Electronegative Electroretinograms in the United Arab Emirates

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Abstract:
PURPOSE: An electronegative electroretinogram (ERG), defined as having a b:a wave ratio ≤1 in the scotopic flash ERG response, indicates relative inner retinal dysfunction. Causes vary depending upon the study population. In the Arabian Gulf, where inherited retinal disease is relatively prevalent, common diagnoses associated with electronegative ERGs have not been described. In this study, we report the frequency and causes of electronegative ERGs in a cohort of Emirati patients with inherited retinal disease.

METHODS: A retrospective review was performed of all full-field ERGs done for Emirati patients in the Ocular Genetics Service of Cleveland Clinic Abu Dhabi from January 2017 to December 2019. Those who had an electronegative ERG in at least one eye were included in the study.

RESULTS: Out of 137 patients, 9 probands (6.6%) had an electronegative ERG. The mean age at presentation was 24 years (range 5–48 years), and five patients (55.6%) were male. The final clinical diagnoses were congenital stationary night blindness (CSNB) (two TRPM1-related and one Oguchi disease), X-linked retinoschisis (XLRS) (one genetically confirmed and two not genetically tested), cone-rod dystrophy (one CRX-related and one not genetically tested), and enhanced S-cone syndrome (ESCS) (one NRL-related). The one patient who did not have bilateral electronegative ERGs was a male with XLRS whose fellow eye had an unrecordable ERG.

CONCLUSIONS: In this series of Emirati patients, an electronegative ERG was most commonly associated with the inherited retinal diseases recessive CSNB and XLRS. An electronegative ERG was noted in a case of NRL-related ESCS.

Keywords: Congenital stationary night blindness, electronegative, electroretinogram, NRL, X-linked retinoschisis

Introduction
In the scotopic flash response of the full-field electroretinogram (ERG), the downward a-wave reflects photoreceptor function, whereas the upward b-wave reflects the activity of the bipolar cells and the inner retinal layers. Normally, the b-wave is larger than the a-wave. If the b-wave is equal to or smaller than the a-wave, the waveform (and the ERG) is termed electronegative.[1] An electronegative ERG indicates relative inner retinal dysfunction. Inherited retinal disorders commonly associated with an electronegative ERG include congenital stationary night blindness (CSNB), X-linked retinoschisis (XLRS), and certain cone-rod disease (e.g., CABP4- and CRX-related retinopathies).[1] Acquired causes include central retinal artery or vein occlusion, carcinoma-associated retinopathy, and autoimmune retinopathy.[1]

We are aware of four prior studies that have assessed the incidence and causes of electronegative ERGs in the United Kingdom, the United States, Germany, and Brazil with a reported incidence of approximately 5.0%, 4.0%, 3.0%, and 2.50%, respectively.[6–9] The incidence and causes of electronegative ERGs in the Arabian Gulf, where recessive diseases can be...
more common,[10] has not been studied to the best of our knowledge. The purpose of this study is to report the incidence and causes for electronegative ERGs in a referral center in the United Arab Emirates.

Materials and Methods

A retrospective chart review for full-field ERGs done for Emirati patients seen in the Ocular Genetics Service of Cleveland Clinic Abu Dhabi was performed (January 2017 to December 2019). ERGs were done according to standards of the International Society for Clinical Electrophysiology of Vision.[11] The inclusion criteria for the study were a:b wave ratio ≤1 in the scotopic flash response in at least one eye.

Results

A total of 137 patients underwent ERGs during the study period. Nine Emirati probands (6.6%) showed electronegative ERG response in at least one eye. The mean age at ERG testing was 24 years (range 5–48 years, median = 19). Five patients (55.6%) were male. Final clinical diagnoses were CSNB (n = 3), XLRS (n = 3), cone-rod dysfunction (n = 2), and enhanced S-cone syndrome (ESCS) (n = 1). Table 1 summarizes the clinical features of the nine probands.

