Nonsedated handheld electroretinogram as a screening test of retinal dysfunction in pediatric patients with nystagmus

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PURPOSE To assess the feasibility, sensitivity, and specificity of nonsedated handheld cone flicker electroretinogram (ERG) as a screening tool to detect retinal dysfunction in children with nystagmus.

METHODS Pediatric patients at a tertiary referral center from December 2015 to July 2016 were enrolled and placed into three age-matched groups: normal, nystagmus with a retinal dystrophy, and nystagmus without a retinal dystrophy. Unsedated 30 Hz cone flicker ERG responses were obtained using a handheld device (RETeval) from both eyes of each patient using skin electrode sensors after pupillary dilation.

RESULTS A total of 71 children were enrolled; amplitudes and implicit times were successfully obtained in 65 (92%): 31 (mean age ± SD, 5.6 ± 2.7 years; range, 1-12 years) without nystagmus and 34 with nystagmus. Nystagmus patients were grouped by those with (n = 15; mean age, 8.5 ± 4.5 [range, 2-17 years) and without (n = 19; mean age, 4.3 ± 3.0 [range, 6 months-10 years]) a retinal dystrophy. The patients with retinal dystrophies had significantly smaller amplitudes and prolonged or nonmeasurable implicit times than the other two groups ($P < 0.001$). Among nystagmus patients, amplitude was able to discriminate between those with and without retinal dystrophies with area under curve of 0.986 (SE = 0.016; $P < 0.001$). An amplitude <5 μV in combination with an implicit time of >33 ms warrants further evaluation.

CONCLUSIONS Unsedated handheld cone flicker ERG is a feasible screening test that effectively detects retinal dysfunction in children with nystagmus. In conjunction with clinical findings, the test helps reduce the need for sedated ERG in children. (J AAPOS 2017;21:384-388)

Abnormalities of the visual sensory pathways account for more than 90% of all causes of nystagmus presenting in infancy.[1] Ocular abnormalities associated with infantile nystagmus include congenital cataracts, corneal opacities, hereditary retinal disorders, and optic disk and foveal hypoplasia. Hereditary retinal disorders associated with early-onset nystagmus often present with a normal clinical retinal appearance and include achromatopsia, Leber congenital amaurosis (LCA), and congenital stationary night blindness.[2,3] Diagnosis in these cases is typically made through a combination of clinical exam, family history, electroretinogram, and genetic testing.[4]

Full-field electroretinography (ERG) provides an objective assessment of retinal rod-cone function by recording electric potentials generated in response to flashes of light under scotopic and photopic conditions as defined by the international standard[5]; it is the clinical gold standard in the identification of hereditary retinal disorders,[6] for which early diagnosis is becoming more important as effective gene therapies are being developed. Availability of standard full-field ERG is geographically variable and is in part related to requirements such as a dark adaptation room, ERG equipment, and availability of ERG specialists. ERG testing is particularly challenging in infants or young children because of poor cooperation, discomfort of contact lens electrodes if used, and the lengthy examination time. Sedation or general anesthesia is often needed to obtain the standard full-field ERG in children. Although sedative and anesthetic agents alter the ERG signals and may make the interpretation of

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ERG findings more difficult, sedated ERG provides accurate diagnosis in most cases.[7-12] However, data suggests that general anesthesia may affect the developing brain in animals[13] and may be associated with a modestly elevated risk of neurodevelopmental disorders in children.[14-16]

A Federal Drug Administration–approved, self-contained, handheld, noninvasive ERG recording system has been recently developed (RETeval LKC Technologies, Gaithersburg, MD). This device has been used to evaluate retinal function in a limited number of studies,[17-21] with only one study[21] evaluating a small number of children with a protocol not compliant with International Society for Clinical Electrophysiology in Vision (ISCEV) standards.[5] The technique uses adhesive skin electrodes and obtains cone flicker ERG readings in less than one minute. With the use of a flicker stimulus, the cone-mediated ERG can be isolated.[7] The flicker ERG of the RETeval device has demonstrated correlation with conventional ERG flicker in adult patients.[20]

