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Cases in Visual Electrophysiology: Unique Insight into Sight

By Carol Westall, PhD

Visual electrophysiology provides unique insight into the functional integrity of different levels of the visual pathway and assists in clinical diagnosis. A common referral to pediatric visual electrophysiology is the child who presents with nystagmus. In the presence of a normal-appearing fundus, the nystagmus may relate to a sensory defect in the visual pathways. Standard tests include an electroretinogram (ERG), which assesses retinal function, and the visual evoked potential (VEP), which demonstrates the integrity of visual pathway function from the retina to the visual cortex. Results from these tests can help distinguish if the basis of the clinical problem lies with rod or cone photoreceptors, the inner retinal layer, the optic nerve or chiasm, or the post-chiasmal pathway. Important for pediatric electrophysiology is the comparison of patient data collected with age-corrected normal data.[1-3] These tests complement and supplement other methods of assessing the visual system. This issue of *Ophthalmology Rounds* presents 3 cases of children with early-onset nystagmus, which illustrate the essential role of visual electrophysiology in their diagnoses.

Electroretinogram

The ERG, typically recorded from an electrode on or close to the cornea, is formed by a series of peaks occurring in the first 200 msec after light stimulation of the retina. Some retinal cells hyperpolarize, while others depolarize in response to changes in retinal illumination. This results in a series of negative and positive voltage changes (peaks), which are recordable at the cornea. The consequence of these summed biopotentials is the ERG. The form and timing of the ERG is related to the eye's state of light adaptation and to the intensity and temporal characteristics of the stimulus. The ERG is generated by a uniform flash of light, usually from a Ganzfeld.

ERGs allow assessment of rod and cone activity separately. Rods and cones can function separately or interactively, depending on the level of illumination. The rod pathway is assessed under fully darkened (scotopic) laboratory conditions. The rod system is activated preferentially by very dim white flashes. Rod ERGs are slow responses and describe activity of the rod bipolar cells. The rod bipolar cells are depolarizing or ON bipolar cells, which receive connections from rod photoreceptors. The cone pathway is assessed when the retina is light adapted at 30 candles (cd)/m^2 for 10 minutes.[4] During light adaptation, the retinal circuitry alters to cater for a million-fold change in visual sensitivity. The cone pathways are stimulated preferentially by high-intensity white light presented in the presence of a rod-saturating background. Cones are involved in the analysis of spatial contrast discrimination mechanisms and detect decrements (OFF changes), as well as increments (ON changes) of light against an illuminated back-

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Table 1: Responses to International Society for Clinical Electrophysiology of Vision (ISCEV)-standard electroretinograms (ERGs) in cases of nystagmus

	Rod response	Mixed rod-cone response	Oscillatory potentials	Cone response	Flicker response
LCA	NR	NR	NR	NR	NR
CSNB – Complete – Incomplete	 NR Diminished	 EN EN	 NR ~ Normal	 ~ Normal Diminished	 ~ Normal Diminished
Rod monochromatism	Normal	Normal	Normal	NR	NR
Ocular albinism	Normal	Normal	Normal	Normal	Normal
Retinoschisis	Diminished/NR	EN	Diminished	Diminished	Diminished
Early-onset cone dystrophy	NR	EN	NR	~ Normal	~ Normal

LCA = Leber congenital amaurosis; NR = non-recordable; CSNB = congenital stationary night blindness; EN = electronegative

ground. Cones contact both cone ON and OFF bipolar cells directly.[5] ERG can help dissect these pathways and improve our understanding of retinal dysfunction. Table 1 provides the key electroretinographic changes that might be found when nystagmus is under investigation.

Visual Evoked Potentials

The VEP is a response evoked from the visual cortex by a changing visual stimulus; ie, a change in luminance, contrast, or colour. The electrical activity contributing to a VEP is recorded from electrodes placed on the surface of the scalp. The VEP is a small-amplitude response of 1–20 µV, embedded in the background brain activity, and recorded by electroencephalograms (EEGs). The VEP is dominated by cone activity and reflects the central 6°–10° of the retina.[6]

The stimuli typically used for the clinical measurement of VEPs are a bright flash and a checkerboard pattern. A flash stimulus may be generated by a photostimulator. The stimulus should subtend at least 20° at the eye, and should have a luminance approximating 3 cd.sec/m^2.[7] In children with nystagmus the flash VEP and a pattern-onset checkerboard provide information that allows evaluation of vision function and assessment of pathways to the visual cortex.