Genetic testing was done for five probands (patients #1, 2, 5, 7, and 9). Their genetic results were previously reported in other cohorts.[5,12,13] Patient #1 (CSNB) was compound heterozygous for TRPM1 (NM_002420.5) pathogenic variant (c. 2782C >T; p.Arg928Trp and c.2999G >A; p.Arg1000Gln). Patient #2 (CSNB) was homozygous for the TRPM1 pathogenic variant c.245_250delinsGTGAAAGAT; p.Asp82_Ser83delinsGlyGluArg. Patient #5 (XLRS) was homozygous for the RS1 (NM_000330.3) pathogenic variant c.304C > T; p.Arg102Trp. Patient #7 (cone-rod dystrophy [CORD]) was heterozygous for CRX (NM_000554.4) deletion [c.(100_1_101‑1)_(c.901_1?) del]. Patient #9 (ESCS) was homozygous for

Table 1: Summary of the clinical and electrophysiological findings in the cohort

| ID | Age (years) | Sex | Visual complaint | BCVA | Refraction | Presumptive diagnosis | Scotopic rod-only response | Scotopic flash a-wave | Photopic | Final diagnosis |
|----|-------------|-----|-----------------|------|------------|-----------------------|--------------------------|----------------------|----------|----------------|
| 1  | 5           | Female | Poor night | 20/30 | −4.00−1.25X117 | CSNB | Flat | WNL | Low, delayed | Same |
| 2  | 16          | Male | Poor night | 20/40 | +0.25−3.00X147 | CSNB | Flat | Broad | WNL | Same |
| 3  | 22          | Male | Poor night | 20/20/20 | Plano | CSNB (Oguchi) | Flat | Low | Low | Same |
| 4  | 38          | Male | Low | 20/20 | +19.00X036 | XLRS | Flat | Low (flat OD) | Low (flat OD) | Same |
| 5  | 18          | Female | Low | 20/50 | +1.00−2.25X141 | XLRS | Flat | WNL | Low | Same |
| 6  | 19          | Male | Poor night | 20/30 | +0.25+1.25X100 | XLRS | Flat | WNL | Low | Same |
| 7  | 48          | Male | Low, photophobia | 20/150 | +2.25 | Maculopathy | Low | Low | Low, delayed | CORD |
| 8  | 39          | Female | Low, photophobia | 20/150 | −1.50−0.50X100 | CORD | Low | Low | Almost flat | Same |
| 9  | 12          | Female | Low, especially night | 20/20 | +7.75−2.25X011 | ESCS | Flat | Low, delayed | ESCS pattern | Same |

BCVA: Best-corrected visual acuity, LP: Light perception, CSNB: Congenital stationary night blindness, XLRS: X-linked retinoschisis, CORD: Cone-rod dystrophy, ESCS: Enhanced S-cone syndrome, WNL: Within normal limits, OD: Right eye, OS: Left eye

Figure 1: Wide-field imaging of patient #3. (Top) Fundus photos of the right eye (left) and left eye (right) showing golden-yellow discoloration of the fundus that disappears after a 2-hours period of dark adaptation patching (bottom left) and gradually reappears after performing the electroretinogram (bottom right). The resolution of the discoloration after dark adaptation is known as the Mizuo–Nakamura phenomenon and is a feature of the Oguchi disease form of congenital stationary night blindness.
the NRL (NM_006177.4) pathogenic variant c. 339C >G; p.Tyr113*.

Two illustrative case histories are as follows:

**Patient #3: congenital stationary night blindness (Oguchi disease)**[^2,^14]

A 22-year-old male presented with nonprogressive poor night vision since early childhood. His best-corrected visual acuity was 20/20 in both eyes. Cycloplegic refraction was plano both eyes. There was no strabismus or nystagmus. Retinal examination was significant for golden-yellow metallic sheen of the posterior pole and mid-periphery in both eyes that disappeared after 2 hours of dark adaptation [Figure 1]. Full-field ERG demonstrated an unrecordable rod response, a small a-wave with an electronegative waveform response to the scotopic flash, and relatively good photopic response [Figure 2].

**Patient #9: NRL-related enhanced S-cone syndrome**[^15]

A 12-year-old girl presented with reduced visual acuity and poor night vision since early childhood. Her best-corrected visual acuity was 20/150 in the right eye and 20/200 in the left eye. Cycloplegic refraction was +7.75-2.25X011 in the right eye and +7.00-2.00X175 in the left eye. Complete ophthalmologic evaluation revealed nystagmus and accommodative esotropia. Fundus examination showed nummular deep hypopigmented lesions around the arcades with hyperpigmented spots and macular schisis in both eyes [Figure 3]. Full-field ERG was pathognomonic for the ESCS – a nonrecordable rod response, a simplified and delayed scotopic flash response which was similar to the photopic flash response, depressed and delayed photopic flicker response, and a photopic flicker amplitude less than that of the photopic flash a-wave [Figure 4]. In addition, the ERG was electronegative [Figure 4]. Genetic analysis was negative for the gene most commonly associated with