There are several reasons why the cone flicker ERG appears to be an ideal diagnostic screening tool in children. First, the majority of nystagmus-inducing retinal disorders of infancy and young childhood, including achromatopsia and LCA (with the exception of congenital stationary night blindness), involve cones.[2,3,11,22,23] Second, each cone flicker recording is usually performed over 10 seconds, requires no dark adaptation and can be performed with the patient previously exposed to typical room light. In addition, cone flicker response is obtained by averaging many responses over a short period resulting in increased signal-to-noise ratio with high reproducibility. Given the potential benefit for portable, nonsedated, efficient cone flicker ERG evaluation in children with low risk to the patient, as well as the lack of data and experience regarding this novel device, we studied the RETeval cone flicker ERG as a screening test for retinal disease in children with nystagmus.

Subjects and Methods

This prospective study was approved by the University of Miami Institutional Review Board and conducted at Bascom Palmer Eye Institute from December 2015 to July 2016. Children with nystagmus undergoing evaluation in the pediatric ophthalmology clinic were invited to participate. A control group of children with normal visual acuity and without nystagmus or structural ocular abnormalities was also enrolled. After a comprehensive explanation of the procedure, an informed consent was obtained from each patient's parent/guardian. Additionally, patients ≥7 years of age gave informed assent.

All patients had a complete ophthalmic examination, with measurements of the best-corrected visual acuity, intraocular pressure, slit-lamp examination, and indirect ophthalmoscopy. Visual acuity was measured appropriate to the patient's age and developmental stage, ranging from fixation behavior and Teller acuity cards to Snellen visual acuity.

RETeval cone flicker ERG testing was performed in all subjects after receiving cycloplegic drops and allowing for appropriate pupillary dilation (minimum, 30 minutes); children were dilated because the device's pupil-tracking function requires cooperative fixation during examination to deliver constant retinal luminance. Skin electrodes were used for recording the ERG readings. Eyelid specula were not used. ISCEV standard 30 Hz cone flicker parameters were followed, which consists of a 3.0 cd-s/m^2 white light flash and a 30 cd/m^2 background.[5] The flicker frequency used was 28.3 Hz.

The flicker b-wave amplitude and implicit time were calculated as the mean of 2 measurements for each eye. Amplitudes and implicit times were based on the fundamental of the response. Unreliable implicit times (reported as not measurable by the device, or a confidence level >1.25 ms) were excluded, whereas the corresponding amplitude was included for analysis because timing errors, unlike amplitude errors, grow arbitrarily large with small amplitudes. The effect of age and sex on measurements were assessed with analysis of covariance. Means of amplitudes and implicit times were averaged for both eyes of each patient and compared between groups with analysis of variance. Post hoc pairwise differences were examined with the nonparametric Mann-Whitney test due to marked heterogeneity of variance among the groups. The ability of the RETeval device to discriminate between patients with and without retinal dystrophies was assessed with receiver operating characteristic (ROC) curves. The correlation between measurements of both eyes of patients was assessed with the intraclass correlation coefficient (ICC) for normal participants and interocular differences were compared between patient groups.

A normative comparison group was constructed from patients with best-corrected visual acuity of at least 20/25 Snellen visual acuity, low refractive errors (myopia or hyperopia < ±5.00 D spherical equivalent), and no structural ophthalmic pathology. Children with amblyopia were not included. Patients with nystagmus were divided into those with and without retinal dystrophies based on clinical examination findings and previous full-field ERG and/or genetic testing when available.

Results

A total of 71 patients were enrolled. RETeval readings were successfully obtained in 65 patients (92%) and were included in the analysis. Six patients were excluded due to inability to cooperate for the examination (crying or eyelids closed during examination).