The following 3 cases represent the importance of these diagnostic tests in patients with nystagmus and normal fundi.

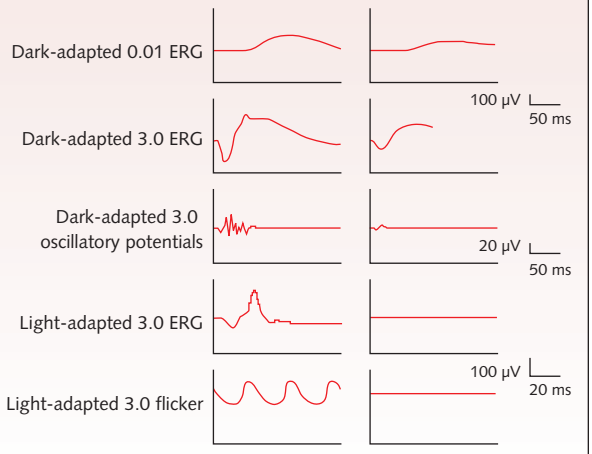
Case 1

A 3-year-old boy in good general health presents with early-onset horizontal nystagmus and photophobia. He is not taking any medications, and there is no family history of nystagmus. The fundus examination is normal. Visual acuity, as assessed with Teller Acuity Cards™ (TAC) was reduced (4.80 cycles/degree) compared with age-matched normal data (20 cycles/degree). An International Society for Clinical Electrophysiology of Vision (ISCEV)-standard ERG was recorded under sedation (Figure 1).

Figure 2 shows the ERG results. Compared with age-matched normal data, the rod response (dark-adapted 0.01 ERG) and mixed rod-cone response (dark adapted 3.0 ERG) were within normal limits. The cone response (light-adapted 3.0 ERG) was non-recordable above noise, as was the 30 Hz flicker (light-adapted 3.0 flicker). These results show normal scotopic (rod-dominated) activity and non-recordable photopic (cone-dominated activity). The non-recordable photopic responses and normal scotopic

Figure 1: Child, sedated with chloral hydrate, lying supine on a stretcher. The Burian-Allen contact lens electrodes can be seen. The ground electrode is seen on the forehead.

Figure 2: ISCEV standard ERG response recorded from control subject (left) and case 1 (right).



responses were consistent with rod monochromatism (Table 1).

Rod monochromatism is a stationary (ie, nonprogressive) disorder. It is a rare, inherited and (most often) an autosomal-recessive condition. Genes identified for rod monochromatism are cyclic nucleotide gated (CNG) channels CNGA3, CNGB3, and CNAT3.[8]

A genetic analysis identified a mutation in the CNGB3 gene. The child was determined to have an autosomal-recessive type of rod monochromatism.

Case 2

This case involves a 14-year-old male with nyctalopia. He was found to have micro-horizontal nystagmus with a latent component in each eye and high myopia (right eye [RE] -7, +2.50 axis 180; left eye [LE] -6.5, +1.50 axis 180. There was no family history of nystagmus. Visual acuity was reduced: RE: 0.5 logMAR (minimum angle of resolution), LE: 0.85 logMAR. He had a normal fundus examination, with the exception of myopic appearance and some blunting of macular reflex.

ERG results are shown in Figure 3. The rod response (dark-adapted 0.01 ERG) was non-recordable compared with age-matched normal data. The mixed rod-cone response (dark-adapted 3.0 ERG) was electronegative. The cone response (light-adapted 3.0 ERG) was normal in amplitude but the a-wave showed a distinctive square-wave configuration. The 30-Hz flicker (light-adapted 3.0 flicker) was within normal limits. The electronegative mixed rod-cone response and configuration of the cone response were consistent with complete congenital stationary night blindness (cCSNB).

cCSNB is characterized by non-recordable rod response and an electronegative mixed rod-cone response.[9] The light-adapted 3.0 cone ERG with a square-wave appearance and 30-Hz flicker response has near normal amplitudes. X-linked cCSNB is related to mutations in the *NYX* gene involving nyctalopin, which is thought to disrupt development of retinal bipolar connections.[10]

There is no known history of nystagmus (as stated) or CSNB in the patient's family. This is thought to be an isolated case and genetic analysis is pending. The diagnosis in this case was considered to be cCSNB.

