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ORIGINAL RESEARCH ARTICLE

Negative electroretinograms in the pediatric and adult population

Johnstone M. Kim · John F. Payne · Jiong Yan · Claire S. Barnes

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Abstract *Objective* To assess the frequency of negative waveform electroretinograms (ERGs) in a tertiary referral center. *Design* Retrospective chart review. *Participants* All patients who had an ERG performed at the electrophysiology clinic at Emory University from January 1999 through March 2008 were included in the study. *Methods* Patients with b-wave amplitude $\leq$ a-wave amplitude during the dark-adapted bright flash recording, in at least one eye, were identified as having a "negative ERG". Clinical information, such as age, gender, symptoms, best corrected visual acuity, and diagnoses were recorded for these patients when available. *Results* A total of 1,837 patients underwent ERG testing during the study period. Of those, 73 patients had a negative ERG, for a frequency of 4.0%. Within the adult ($\geq$18 years of age) and pediatric populations, the frequencies of a negative ERG were 2.5 and 7.2%, respectively. Among the 73 cases, negative ERGs were more common among male than female patients, 6.7% versus 1.8% ($P < 0.0001$). Negative ERGs were most common among male children and least common among female adults, 9.6% versus 1.1%, respectively, ($P < 0.0001$). Overall in this group of patients, the most common diagnoses associated with a negative ERG were congenital stationary night blindness (CSNB, $n = 29$) and X-linked retinoschisis (XLRS, $n = 7$). *Conclusions* The overall frequency of negative ERGs in this large retrospective review was 4.0%. Negative ERGs were most common among male children and least common among female adults. Despite the growing number of new diagnoses associated with negative ERGs, CSNB, and XLRS appear to be the most likely diagnoses for a pediatric patient who presents with a negative ERG.

Keywords Negative electroretinograms · Pediatric · Congenital stationary night blindness · Retinoschisis

J. M. Kim · J. F. Payne · J. Yan · C. S. Barnes
Department of Ophthalmology, Emory University, Atlanta, GA, USA

C. S. Barnes
Rehab R&D Center of Excellence, Veterans Affairs Medical Center, Decatur, GA, USA

C. S. Barnes (✉)
VA Palo Alto HCS (154 U), 3801 Miranda Avenue, Palo Alto, CA 94304, USA
e-mail: claire.barnes@va.gov; claire_barnes@att.net

Introduction

Electroretinograms (ERGs) record the electrical responses of various cells of the retina, by presenting different stimuli in order to selectively induce certain cells to respond. In the "Dark-adapted 3.0 ERG" test condition [1], a bright flash of light is presented to the dark-adapted eye. Under these conditions, the normal response consists of an initial negative-going a-wave, produced primarily by the photoreceptors, followed by a larger positive b-wave, reflecting inner retina activity [2]. However, some disorders cause a selective b-wave amplitude reduction in the ERG, with a less-attenuated or normal a-wave, indicating inner retinal dysfunction. This characteristic waveform is commonly known as a “negative ERG” [3].

Retinal diseases associated with negative ERGs include inherited disorders such as congenital stationary night blindness (CSNB) and X-linked retinoschisis (XLRS) [4, 5]. Acquired causes of negative ERGs include melanoma-associated retinopathy (MAR), central retinal artery and vein occlusions, as well as quinine-, and methanol-induced retinopathy [6–10]. At least 33 disorders with negative ERGs had been reported by 2001 [11], and the list has continued to grow [12–15].

While there have been many articles on negative ERGs in the past couple of decades, most are single case reports focused on a particular disease. However, two studies have assessed the frequency and various causes of negative ERGs: Koh et al. [16] and Renner et al. [17] reported negative ERG frequencies of 4.8 and 2.9%, respectively, at their centers. Although some of the disorders associated with negative ERGs would be expected to be more common in children, such as Juvenile Neuronal Ceroid Lipofuscinosis or Duchenne Muscular Dystrophy [18, 19], many others seem more likely to be diagnosed in adults (e.g. retinal vascular occlusions, methanol toxicity, MAR, or birdshot chorioretinopathy) [8, 10, 20, 21]. Thus, it is of interest to know the relative rates and causes of negative ERGs for both adults and children, to aid clinicians in narrowing their differential diagnoses for patients of different ages with a negative ERG. Perhaps surprisingly, that information does not seem to be available in the literature; Renner’s group [17] only provided the range of ages for their patients, and Koh et al. [16] did not provide age details on their patients. Furthermore, it is of interest to know whether negative ERGs are at all common in females, because of the preponderance of genetic causes that are X-linked disorders. Additionally, identifying the common causes of negative ERGs, and the age and gender distributions of such patients, could be useful for estimating possible numbers of prospective subjects for future research trials. Therefore, this study aimed to determine whether there are differences in the frequency of negative ERGs between children and adults, as well as between males and females. Finally, we sought to examine the clinical differences between these subgroups of patients.