Of the 31 normal subjects, 18 (58%) were male, with a mean age of 5.6 years (range, 1-12 years). Among the 25 normal subjects old enough for Snellen visual acuity measurement, the median best-corrected visual acuity in the better seeing eye was 20/20; among the 6 participants (mean age, 21 months; range, 13 months to 2 years 6 months) with Teller measurements, the median converted visual acuity was 20/180 (range, 20/89-20/270), and the mean refractive error was +1.06 spherical equivalent (range, −1.4 to + 4.5). There was no correlation with age for either RETeval cone flicker implicit time ($P = 0.322$) or amplitude

Table 1. Diagnoses of patients with nystagmus[a]

Nystagmus patients	No. cases[a]
With a retinal dystrophy	
Achromatopsia	7 (4)
Alström syndrome	1 (1)
Combined rod-cone dystrophy without genetic diagnosis	4
LCA	3 (2)
Without a retinal dystrophy	
Aniridia	1
Bilateral Peters anomaly	1
Congenital motor nystagmus	10
Oculocutaneous albinism	2
Optic nerve hypoplasia	4
Pontocerebellar hypoplasia	1

LCA, Leber congenital amaurosis.
[a]Number of genetically confirmed diagnoses in parentheses.

($P = 0.316$). Females had larger amplitudes (average difference, 4.0 μV [$P = 0.062$]) and shorter implicit times (average difference, 0.9 ms [$P = 0.039$]) than males. There was no age difference between males and females (mean age, 5.3 vs 6.5 years; $P = 0.45$), and amplitudes in normal patients and nystagmus patients without retinal dystrophies did not show an age dependence.

The 34 patients with nystagmus were subdivided into two groups: those with (n = 15) and without (n = 19) a retinal dystrophy. See Table 1 for patient diagnoses.

The 15 patients with nystagmus and a retinal dystrophy averaged 8.5 years of age (range, 2-17 years) and had a median best-correct visual acuity in the better seeing eye of 20/200 (range, 20/40-LP) and average spherical equivalent of 2.45 (range, −1.88 to +7.5). All but 3 patients had validation of retinal dysfunction by full-field, standard ERG evaluation performed prior to this study at the discretion of their pediatric ophthalmologist. All full-field ERGs required general anesthesia. One patient underwent sedated ERG testing at an outside institution. For 2 children parents declined sedated ERG: one has a clinical diagnosis of achromatopsia; the other, clinical features consistent with Bardet Biedl syndrome. Genetic testing and ERG have been recommended for both patients. Of the 15 patients, genetic testing was performed in 11, in 7 of whom disease-causing mutations were detected (Table 2).

Of the 19 patients with nystagmus without a retinal dystrophy, 14 subjects (mean age, 6 years; range, 2 years 4 months to 10 years) old enough for Snellen visual acuity measurements had a median best-correct visual acuity in the better seeing eye of 20/65 (range, 20/40-20/360); in the 5 participants (mean age, 19 months; range, 12-25 months) with Teller measurements the converted Teller-to-Snellen visual acuity was a median of 20/270 (range, 20/130-20/1400). The mean age of patients with nystagmus without a retinal dystrophy was 4.3 years (range, 6 months to 10 years), and the mean refractive error was 0.59 spherical equivalent (range, −5.62 to +5.25). The most frequent diagnosis was congenital motor nystagmus, diagnosed clinically by relatively good visual acuity (mean

Table 2. Confirmed genetic mutations and patient demographics

Patient	Diagnosis	Mutation	Sex	Age at Reteval test, years
1	Achromatopsia	*GNAT2*	M	10
2	Achromatopsia	*CNGB3*	F	2.5
3	Achromatopsia	*GNAT2*	F	14
4	Achromatopsia	*CNGB3*	M	3
5	Alström syndrome	*ALMS1*	M	7
6	LCA	*GUCY2D*	M	15
7	LCA	*CRB1*	F	6

LCA, Leber congenital amaurosis.

Snellen visual acuity, 20/60), absence of nerve or retinal pathology on examination, family history, and absence of night blindness and high myopia. Optic nerve hypoplasia was the second most frequent diagnosis, confirmed by fundus examination, optical coherence tomography of the optic nerve, and fundus photography. Of the 19 patients, only 2 had a history of full-field ERG testing prior to the current study; both patients were in the congenital motor nystagmus group, and their ERGs showed normal rod and cone responses.