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[^2]: Reference 2
[^14]: Reference 14
[^15]: Reference 15

Figure 2: Right eye electroretinography of patient #3. (Top) Scotopic isolated rod response (left) is nonrecordable, whereas the scotopic flash response (right) shows a small a-wave and an electronegative waveform. (Bottom) Photopic flash response (left) and the 30 Hz flicker (right) are within the normal limits. Tracings for the left eye were similar (not shown).
ESCS, NR2E3, but did reveal a homozygous pathogenic variant in the other gene associated with ESCS, which is NRL (c. 339C > G; p.Tyr113*).

**Discussion**

The incidence of negative ERGs in our series was 6.6%. Associated diagnoses included autosomal recessive CSNB (AR-CSNB) (3/9), XLRS (3/9), and CORD (2/9). Our findings are consistent with results from the four previous studies from different areas of the world that assessed the incidence and causes of negative ERGs. Koh et al. (the United Kingdom) reported a 5.0% incidence, the most common diagnoses being photoreceptor dystrophy (34/128), XLRS (19/128), and CSNB (17/128). Kim et al. (the United States) reported a 4.0% incidence, the most common diagnoses being CSNB (29/73) and

![Figure 3: Wide-field imaging and spectral-domain optical coherence tomography findings of patient #9. (Top) Fundus photos of the right eye (left) and left eye (right) show nummular deep hypopigmented lesions around the arcades with hyperpigmented spots and evidence for macular schisis in both eyes. (Bottom) Corresponding optical coherence tomography confirms the presence of macular schisis in both eyes.](image)

![Figure 4: Right eye electroretinography of patient #9. (Top) Scotopic isolated rod response (left) is nonrecordable, whereas the scotopic flash response (right) shows a simplified and delayed response with an electronegative waveform. (Bottom) Photopic flash response (left) is also simplified and delayed, and the photopic 30 Hz flicker (right) is delayed and depressed, with an amplitude less than that of the photopic flash a-wave. These scotopic and photopic tracings (other than the electronegative waveform) are pathognomonic for the enhanced S-cone syndrome. Tracings for the left eye were similar (not shown).](image)
XLRS (7/73). Renner et al.[8] (Germany) reported a 3.0% incidence, the most frequent diagnoses being XLRS (17/47) and CSNB (6/47). Rocha et al.[9] (Brazil) reported a 2.5% incidence, the associated diagnoses being photoreceptor dystrophies (n = 17), XLRS (n = 3), and CSNB (n = 1).

In our series of electronegative ERGs, CSNB was the most common associated diagnosis. All our CSNB patients had AR-CSNB rather than the X-linked form, the latter being the form that is more common in other studies. Our findings are related to regional social preferences of endogamy, consanguinity, and multiplicity which increase homozygosity and thus the incidence of recessive disease.[10]

The second most common diagnosis in our series was XLRS, a diagnosis that in males is not related to increased homozygosity. This is a reflection of the frequency of XLRS as a cause for inherited retinal disease worldwide. We did have one case of an affected homozygous female, who was part of a previous report.[12] A cone-rod phenotype was seen in two probands from our series. One of these two probands had heterozygous mutation in CRX (his family was the subject of a prior report)[3]; the other did not undergo genetic testing. One proband in our series had NRL-related ESCS. ESCS is not typically a diagnosis considered in the differential of electronegative ERGs. However, a review of the literature reveals that there are at least two prior studies that documented an electronegative ERG in NRL-related ESCS.[16,17] In addition, there is a third study which when carefully reviewed shows an electronegative ERG in NRL-related ESCS.[12] Taken together, these prior cases and the current case suggest that an electronegative ERG can be associated with NRL-related ESCS. Interestingly, NRL interacts with CRX,[14] and as mentioned above, CRX mutation can be associated with an electronegative ERG.

Limitations of this study include the limited number of patients, the retrospective nature, and lack of the photopic ON- and OFF recordings. In addition, as we do not typically perform ERGs for classic retinitis pigmentosa or retinal vascular or inflammatory disease, patients with these diagnoses from our population who may have had electronegative ERGs are not represented.

**Conclusion**

An electronegative ERG in our inherited retinal disease practice is most commonly associated with recessive CSNB and XLRS. Furthermore, an electronegative ERG in a patient with ESCS may be more suggestive of biallelic mutations in NRL rather than in NR2E3.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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