Subjects and methods

Subjects

This study was approved by the Emory University School of Medicine Institutional Review Board. A retrospective review of all ERGs performed from January 1999 through March 2008 at the electrophysiology clinic of Emory University was performed. All patients with a negative ERG in at least one eye (defined as b-wave amplitude $\leq$ a-wave amplitude for the dark-adapted bright flash test) were identified. Clinical charts were examined when available (50 of the patients with negative ERGs). The patient demographics, including clinical diagnosis, age at presentation, sex, presenting complaints, refractive error (in spherical equivalents), and best corrected visual acuity were recorded. Patients were considered to be in the pediatric population if they were less than 18 years old at the time of their initial ERG and in the adult population if they were 18 years of age or older at the time of their initial ERG.

Methods

Full-field ERGs were recorded in accordance with the International Society for Clinical Electrophysiology of Vision (ISCEV) protocol [1] on a Nicolet Bravo system (Madison, Wisconsin). Most ERGs were recorded using DTL-Plus eye electrodes (Diagnosys LLC, Lowell, MA, USA) [22], but some were recorded using “Jet” contact lens electrodes (Universo Plastique SA, Switzerland) [23] with a small cylinder inserted between the pegs, to keep the eyelids open. Each patient was dark-adapted for 30 min after topical administration of 2.5% phenylephrine hydrochloride and 1% tropicamide drops. Proparacaine was used as the topical anesthetic. Methylcellulose was applied to the Jet electrodes before use. The ERG examination protocol included dim white flashes (“Dark-adapted 0.02 ERG”; 2 s apart) and bright white flashes (“Dark-adapted 2.5 ERG” and “Dark-adapted 2.5 oscillatory potentials”; 10 s apart) in the dark. Photopic flashes (“Light-adapted 2.5 ERG”; 3 s apart) and 30-Hz flickering stimuli (“Light-adapted 2.5 flicker ERG”) were presented after 10 min of adaptation to the 23.4 cd/m^2 background. The filter settings were from 0.3 to 500 Hz for all recordings except the oscillatory potentials (OPs) and from 75 to 500 Hz for the OPs. The recording interval was 150 ms (following 1.50-s adaptation) for the flicker and 256 ms for the other conditions. The ERG recordings were binocular except in the case of some very young patients, on whom monocular recordings were performed, to minimize patient distress. All ERGs were performed without sedation.

Statistical considerations

Statistical calculations were performed using Predictive Analytics SoftWare (PASW) Statistics for Windows, Release 18.0.0 (IBM, Inc., Somers, NY, USA) and statistical significance was set as $P < 0.05$. Univariate analyses were done using Chi-squared tests and t-tests to look for statistically significant differences between groups. Values of refractive error (in diopters) and visual acuity (converted to logMAR) were averaged for the two eyes per subject, prior to group analyses.

Results

A total of 1,837 patients underwent at least one ERG during the study period. Of those, 73 patients with a negative ERG response were identified. Example waveforms from a child with a negative ERG (in this case, due to CSNB) and one with a normal ERG are shown in Fig. 1 (left and right panels, respectively). Overall, the frequency of negative ERGs was 4.0%, but the frequency varied based on study subgroup, which can be seen in Table 1 (and in Table 2, which concentrates on the frequencies within the group of 73 negative ERG cases). The negative ERG frequency among children was significantly higher than that in adults, at 7.2% versus 2.5% ($P < 0.0001$). There was a statistically significant difference between the negative ERG frequency among males and females in the group of 73 patients at 6.7 and 1.8%, respectively, ($P < 0.0001$). Negative ERGs were most common among male children and least common among female adults, 9.6 and 1.1%, respectively, ($P < 0.0001$). Overall, the median age at presentation was 15.0 years (0.3–65.7 years, see Fig. 2). The median ages at presentation for the pediatric and adult subgroups were 8.8 and 42.6 years, respectively.

