

Electroretinographic assessment and diagnostic reappraisal of children with visual dysfunction: A prospective study

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Purpose: To assess the presence or absence of a retinal cause of visual impairment using electroretinography (ERG) in children with no obvious discernable cause on ocular examination.

Design: Prospective observational case series.

Materials and Methods: A prospective study was carried out involving 120 children with the mean age 4.4 ± 3.2 years with visual dysfunction. All children underwent ERG under general anesthesia using a special handheld mini-Ganzfeld (Kurbisfeld) dome.

Results: Fifty-two (43.3%) children were male and 68 (56.7%) were female. The clinical diagnosis was as follows: Leber's congenital amaurosis (LCA) (n=47), achromatopsia (n=25), congenital stationary night blindness (CSNB) (n=9) and others (unclassifiable, n=39). The visual acuity ranged from perception of light (PL) to PL with projection in children with LCA. In the rest (n=73), some sort of visually guided behavior was discernable. Following ERG, a diagnostic reappraisal resulted as follows: LCA (n=49), achromatopsia (n=28), CSNB (n=4), cone-rod dystrophy (n=22), rod-cone degeneration (n=7), normal (n=8) and others (unclassifiable, n=2). Except for the two unclassifiable cases, ERG was successful in the diagnosis or exclusion of retinal dysfunction in the rest. By Pearson Chi-square test, there was a statistically significant association between the clinical and ERG diagnosis ($P < 0.001$).

Conclusion: LCA was the commonest cause of visual dysfunction in our series. A statistically significant correlation between clinical and electrophysiological diagnosis was seen. ERG helped in firmly establishing the presence or absence of global retinal dysfunction in the majority (118/120) of pediatric patients with visual dysfunction.

Key words: Anesthesia, electroretinography, Ganzfeld, Kurbisfeld, visual dysfunction, visual evoked potential.

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Visual dysfunction in children presents a diagnostic challenge.¹ The possibility of a retinal disorder has to be ruled out especially in the presence of normal fundi in order to exclude other causes of visual impairment such as optic nerve head disorders (for example, hereditary optic atrophy), cortical visual impairment (CVI) and delayed visual maturation (DVM). Although objective signs such as nystagmus, sluggish pupillary reaction and high refractive errors (in the presence of a clear lens and cornea), might point towards an organic reason for the visual loss,^{2,3} electroretinography (ERG) can be carried out in order to confirm and qualify the presence of retinal disorder.¹⁻⁵ The aim of the study was to find out the utility of ERG under general anesthesia in establishing the

diagnosis in children referred for visual impairment with no obvious discernable cause on ocular examination.

Materials and Methods

A prospective study was carried out involving 120 children with the mean age of 4.4 ± 3.2 years with visual dysfunction. Children with obvious discernable cause of visual dysfunction on examination such as cataract, glaucoma, corneal scars, and retinal detachment were excluded. The study was approved by our institutional review board. All the children underwent ERG under general anesthesia in order to establish a possible retinal cause for their visual impairment. Prior to the ERG, all the patients had an estimation of their visual capacity by suitable visual acuity tests commensurate with their age, by a single examiner experienced in the visual assessment of infants and children. The visual acuity was graded into five grades: no perception of light (no PL), PL only, PL with projection, visually guided behavior (ability to fix and follow a light, toy or face or reach for a seen object) and measurable grating acuity.

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All children underwent cycloplegic retinoscopy, detailed assessment of their anterior segments and fundi. This was carried out either in the outpatient clinic itself or under general anesthesia while doing ERG in uncooperative cases. Presence of oculodigital sign, nystagmus, strabismus, keratoconus, high refractive error, salt and pepper and other pigmentary fundus abnormalities were carefully documented in all cases. A clinical diagnosis was made in all cases which included Leber's congenital amaurosis (LCA) as per Lambert's criteria,² achromatopsia and congenital stationary night blindness (CSNB). Cases which did not fit into these three categories including possibly normal cases, suspected DVM and CVI cases were classified as others. A separate definitive diagnosis in all the cases was made by ERG. The clinical and electrophysiological examination was performed by a single examiner (VV and JJ respectively).

