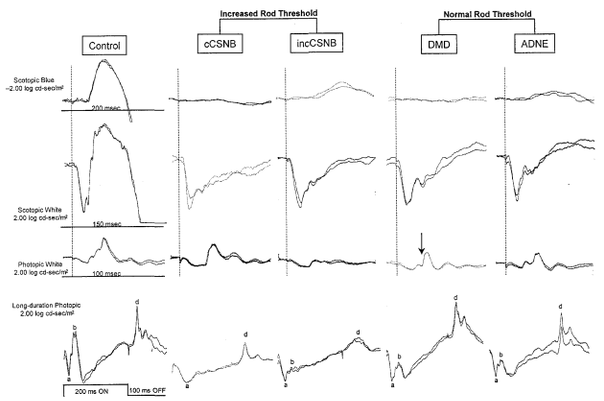

FIGURE 2

Representative electroretinograms (ERGs) of controls and subjects with complete congenital stationary night blindness (cCSNB), incomplete congenital stationary night blindness (incCSNB), Duchenne muscular dystrophy (DMD), and autosomal dominant negative ERG (ADNE). Details of the ERGs are described in detail in the text. Dashed vertical line represents stimulus onset to a brief-duration flash. Long-duration flash is illustrated on bottom left as a square wave stimulus with a duration of 200 msec ON and 100 msec OFF. Waves a, b, and d are labeled in the long-duration photopic condition. Arrow in DMD panel points to missing photopic second oscillatory potential (O2).

wasting muscle disease and death in the second decade of life. Mutations in the gene for dystrophin, a cytoskeletal protein, result in the disease. A negative ERG is associated with DMD when the mutation disrupts the translation of the smaller dystrophin isoform, Dp260 (260kDa)[12-15] (Fig 3). Mutations involving exon 30 and higher of the dystrophin gene result in the negative ERG phenotype, while upstream mutations result in a near normal ERG.[16] Despite the abnormal ERG, there is no visual abnormality associated with DMD, and rod threshold is normal.[17] The DMD ERG shows severely reduced amplitude to the dim blue stimulus (Fig 2). The b wave is barely recognizable. The response to a bright white flash is negative. The cone-derived response to a short flash shows a nearly normal response with the exception of the absence of the second oscillatory potential, O2. In normal subjects, there are 2 small oscillations that ride the ascending limb of the b wave. The long-duration flash shows a normal cone-generated a wave followed by a subnormal ON response.[18] The ON response retains the oscillatory potentials but also shows a low amplitude and rapid depolarization followed by the hyperpolarizing trough. The OFF response is normal.

AUTOSOMAL DOMINANT NEGATIVE ERG (ADNE)

We have identified a family with a negative ERG phenotype with no muscle or eye disease.[19] Visual acuity, visual fields, and rod threshold are normal. No genetic mutation has yet been identified in this family. We investigated the possibility of a mutation in the gene for mGluR6, the metabotropic glutamate receptor subtype 6 specific to depolarizing bipolar cells. When mGluR6 is knocked out in gene-targeted mice, they exhibit a negative ERG. No mutation was found in this family. The ERG shows a recordable but diminished b wave to the dim blue flash under scotopic testing conditions. The response to the bright white stimulus is negative (Fig 2). The photopic response to the brief flash is normal; however, when the flash duration is extended, it is apparent that the ON response is attenuated. Like incCSNB and DMD, the oscillatory potentials are retained. Like cCSNB and DMD, the OFF response is preserved.