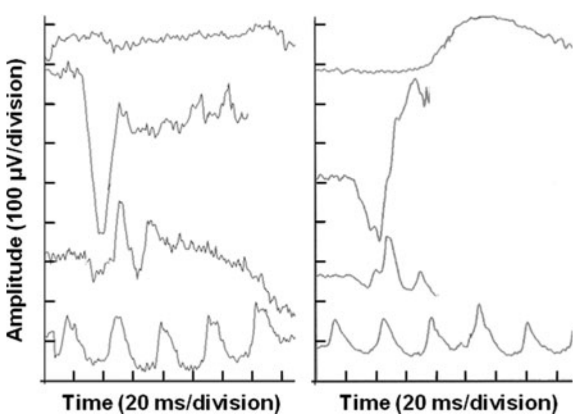


Fig. 1 ERGs recorded from a 4-year-old male patient with CSNB (*left panel*) and a 13-year-old female patient with normal responses (*right panel*). From the top, the waveforms show the responses to the dark-adapted 0.02 and 2.5 flashes, the light-adapted 2.5 flashes and the light-adapted 2.5 flicker. Note the boy's negative waveform in response to the dark-adapted 2.5 flash (*left panel*, second-to-top trace). His responses to the 0.02 flashes were not distinguishable from noise for either eye, but his light-adapted responses fell within the normal amplitude and implicit time ranges for both eyes

Of the 73 patients included in this study, 45 had a known clinical diagnosis (the remaining 5 charts, out of 50 available for review, did not list a diagnosis). Table 3 illustrates the diagnoses associated with negative ERGs among the various subgroups of patients. The most common diagnoses were CSNB ($n = 29$), XLRS ($n = 7$), and retinitis pigmentosa (RP, $n = 3$). Of note, approximately 80% of the patients with CSNB were men and most (86%) were children.

The three most common complaints across the study population were decreased vision, nystagmus, and nyctalopia (41, 29, and 26%, respectively). When the population was subdivided, the principal presenting complaints in adults were decreased vision (58%) and nyctalopia (29%). Children most often presented with nystagmus (48%), decreased vision (29%), and nyctalopia (24%). Patients with CSNB often presented with nystagmus (45%) and nyctalopia (38%) and patients with XLRS mostly presented with decreased vision (71%).

Sixty-nine of the patients had detectable ERG responses recorded from both eyes, so that the rate of binocular versus monocular negative ERGs could be examined for those patients. In the vast majority of cases (60/69, 87%), the responses from both eyes showed a negative waveform. However, three adults had a negative ERG from one eye, with a normal or

Table 1 Distributions of negative ERGs across all patients tested from January 1999 through March 2008

	Total patients	Non-negative ERG	Negative ERG	Frequency (%)
All patients	1,837	1,764	73	4.0
Male	827	772	55	6.7
Female	1,010	992	18	1.8
All adults	1,257	1,226	31	2.5
Men	494	471	23	4.7
Women	763	755	8	1.1
All children	580	538	42	7.2
Boys	333	301	32	9.6
Girls	247	237	10	4.1

Table 2 Summary of negative ERG frequencies for the 73 cases (as a percentage of all patients in each age/gender group)

	Child (%)	Adult (%)
Male	9.6	4.7
Female	4.1	1.1

nearly normal a-wave amplitude, whereas the ERG from their other eye had both normal a-wave and b-wave amplitudes. One of those three patients had a retinal vascular occlusion in her affected eye. Finally, there were six cases in which both the a- and b-waves amplitudes were smaller than normal for both eyes, but one eye showed a negative waveform and the other remained positive. Of those cases, one patient had RP, one had XLRS, and one had a history of vasculitis; the diagnoses for the final three are not known. Therefore, a total of 13% of the patients with detectable ERGs OU had a monocular negative recording.

Visual acuity measures were available for 50 pediatric and adult patients. In addition, two infants (<1 year old) were listed in their charts as "fix-and-follow"; they were not included in the calculations as a corresponding numerical value could not be determined. Figure 3 shows the presenting visual acuity results for the various subgroups. Adult women with negative ERGs were the most likely to present with good visual acuity, with half achieving 20/40 acuity or better, although the relatively small number of affected women should be kept in mind. There was no significant difference in visual acuities between the sexes in the pediatric subgroup ($P = 0.65$). Overall, CSNB patients presented with better visual acuities than patients with XLRS ($P = 0.01$). One-third of patients with CSNB had visual acuity better than or equal to 20/40, compared to none of the patients with XLRS. The refractive error in average spherical equivalents was also evaluated for those patients with the two most common diagnoses, CSNB and XLRS (Fig. 4). The median spherical equivalent in patients with XLRS was +1.1 diopters, whereas the median spherical equivalent in all patients with CSNB was −9.1 diopters ($P < 0.0001$). On average, children were more myopic than adults on presentation