General anesthesia was administered to dark-adapted infants by ketamine with inhalation in certain cases as decided by the anesthesiologist. All the patients received noninvasive monitoring of the oxygen levels. Bipolar Burian-Allen electrodes were placed alternately on each cornea to record the scotopic responses first, followed by the photopic responses. The handheld mini-Gansfeld (Kurbisfeld, UTAS 3000, LKC Technologies) was used to provide the flash and flicker stimuli. The steps consisted of: 20 min of dark adaptation, scotopic 24dB single flash (isolated rod response), scotopic 0dB single flash (Maximum combined response; MCR), oscillatory potentials, 10 min of light exposure, photopic 0dB single flash and finally photopic 30Hz flicker. All the steps were repeated at least twice at the same sitting by the same examiner to ensure reproducibility. The normative data of our lab was used as a baseline for comparison [Table 1].

An extinguished ERG was considered for the diagnosis of LCA, while achromatopsia was characterized by absent photopic and normal scotopic responses. Abnormal ERG which is often negative (preserved 'a' wave in the presence of a subnormal 'b' wave) occurs in CSNB with visual dysfunction. Cases were classified as rod-cone degeneration if the ERG demonstrated grossly subnormal amplitudes in both the scotopic and photopic phases and cone-rod dystrophy if the photopic phases were extinguished in the presence of subnormal scotopic phases. Cases which had equivocally mild abnormalities of the ERG amplitudes or implicit times which did not commensurate with any of the above mentioned conditions were classified as others (unclassifiable) and these were advised to undergo a clinical and ERG re-evaluation after six months. Cases which had good ERG parameters were classified as normal.

In addition, all the children underwent flash visually evoked potential (VEP) using the same Kurbisfeld as the

source of the flash, with positive electrode placed at Oz (10% of the nasion-to-inion separation), negative electrode in the midfrontal area and ground electrode on the forehead. Since the children were anesthetized and not alert, pattern VEP was not carried out at the same sitting. Children with a normal ERG and flash VEP and with a clinical diagnosis of postretinal dysfunction such as optic nerve dysfunction, CVI, etc, were referred to a pediatric neurologist for further management. Pattern VEP was attempted in all such cases, however it remained undefined due to poor and transitory cooperation of the children. Statistical analysis in the form of Pearson chi-square test was carried out to look for any association between clinical and ERG diagnoses. All the patients received optical and rehabilitative care appropriate to their condition.

Results

All the examinations were free of untoward complications. Fifty-two (43.3%) of the 120 children were male and 68 (56.7%) were female. The clinical diagnosis was as follows: LCA (n=47), achromatopsia (n=25), CSNB (n=9) and others (unclassifiable, n=39) [Table 2]. The visual acuity ranged from PL to PL with projection in all the children clinically diagnosed to have LCA (n=47). In the rest (n=73), some sort of visually guided behavior was discernable. None of the children had no PL vision. Measurable grating acuity was not clearly elicitable in any of the children. The refractive errors ranged from hypermetropia (range +2 to +6 dioptres) in all children clinically diagnosed to have LCA (n=47) and myopic astigmatism (range -1.5 to -3.5 D of spherical equivalent) in the rest (n=73).

Following ERG, a diagnostic reappraisal resulted as follows: LCA (n=49), achromatopsia (n=28), CSNB (n=4), cone-rod dystrophy (n=22), rod-cone degeneration (n=7), normal (n=8) and others (unclassifiable, n=2) [Table 3]. LCA was the commonest clinical and electrophysiological diagnosis of visual dysfunction in our series. The commonest fundus finding in the cases diagnosed by ERG as LCA was attenuated retinal vessels (seen in all 49 cases) which was similar to the series of Al-Salem.⁶ ERG corroborated the clinical diagnosis

Table 1: Normative data of Electroretinography

Step of Electroretinography	Amplitude	Implicit time
Scotopic 24dB	211.5 ± 46.5 mv	112 ± 8 msec
Scotopic 0dB	439.5 ± 79.5 mv	46 ± 2 msec
Oscillatory potentials	178 ± 35 mv	-
Photopic 0dB	101 ± 32 mv	28 ± 1 msec
Photopic 36Hz	64.4 ± 17.1 mv	28.3 ± 1 msec