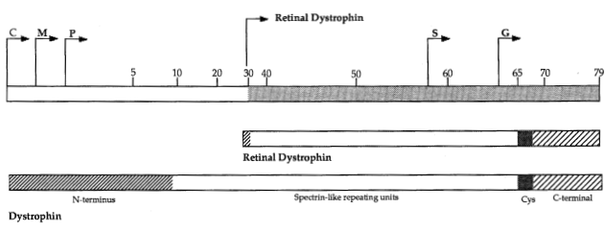

FIGURE 3

Schematic drawing of dystrophin gene, retinal dystrophin (Dp260), and full-length dystrophin (Dp427). The gene comprises 79 exons. Promoters for full-length isoforms found in cortex, muscle, and brain (C, M, and B) are at the 5′ region. Smaller isoforms found in Schwann (S) cells (Dp116) and glia (G) (Dp71) have promoters in downstream 3′ region. Location of first exon used in retinal dystrophin is indicated. Boys with mutations involving exons 30 through 79 have an abnormal electroretinogram.

DISCUSSION

We have described the negative ERG phenotypes in 4 genetically distinct disorders. In 2 of these disorders (DMD and ADNE), there is no visual abnormality associated with the abnormal ERG. Unlike cCSNB or incCSNB, rod threshold is normal. Rod threshold in

incCSNB is elevated but not to the extent of cCSNB, where there is no measurable rod threshold.

In these 4 distinctly different groups, the scotopic ERG to the bright white flash fits the Schubert-Bornschein eponym (Fig 4). From these 4 waveforms, it is impossible distinguish one disorder from the other despite their very different clinical phenotypes. Since rods

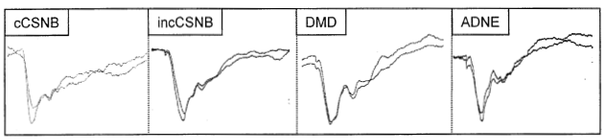

FIGURE 4

Schubert-Bornschein type electroretinograms in all 4 conditions: complete congenital stationary night blindness (cCSNB), incomplete congenital stationary night blindness (incCSNB), Duchenne muscular dystrophy (DMD), and autosomal dominant negative ERG (ADNE). All responses were recorded under scotopic testing conditions in dark-adapted subjects. Stimulus was a bright white (2.00 log cd-sec/m^2) flash designed to elicit responses from both rods and cones.

communicate only with a single rod bipolar cell and the intensity of the bright white flash is high enough to also generate cone activity, the response to a bright flash under scotopic testing conditions is a mixture of rod-to-rod depolarizing bipolar cell signals, cone-to-cone depolarizing and hyperpolarizing bipolar cell signals, as well as responses from horizontal and amacrine cells. Under standard clinical testing conditions, it is difficult to separate these multiple postsynaptic responses from each other. At best, we can attribute the leading edge of the a wave to photoreceptor hyperpolarization. More informative is the response to long-duration photopic stimuli. These responses make the distinctions between the 4 groups and may explain the difference in visual outcome.

While the response to the long-duration stimulus under photopic testing conditions is also a response of multiple cell types, there is still a sense of how each cell type is contributing to the response. There should be no rod contribution to the response, since the subject is light-adapted and there is a bleaching background light. Therefore, the leading edge of the a wave is a cone response. The ON response is a mixture of rapid depolarization of the sign-inverting depolarizing bipolar cells and slower hyperpolarization of the sign-conserving hyperpolarizing bipolar cells and horizontal cells, resulting in a long hyperpolarizing trough prior to the OFF response. The rapid oscillations are most likely generated by amacrine cells in the more proximal retina. The OFF response is also a combination of events, including the hyperpolarization of depolarizing bipolar cells and depolarization of hyperpolarizing bipolar cells and horizontal cells at the offset of light.

In cCSNB, there is a complete block at the photoreceptor to depolarizing bipolar cell synapse. There remains a hyperpolarizing trough, presumably initiated by the horizontal cells and hyperpolarizing bipolar cells, and there is normal depolarization of the sign-conserving cells at the offset of light. As suggested by others, it appears that both rod and cone ON pathways are blocked, which results in the more significant vision loss and no measurable rod threshold.[20]

In incCSNB, there remains a slow, subnormal depolarizing bipolar cell response with rapid oscillations. This would indicate that some signal is still reaching the depolarizing bipolar cell and more proximal areas of the retina, as indicated by the oscillatory potentials. The hyperpolarizing bipolar cell signal is also attenuated, low in amplitude, and prolonged in time. This would indicate that both ON and OFF pathways are affected, but enough transmission of signal occurs to allow for measurable rod threshold and better visual outcome than cCSNB.