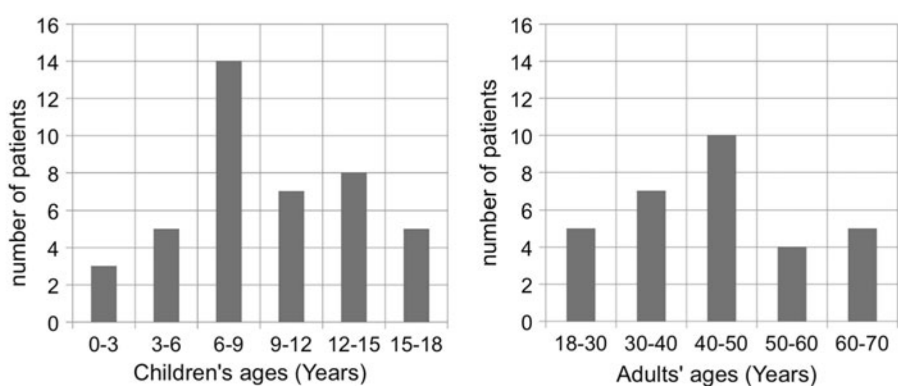


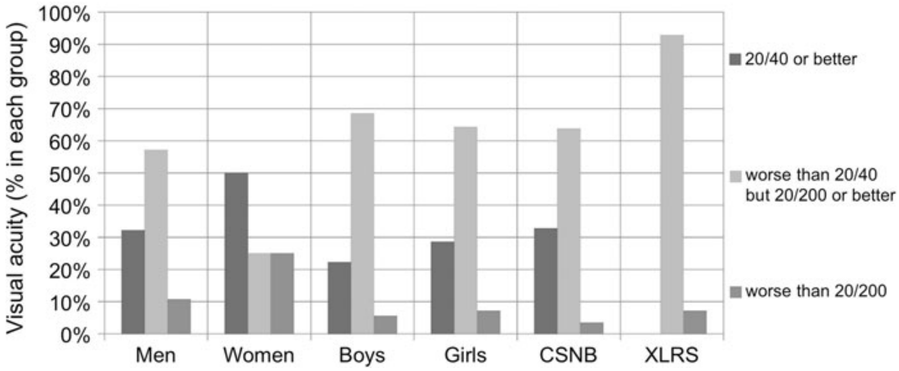
Fig. 2 Histograms of the patients' ages within the pediatric and adult groups with a negative ERG

Table 3 Diagnoses of patients with a negative ERG

	Total	Male	Female	Children	Boys	Girls	Adult	Men	Women
CSNB	29	23	6	25	19	6	4	4	0
XLRS	7	7	0	3	3	0	4	4	0
RP	3	1	2	1	1	0	2	0	2
Retinal vasculitis/occlusion	2	1	1	0	0	0	2	1	1
Cone-rod dystrophy	1	1	0	0	0	0	1	1	0
Methanol toxicity	1	1	0	0	0	0	1	1	0
Multiple system atrophy	1	1	0	0	0	0	1	1	0
Autoimmune retinopathy	1	0	1	0	0	0	1	0	1
Total	45	35	10	29	23	6	16	12	4

CSNB congenital stationary night blindness *RP* retinitis pigmentosa *XLRS* X-linked retinoschisis

Fig. 3 Visual acuity results for the various subgroups of patients with a negative ERG



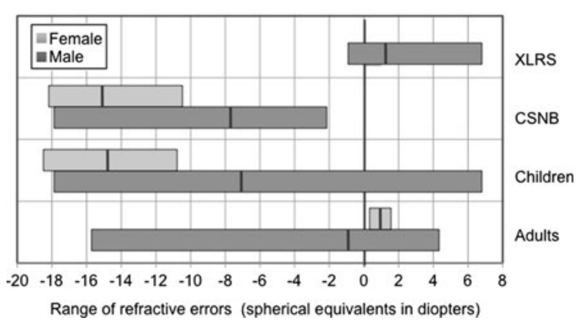


Fig. 4 Refractive errors, in spherical equivalents, for the patients with a negative ERG. The *bars* indicate the refractive range in each subgroup and the *solid lines* indicate the median values

($P = 0.047$), and, interestingly, female children were more myopic than male children ($P = 0.001$).

No genetic information is available on the patients diagnosed with CSNB in this study. However, based on the criteria for "complete" versus "incomplete" (i.e., complete CSNB has a relatively normal photopic flash and flicker response, whereas incomplete CSNB has markedly abnormal photopic responses and a greater likelihood of a measurable dim white flash response) [24–26], it appears that 12 cases would be classified as complete (ages 0.33–17.1 years) and 11 as incomplete (ages 5.9–61.3 years), with 6 cases (ages 2.9–14.9 years) that could not be judged conclusively based on the ERGs.