Table 2: Distribution of the patient population based on clinical diagnosis and gender

Clinical diagnosis	Gender	Frequency	Percentage
Leber's congenital amaurosis	Male	20	42.6
	Female	27	57.4
	Total	47	100.0
Achromatopsia	Male	9	36.0
	Female	16	64.0
	Total	25	100.0
Congenital stationary night blindness	Male	4	44.4
	Female	5	55.6
	Total	9	100.0
Others	Male	19	48.7
	Female	20	51.3
	Total	39	100.0

Table 3: Distribution of the patient population based on electrophysiological diagnosis and age

Electroretinography diagnosis	Number	Minimum age (months)	Maximum age (years)	Mean (years)	Standard deviation
Leber's congenital amaurosis	49	3	13	4.93	3.15
Achromatopsia	28	5	9	3.52	2.82
Cone-rod dystrophy	22	1	8	4.23	2.46
Congenital stationary night blindness	4	24	3	2.75	0.5
Rod cone degeneration	7	9	10	4.46	4.12
Others	2	24	4	3.0	1.41
Normal	8	7	14	5.52	5.58

of LCA in 80.9% of the cases (38/47 of the cases), the clinical diagnosis of achromatopsia in 44% of the cases (11/25 cases), the clinical diagnosis of CSNB in 33.3% of the cases (3/9 cases) and the clinical diagnosis of others in a mere 5.1% of the cases (2/39 cases) [Table 4]. Hence ERG was most useful in the diagnostic reappraisal of cases which were unclassifiable by clinical examination (others, n=39). Except for the two unclassifiable cases, ERG was successful in establishing the diagnosis or exclusion of retinal dysfunction in the rest. By Pearson chi-square test, there was a statistically significant association between the clinical and ERG diagnosis (P value: <0.001). All the children including those with LCA had elicitable flash VEP responses.

Discussion

Of all the retinal causes of visual dysfunction in infants and children, the commonest is LCA,^{2,3,5,6} which comprises a group of hereditary disorders inherited as an autosomal recessive trait characterized by poor vision since birth, oculodigital sign, roving eye movements, sluggish pupillary responses and high hyperopia.⁶⁻⁸ The majority of the patients with LCA have normal appearing fundi during infancy. As they grow older, patches of peripheral chorioretinal atrophy, macular colobomata and mottling develop. These children may or may not be mentally retarded. Some of them thought to be mentally retarded demonstrate normal intelligence when tested later in childhood. This is probably because visually impaired children reach certain developmental milestones later than normally sighted ones, regardless of their intelligence.⁹ The visual acuity in LCA is usually counting fingers or worse. Lambert *et al.*² have laid down three criteria for diagnosing LCA: 1) A nonrecordable or highly attenuated ERG, 2) A severe visual deficit since infancy, 3) The absence of another specific retinal or multisystem disorder. We followed these criteria in the diagnosis of LCA in our series as well, with the

second and third criterion necessary for the clinical diagnosis and all three for the final diagnosis.

Other retinal disorders that can present in infancy or childhood include achromatopsia, CSNB and cone-rod or rod-cone degenerations. Achromatopsia is a condition characterized by a partial or complete absence of cone function.² Visual acuity is usually in the range of 20/80-20/200. The affected children manifest photoaversion, nystagmus and defective to absent color perception. The fundi are usually normal or may demonstrate temporal pallor of the optic discs and subtle macular changes. It is inherited as either an autosomal recessive or X-linked recessive trait. It is of two varieties: complete and incomplete. The electrophysiological features of complete achromats are characterized by a complete absence of cone responses with normal rod-mediated components. The incomplete achromats however, demonstrate various degrees of cone function. The ERG findings do not change with time as the children get older.¹⁰