RETeval unsedated cone flicker ERG differences between all groups were highly significant for both amplitude and implicit time (both $P < 0.001$) with or without accounting for sex. See Table 3. Pairwise post hoc comparisons demonstrated that nystagmus patients with retinal dystrophies had significantly lower amplitudes and longer implicit times than both nystagmus patients without retinal dystrophies and normal controls (both $P < 0.001$). Nystagmus patients without retinal dystrophies also had different amplitudes and implicit times from controls but at a reduced level of significance (amplitude $P = 0.010$, implicit time $P = 0.016$). Figure 1 shows the distribution of individual patients in the three groups for ERG implicit times and amplitudes.

Among nystagmus patients, amplitude distinguished between those with and without retinal dystrophies with an area under the receiver operating characteristic curve of 0.986 (SE = 0.016; $P < 0.001$). A 100% specificity and 93% sensitivity was achieved, with a cut-off of 2.54 μV, and 94.7 % specificity and 93% sensitivity was achieved with a cutoff of 5μV. Only 5 patients with retinal dystrophies had measurable implicit times.

In the normal participants, the intraclass correlation coefficients for interocular amplitude and implicit time were 0.82 and 0.71, respectively, indicating good to excellent agreement between eyes.[24] The mean interocular difference was 3.1 ± 2.0 μV for amplitude and 0.8 ± 0.7 ms for implicit time in normal patients. Mean interocular differences in amplitude were 4.8 ± 3.7 μV for nystagmus patients without retinal dystrophies and 0.5 ± 0.7 μV for patients with retinal dystrophies. Interocular differences in amplitude were highly significantly different between patients with nystagmus and retinal dystrophies and the other patient groups (both $P < 0.001$ [Mann-Whitney test]) but not between normal

Table 3. Reteval device results by group

Patient group	No.	Amplitude, μV, mean ± SD	No. patients (%) unmeasurable implicit time		Implicit time, ms, mean ± SD
			One eye	Both eyes	
Normal	31	22.5 ± 5.9	0	0	25.8 ± 1.3
Nystagmus without a retinal dystrophy	19	16.8 ± 7.5	2[a] (11)	0	26.9 ± 1.9
Nystagmus with a retinal dystrophy	15	1.48 ± 2.3	4 (27)	10 (67)	38.7 ± 9.2[b]

[a]Two patients with nystagmus without a retinal dystrophy had measurable implicit times in only one eye because of compliance issues during testing.
[b]Only 5 patients with nystagmus and a retinal dystrophy had measurable implicit times in at least one eye.

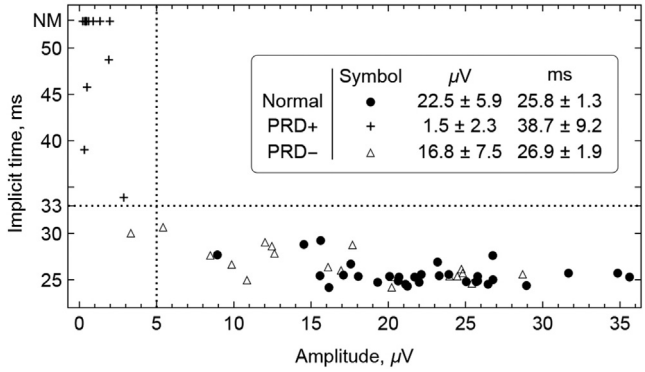

FIG 1. Distribution of amplitudes and implicit times for the three RETeval device study groups: *NM*, non-measurable; *PRD+*, patients with nystagmus and a retinal dystrophy; *PRD−*, patients with nystagmus without a retinal dystrophy.

controls and nystagmus patients without retinal dystrophies ($P = 0.13$ [Mann-Whitney test]). Mean interocular differences in implicit time could not be calculated for patients with nystagmus and retinal dystrophies because of the unmeasurable implicit time for both eyes in all but 1 patient. The average interocular difference in implicit time for nystagmus patients without retinal dystrophies was 1.7 ± 1.9 ms, which was not significantly different from normal patients ($P = 0.10$ [Mann-Whitney test]).