The long-duration photopic ERG in DMD retains more of the ON response than either of the 2 preceding conditions. The OFF response is well preserved, presumably normal. There are no clinically measurable visual abnormalities in this population, which would indicate that despite the abnormal ERG, the signals are reaching the proximal retina and brain. When the ON response is isolated by pharmacologically blocking the hyperpolarizing bipolar cells, it was shown to be a large-amplitude response with a rapid time course.[21] Sieving[22] created a model in which he introduced a series of timing delays in the ON response to demonstrate the effect of the delay on the ON response amplitude. With a 5 msec delay, the model is nearly identical to the response seen in DMD. Therefore, we believe the ON response is present in DMD, but the time course is altered, allowing for clinically normal vision but resulting in alterations in the ERG. Dystrophin is found at the outer plexiform layer in retina, most likely in photoreceptor cells. In DMD, only the rod and cone depolarizing bipolar signals are altered; therefore, we propose that the role of Dp260 is to stabilize the photoreceptor/depolarizing bipolar cell/horizontal cell invaginating synapse and that instability of this connection allows for an alteration in signal time course and the ERG phenotype without loss of vision.

The etiology of the abnormal ERG in ADNE remains unknown. While the ERG phenotype is most similar to that seen in DMD, there is no muscle disease in this family and the inheritance pattern is autosomal dominant, ruling out a role for dystrophin. Furthermore, there were no mutations in the gene for the mGluR6 receptor. It is possible in this family, as in DMD, that the signals from photoreceptors to second-order neurons are delayed, not blocked, which results in an abnormal ERG phenotype with no clinically measurable loss of vision or abnormal

fundus findings.

All of these cases show a Schubert-Bornschein ERG phenotype to a single bright flash under scotopic testing conditions in the dark-adapted patient, yet there are significantly different clinical outcomes. None of these disorders are progressive or are a result of abnormal photoreceptor phototransduction. Use of the long-duration photopic ERG was instrumental in demonstrating the differences in retinal signals of the cone pathway. We suggest that each of these disorders represents a signal transmission error at the photoreceptor to depolarizing bipolar cell synapse that affects both rod and cone output. We propose that vision is spared in DMD and ADNE because of timing errors in the transmission of signals between first- and second order-retinal neurons.

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DISCUSSION

DR BARRETT KATZ. John Dowling claimed the B wave, as conventionally elicited, emanated from the Mueller cell; Herman Burian recognized the extensive subtleties this analysis overlooked. As Dr Cibis reminded the AOS before, Burian taught that such a simplification was like going to the elevator shaft of a tall building, placing one's ear against that elevator shaft, and then claiming that all the noises coming from each and every floor of that tall building (transmitted up the elevator shaft) were somehow generated by that elevator shaft. Dr Cibis leads the charge that cries, there is more going on in generating the B wave than just the Mueller cell.

In this paper, Dr Cibis convincingly demonstrates that there are neuronal junction defects as well as blocking defects that may arise between the photoreceptors and the depolarizing bipolar cells. Both defects alter the physiology within proximal retina, leading to an ERG that looks to most of the rest of us, for all intents and purposes, like that expected in CSNB, yet when analyzed with long duration photopic ERG methodology, yields singular defects that allow for finer discrimination of retinal anomaly. And each defect has its characteristic ERG markers.