CSNB is a condition which may also be associated with congenital nystagmus, decreased vision, especially in the dark and normal-appearing fundi.² The visual acuities range from 20/20 to 20/200. It is most commonly inherited as an X-linked recessive trait. The other modes of inheritance are autosomal dominant (which is not associated with decreased vision) and autosomal recessive. Patients with CSNB and myopia (who most commonly have defective vision and hence seek an ophthalmic referral earlier in childhood itself) have a characteristic negative wave in ERG: A normal 'a' wave and an attenuated 'b' wave in the scotopic 0dB response. Cone responses are also frequently abnormal. In this condition, too, the ERG findings do not change with time as the children get older.¹¹ Miyake *et al.* have further subdivided such patients into complete (with no electrophysiological evidence of rod function) and incomplete types (with partial rod function on ERG).¹²

Table 4: Cross-tabulation of clinical diagnosis with electroretinography diagnosis

Clinical diagnosis	Electroretinography diagnosis							Total
	LCA	Achromatopsia	CSNB	Cone-rod dystrophy	Rod-cone degeneration	Normal	Others	
LCA	38	1	0	5	3	0	0	47
Achromatopsia	3	11	0	9	0	2	0	25
CSNB	3	1	3	0	2	0	0	9
Others	5	15	1	8	2	6	2	39
Total	49	28	4	22	7	8	2	120

P value: <0.001 by Pearson chi-square test (for association between clinical and electrophysiological diagnosis). CSNB: Congenital stationary night blindness, LCA: Leber's congenital amaurosis

There are other conditions characterized by retinal dystrophy and attenuated ERG such as Joubert's syndrome, peroxisomal disorders, neuronal ceroid lipofuscinosis, osteopetrosis, Jeune syndrome, Alstrom syndrome etc, that have characteristic systemic abnormalities and can hence be distinguished from LCA, achromatopsia and CSNB, which do not have such associations.^{2,13} The diagnosis of congenital retinal disorders in infancy and childhood involves a careful history (onset and nature of the visual dysfunction, whether it is worse at day or night time, and ability to perform visual tasks) clinical examination (including estimation of best corrected visual acuity, retinoscopy, slit-lamp evaluation of the anterior segment, keratometry and viewing the cornea with Placido's disc to rule out keratoconus, intraocular pressure (IOP) assessment and fundus examination by indirect ophthalmoscopy) and electrophysiological assessment of the cases and their family members. An ERG should be recorded both under scotopic and photopic conditions to distinguish between disorders predominantly affecting the rod and cone photoreceptors. It is crucial to distinguish between retinal disorders with a stationary course and those with progressive visual and neurological deterioration.

To the best of our knowledge, this is the largest series of children to be studied using electrophysiology (computerized search using Medline). The previous highest series of electrophysiological assessment (in LCA alone) was by Lambert *et al.* involving 43 children.³ In addition, this is the first study in the Indian population involving ERG under general anesthesia and employing the handheld Kurbisfeld (Medline search). Ours was a prospective study in which the electrophysiological recordings were evaluated without the knowledge of the results of the clinical tests and the correlation between the clinical and electrophysiological assessment was also assessed statistically.

Conclusion

ERG helped in firmly establishing the presence or absence of global retinal dysfunction in the majority (118/120) of children, clearly establishing its importance in the evaluation of pediatric patients with visual dysfunction. The ERG parameters recorded under general anesthesia were reproducible and provided a reliable means of diagnosing the cause of visual dysfunction in children.

A good statistically significant correlation between clinical and electrophysiological diagnosis with a *P* value <0.001 was seen in our series which is essential in the diagnosis of visual dysfunction in children especially of the preverbal age group as suggested by Cibis *et al.*¹⁴ Of note, all the children including those with LCA in this study had elicitable flash VEP responses as was noted previously.³ This commensurates with the diagnosis of retinal dysfunction in cases with an abnormal global ERG. This also possibly ruled out significant postretinal dysfunction in most of the children in our series (except the

eight children who had normal ERG values and two unclassifiable cases). This exclusion or diagnosis of a visual pathway defect in early life is crucial for the facilitation of early learning by proper rehabilitation, follow-up care and functional prognosis, genetic counseling, as well as in the avoidance of unnecessary neuroimaging studies in certain cases.

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