Normally, the mixed rod-cone ERG has a b-wave that is 1.5- to 2-fold the size of the a-wave. When the dark-adapted rod response (0.01 ERG) and dark-adapted mixed rod-cone b-wave response (3.0 ERG b-waves) are markedly attenuated or non-recordable and the dark-adapted 3.0 ERG a-wave may be larger than average, this a-wave-dominated ERG is described as a "negative" ERG. The differential diagnosis of negative scotopic ERG is listed in Table 2.

Figure 3: ISCEV standard ERG response recorded from control subject (left) and case 2 (right).

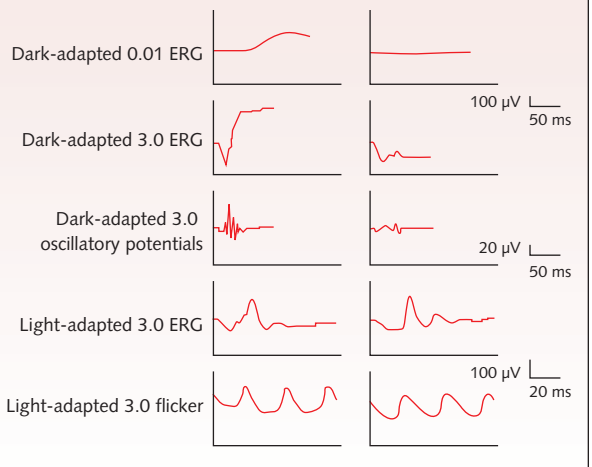


Table 2: Differential diagnosis for negative scotopic ERG

- CSNB[11]
- X-linked retinoschisis[12]
- Infantile and juvenile neuronal ceroid lipofuscinosis[13]
- Duchenne muscular dystrophy[14]
- Early RP in a subset of RP patients[15]
- Bull's eye maculopathy[16]

Case 3

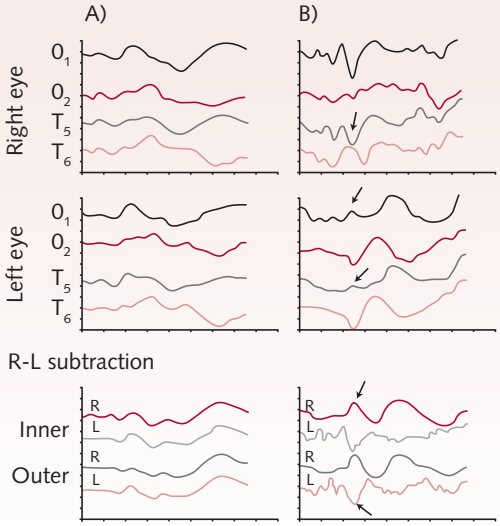
A 1-year-old boy, born as a twin (heterozygous) at 28 weeks gestation, presents with nystagmus which was noticed by his mother at 1.5 months of age. The child is in good general health and is not currently receiving any medications. He is photophobic, has blonde fundi, small optic nerves, a minimal macular reflex, and an otherwise normal fundus with no evidence of retinopathy of prematurity. TAC acuity, under binocular viewing, was reduced at 4.80 cycles/degree compared with 8 cycles/degree for a visually normal 1-year-old. Refractive error was +6.50 in both eyes. There was no family history of nystagmus. The ERG was normal. To rule out a disorder of the optic nerve or optic chiasm or a postchiasmal defect, the VEP was measured.

Pathways from the retina to the striate cortex normally undergo partial decussation at the optic chiasm; nasal retinal fibres cross to the *contralateral* cortex and temporal retinal to the *ipsilateral* cortex. There are some conditions when there is an excess or depletion of fibres crossing at the optic chiasm to the contralateral cortex. Nystagmus is common in conditions having such misrouting patterns. In albinism, many more fibres than normal cross from the retina to the contralateral cortex.[17] In achiasmia or chiasmal hypoplasia most fibres project from the retina to the ipsilateral hemisphere.[18]

To detect visual pathway misrouting, VEPs are recorded with a transoccipital montage of 5 electrodes positioned centrally over the visual cortex (0z) and at 4 lateral placements over the left and right cortical hemispheres. Specifically, VEPs are recorded at electrode positions 0z, 0_1, 0_2, T_5, and T_6 for the assessment of ipsilateral and contralateral cortical signals.[19] Soong, Levin, and Westall[19] found that the most accurate technique for detecting chiasmal misrouting involved subtracting the right occipital response from the left to create an interhemispheric difference potential.