Discussion

The purposes of this study were as follows: (1) to calculate the frequency of negative ERGs at our tertiary referral center, and then, more particularly, (2) to determine whether there were differences in the frequency of negative ERGs between children and adults, as well as between males and females, and (3) to examine possible clinical differences between patient groups (e.g., in terms of visual acuity). The negative ERG frequency at our institution was 4.0%, which was fairly similar to the values from the two other studies on this subject [16, 17]. Interestingly, the negative ERG frequency varied between the study subgroups. For example, the negative ERG frequency in children was 7.2% compared with 2.5% among adults. Additionally, the rate of negative ERGs was also significantly higher in males compared with females (6.7% versus 1.8%). The primary diagnoses associated with a negative ERG, particularly in children, were CSNB and XLRS.

It is interesting to note that there was a large sex difference in the number of cases referred for ERG testing within the adult group, with many more women than men (Table 1). One might expect it to be the other way around as males with retinal dystrophies are likely to be more numerous because of the additional burden of X-linked disease. Consistent with that, in fact, more boys than girls were sent for ERGs during this time period. However, the reason why there were approximately 1.5 times as many women referred as men during the study period is unknown.

It is also of interest that the pediatric group included so many female patients with negative ERGs. All of these patients were diagnosed as having autosomal recessive-CSNB (AR-CSNB) based on family history and ERG pattern profile. Although less commonly studied than the X-linked forms, some genes for AR-CSNB have now been identified, which may account for the female cases in this study [27–29]. Clinically, these patients were on average more myopic than their male counterparts (Fig. 4), and none of them had vision worse than 20/100.

Studies on negative ERG rates have now been completed in three countries, Germany [17], United Kingdom [16], and now the United States. Although the patient population is likely to vary somewhat between these studies, the majority of verified diagnoses were uniformly CSNB, XLRS, and RP, although to varying degrees across sites. Virtually all of the children in the present study had a diagnosis of CSNB or XLRS, and the adult group, although showing more variability, still had CSNB and XLRS as the most common diagnoses. It should be noted that the median age of our study population was younger than that reported by Renner et al. [17] (15.0 years in our study versus 35.3 years), which may contribute to differences in the distribution of diagnoses between the two studies.

This study helps to characterize patients with negative ERGs. The most common presentation in children was nystagmus (48%), whereas adults most often complained of decreased vision (58%). Given that the majority of children in this study had CSNB, it was not surprising that nystagmus, a well-known finding in CSNB [30] was the most common presenting sign. Few patients in the study group had vision worse than 20/200 (11%). The prior studies [16, 17] do not mention the refractive error or visual acuities of their patients. Patients with CSNB had better visual acuities than did patients with XLRS (Fig. 4). The majority of patients presented with myopia, which coincides with the most common diagnosis being CSNB.

Given the retrospective nature of the study, there were limitations. There were 28 patients (38%) who had a negative ERG but no available clinical diagnosis. The absence of clinical information in those patients (diagnoses, refractive errors, etc.) was due to the fact that some patients are referred to the electrophysiology laboratory by community ophthalmologists for an ERG only. Thus, it is possible that the results in this study could have been skewed by the absence of such clinical information. Negative ERGs are relatively rare and due to the small sample size, there are limited statistical inferences that can be made. Recording of long-flash ERG responses (i.e., cone-mediated responses to (approximately) 100 ms flashes of light) or sawtooth-flicker responses (flicker with either an abrupt onset (rapid-on) or offset of light (rapid-off) and slower luminance change in the opposite direction) would have provided useful information regarding possible ON- or OFF-pathway dysfunction in the patients with negative ERGs [31–34]. However, unfortunately, the Nicolet Bravo does not have that capacity. Finally, it should be remembered that the disease frequencies reported here reflect the rates seen "in the clinic" not necessarily the rates of these diseases in the population at large. The distribution of diagnoses may likely be skewed because patients with obvious diagnoses such as typical RP or acquired diseases such as retinal vascular occlusions are not necessarily referred for ERGs.

Regardless, a finding of a negative ERG serves as a useful clinical tool in making a diagnosis, especially in the pediatric population. In this study, children with negative ERGs were either diagnosed with CSNB, XLRS, or RP. This is not to say that other diagnoses should not be explored, but that these diagnoses should be strongly considered. Additionally, highly myopic children with a negative ERG are more likely to have

CSNB, whereas mildly hyperopic boys are likely to have XLRS. In adults, the diagnoses are more likely to be varied because childhood conditions can present in adulthood as well as acquired diseases that manifest later in life.

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Conflict of interest None.

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