Most of us knew the ERG allows one to make inferences about retinal function not possible upon clinical or histopathological observations alone. Yet Dr Cibis has demonstrated that the conventional ERG misses many of the subtleties of visual physiology. Specifically, cone visual signals within the retina are processed through 2 separate pathways, one an ON-center bipolar cell path, the

other, an OFF-center bipolar cell pathway. While we are just learning about what different psychophysical parameters these pathways subserve, we are more and more convinced that each can suffer preferential insults declared phenotypically as different retinal processes. Dr Cibis brings us just such an analysis here. He persuasively demonstrates that when the ERG is elicited with the technique of long duration light flashes, we can sort out ON versus OFF pathway changes within the visual system.

The clinical import of this modality is apparent. By analyzing the depolarizing [ON] and hyperpolarizing [OFF] pathways of cone vision post-synaptically to photoreceptors, one can differentiate at least 4 sub-types of "negative ERGs" that are genetically distinct, and clinically disparate. These entities are complete CSNB, incomplete CSNB, Duchenne's Muscular Dystrophy, and Autosomal Dominantly inherited Negative ERG. Each is non-progressive. Each seems to be caused by synaptic irregularity, rather than a result of abnormal photoreceptor phototransduction. Two are not associated with recognizable defects of the visual system.

What does all this imply?

1. In the retina, as in life, timing is everything; if vision is spared, as in Duchenne MD, and AD Negative ERG, then visual information is reaching appropriate areas of both retina and brain; complete signal blockage is expected to affect vision, timing errors do not;
2. By expanding one's ERG protocol, the use of the long duration photopic ERG to separate ON- and OFF-bipolar cell contributions to the photopic ERG allows a finer understanding of the functional implications of retinal disorders;
3. Altered retinal physiology may be a manifestation of disease localized at the level of the synapse, analogous to the synaptic anomaly most commonly seen in ophthalmology and neurology - myasthenia gravis.
4. The ERG can provide a laudable clinical addition to the understanding and classification of such retinal disorders, and the new and improved ERG may be the ancillary test to bring the neurologist and the ophthalmologist together again.

I ask Dr Cibis to speculate:

- Why doesn't the alteration of timing postulated in Duchenne's MD and Autosomal Dominantly inherited Negative ERG degrade vision? When demyelination of the optic nerve occurs, and causes dispersion problems of the visual signal, as in garden variety optic neuritis, vision is degraded.
- What candidates do you have for us, as unifying etiologies of these anomalies of retina and nervous system?
- What are the sites of the effects of these shared selfish genes in MD, and cCSNB?

I commend Dr Cibis for the work, the paper, and the creativity of thought and reason that they demonstrate.

DR GERHARD W. CIBIS. Thank you very much, Dr Katz. Dr Lichter says that this organization represents if nothing else, history. Also, I thank you very much for the mention of my mentor Dr Burian.

I can answer the first question about why doesn't timing degrade vision. Dr Paul Sieving speculates that a 5 ms delay in the transmission can create the negative ERG. So that is a very subtle timing which can only be found in very subtle ways. In collaboration directed by Dr Vance Zemon of Yeshiva University we reported at the last ARVO meeting that in some Visual Evoked Response testing on patients with Duchenne's muscular dystrophy where they presented a center stimulus with an isoluminent surround, they were able to tease out a VER abnormality between the parvocellular and magnocellular system. If you know this is a timing defect and you now structure your vision tests not on a 20/20 Snellen chart or a Goldman Visual Field machine but a very sophisticated VER analysis you can find defects in the vision that you would expect to have.

Can you give us some speculation about the underlying unity of these anomalies that cause such disparate clinical declarations?

We believe that the proteins play a structural role somewhere in the anatomy of the synapse that I showed you. The dystrophin protein specifically, we think, somehow stabilizes the glutamate release mechanism and if that structure is not anchored properly the neurotransmitter would not be released in a timely fashion. Similarly we don't know where the calcium channels are in this system. We do know what sort of a role they play but not if they are either positioned inappropriately or the mechanism is timed inappropriately.