When compared with a 7-month control (Figure 4A), multichannel VEP testing in this patient (4B) shows a classical picture of chiasmal misrouting. Positive and negative peaks appear at around 150 msec (arrows) in the opposite directions for the outer (T_5 and T_6) electrode position in the right eye and both the inner (0_1 and 0_2) and outer electrode positions in the left eye. The interhemispheric difference potential (bottom graphs) displays marked variance between the case patient and the control for both inner and outer electrode placements.

Figure 4: ISCEV standard-flash VEP responses in a 7-month control (A) and the case 3 patient (B), recorded with a transoccipital montage of 5 electrodes. The top 2 plots represent right and left eye recordings, respectively. The bottom plot is the subtraction of the right occipital response (R) from the left (L) to create the interhemispheric difference potential. The upper 2 traces are from the innermost electrodes and lower 2 from the outermost electrodes.



O_1 = inner-left electrode; O_2 = inner-right electrode; T_5 = outer-left electrode; T_6 = outer-right electrode

Soong, Levin, and Westall[19] compared the interhemispheric difference potentials between the left and right eye recording, using the Pearson correlate, for the detection of chiasmal misrouting. They determined that this method was associated with approximately 80% accuracy. Patients with a confirmed molecular diagnosis of albinism were found to have symmetrical responses for all 5 paradigms.

The child in this case was diagnosed with visual pathway misrouting, which is believed to be secondary to ocular albinism with an autosomal-recessive inheritance pattern. The mutation analysis is pending (testing albinism genes).

Conclusion

The 3 case patients all presented with nystagmus and normal appearing fundi. Visual electrophysiological workup enables one to distinguish sensory visual pathway dysfunction from idiopathic early-onset nystagmus. Examples of conditions (or diseases) with identifiable electrophysiological findings are Leber congenital amaurosis (LCA), congenital stationary night blindness (CSNB), rod monochromatism, ocular albinism, retinoschisis, and cone dystrophy.

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Abstracts

Development of ERG responses: the ISCEV rod, maximal and cone responses in normal subjects.

Fulton AB, Hansen RM, Westall CA.

PURPOSE: Summarize ISCEV ERG responses from normal infants and children.

METHODS: The amplitudes and implicit times of the ISCEV rod, maximal dark-adapted and cone responses from a total of 409 normal infants (n = 128), children and adult controls were compiled. The subjects, aged 1 week to 52 years, were divided into seven age groups, including four in infancy (< 52 weeks). The response parameters for each age group were summarized as percentiles.

RESULTS: In each ISCEV condition, the youngest infants (1-5 weeks) had significantly smaller amplitudes and longer implicit times than adults. Amplitude increased and implicit time decreased systematically with age.

CONCLUSIONS: The developmental changes in ERG responses are significant. The medians and ranges herein provide provisional norms against which the ERG responses from pediatric patients can be compared.

Doc Ophthalmol. 2003;107(3):235-241.

Comparison of techniques for detecting visually evoked potential asymmetry in albinism

Soong, F., A. V. Levin and Westall C.A.

PURPOSE: We compared techniques for analyzing visually evoked potential (VEP) asymmetry in children with albinism to find one that could be used effectively and efficiently.

METHOD: Subjects included 21 child volunteers, ages 10 months to 6 years (control group) and 21 children with albinism, ages 2 months to 6 years (albinism group). Five-channel flash VEP was performed on all subjects. Electrodes were positioned at Oz, O1, O2, O3, and O4 (10/20 system). Data were analyzed by use of techniques previously described. These included inspection of the VEP waveforms, measurement of hemispheric waveform parameters, calculation of an asymmetry index, and use of a bipolar derivation between left and right hemispheric responses (interhemispheric difference potential). In addition, we quantified the interhemispheric difference potential by use of Pearson's correlation coefficient. Measurements of sensitivity and specificity determined the success of the 5 analysis paradigms. The accuracy of each paradigm represented the ability to classify the data according to volunteer or albinism group and is derived from both sensitivity and specificity measures.

RESULTS: Measurement of hemispheric differences in VEP waveform parameters was the least sensitive measure method for detecting multichannel VEP asymmetry in albinism. Comparison of left and right eye interhemispheric difference potential increased accuracy to 67%. Nonquantitative inspection of waveform demonstrated an accuracy of 76%. The asymmetry index and Pearson's correlate measure yielded accuracy rates of 79% and 83%, respectively.

CONCLUSION: The efficiency and capability of Pearson's correlate measure in quantifying interhemispheric difference potentials to detect albinotic misrouting makes this a useful and practical technique in a pediatric clinic.

J AAPOS. 2000;4(5):302-310.

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