Discussion

The results of our study indicate that nonsedated handheld cone flicker ERG using skin electrodes is a feasible, fast, and effective screening test to detect retinal dysfunction in children with nystagmus with minimal discomfort and risk. The RETeval cone flicker ERG performed in dilated eyes demonstrates the ability to detect lower amplitudes and delayed implicit times in nystagmus patients with retinal dystrophies with reasonable sensitivity and specificity and can differentiate these patients from nystagmus patients without retinal dystrophies and from normal patients.

RETeval amplitudes are lower in comparison to published conventional sedated ERG values with contact lens electrodes, mostly attributable to the use of skin electrodes with the device, and this relationship merits further investigation. However, in our study we were able to determine recording value cutoffs that demonstrate its utility in screening for a retinal dystrophy. In our patients, an amplitude of ≥2.54 μV was associated with more than a 90% probability of no disorder of cone function. Further, a patient with an amplitude less than 5 μV in combination with an implicit time of >33 ms warrants further exploration, as illustrated by the dotted line in Figure 1. Additionally, if the device is not able to measure an implicit time, there should be a high concern for retinal disease: only 5 of 15 (33%) patients with nystagmus with an underlying retinal disorder had a measurable implicit time in at least one eye.

In addition to distinguishing patients with retinal dystrophies from those without, differences were detected between nystagmus patients without a retinal dystrophy and controls. The difference was smaller, and may be attributable to the fact that nystagmus likely reduces the measured ERG amplitudes due to eye movement artifacts that interfere with the averaging calculations. However, given the low amplitudes and prolonged implicit times demonstrated in patients with retinal dystrophies, it is easy to differentiate between groups.

We found no age effect on the RETeval cone flicker amplitudes and implicit times. Of the limited studies of normative ERG data in children, it is suggested that cone responses mature earlier than those of rods and that recordings in children >1 year of age may not differ from those of older children and even adults.[25] However, there are a small number of studies that show a trend of gradual cone flicker maturation in early childhood based on both sedated and nonsedated conventional recordings from contact lens electrodes.[26,27] Further study with the RETeval device in larger numbers of children is needed to establish normative data. In the normal group, we found a nonsignificant trend for larger amplitudes in females, even though there were no significant age differences between groups. As sex has no significant influence on the ERG, a likely explanation is that the young female children often were more cooperative with testing than young males.

The RETeval device demonstrated good agreement between eyes in measuring implicit time and amplitude in both normal subjects and in nystagmus patients without retinal dystrophies. The presence of nystagmus in a patient with a normal retina did not affect the reliability of measurements between eyes in comparison to normal patients. The interocular differences in amplitudes in patients with nystagmus and a retinal dystrophy are small, reflecting the almost flat amplitudes. In patients with poor

agreement on repeat testing or a lack of clinical correlation the authors recommend conventional ERG.

An additional limitation of this study is the grouping of patients into the nystagmus without a retinal dystrophy group without full-field ERG testing. Using only a cone flicker protocol could miss complete congenital stationary night blindness (CSNB) patients that have nystagmus and primarily rod dysfunction, although these patients typically have high myopia and nyctalopia that aid diagnosis. Incomplete CSNB patients lack these characteristic symptoms, however, and typically have mildly decreased visual acuity and decreased rod and cone responses.[28] If there is suspicion for CSNB, or if the screening test does not correlate, the authors recommend proceeding with a full-field ERG.

A notable limitation of this study is the lack of infants. It is generally recommended, however, to wait for ERG testing on infants until age 1 year given the natural and rapid maturation of the ERG during the first year of life and the difficulties of interpretation in the developing infant retina.[26,29]

When the nonsedated RETeval cone flicker ERG with skin electrodes is impaired or equivocal, options for further diagnostic evaluation include sedated full protocol international standard full-field ERG, or genetic testing, which can be directed based on clinical findings but may not be covered by insurance. Advantages of proceeding to sedated full protocol ERG with corneal electrodes include better quality phototopic as well as scoptopic ERG responses with increased sensitivity to low amplitudes, which may be necessary to establish baseline retinal function and monitor disease over time.

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