A Case Series Study of Leber's Congenital Amaurosis: Clinical Description and ERG Findings

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Abstract

Purpose: To evaluate the incidence of Leber's Congenital Amaurosis (LCA) in low vision children referred to electrophysiology ward of Farabi Eye Hospital, and review the clinical features of disease and Electroretiongraphy (ERG) test values to confirm the diagnosis and severity of the disease in Iran.

Design: Prospective observational case series

Methods: Two-hundred and fifteen cases of low vision infants and young children were referred to electrophysiology ward of Farabi Eye Hospital during 18 months. Clinical LCA diagnosis was made and ERG tests were done and LCA diagnosis was confirmed. The symptoms, signs and the results of eye examination and ERG findings were recorded.

Results: The mean age of the patients was 27.43 (range, 1-120 months). Among low vision patients fourteen percent of patients had LCA. Fifty-four percent of the patients were female. Nystagmus and low vision were the two most common clinical manifestations of these patients. Hyperopia was the main refractive error (54.80%) and mild abnormalities in fundus examinations were found in 67.70% of cases. In nearly 90% of cases consanguinity was found. ERG was flat or unrecordable in more than 90% of cases, but in less than 10% of cases with recordable curves, severe decrease in amplitude of waves was encountered. ERG confirmed LCA diagnosis in 31 out of 37 patients (positive predictive value of 83.7%).

Conclusion: The incidence of LCA in low vision children is similar to other studies. ERG helped in confirmation of presence or absence of overall retinal dysfunction in the majority $^{31}/_{37}$ (83.7%) of LCA patients. It can differentiate these cases from other cases with poor vision in infantile age but genetic testing is recommended.

Keywords: Leber's Congenital Amaurosis, Electroretinography, Congenital Retinitis Pigmentosa, Congenital Nystagmus, Congenital Stationary Night Blindness

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Introduction

Leber's congenital amaurosis (LCA) is a congenital retinal dystrophy described almost 150 years ago.[1] LCA prevalence is 1:50,000-100,000 and is an early-onset inherited cause of childhood blindness characterized by a severe retinal dysfunction.[2] It is a group of disorders with little or no vision, slow nystagmus-like movements, abnormal amounts of hyperopia, and an extinguished (flat) electroretinography (ERG). LCA is considered as an autosomal recessive genetically heterogeneous condition.[3] Six genes have role in this disease, and they participate in a wide variety of retinal pathways.[1]

Histopathological analyses are diverse; most cases have extensive retinal changes, some have an entirely normal retinal architecture, whereas others have primitive, poorly developed retinas. Gene therapy for RPE65 deficient dogs could restore sight, partially; so it provides the first hope of treatment for this blinding condition.[1]

Ethnic differences and geographic variations may affect the frequencies and genetic pattern. Most of the molecular genetic studies of LCA are generally based on Caucasian populations.[4] No data concerning LCA in Iranian patients have been reported before. It seems that characterization of patients is an important issue to be discovered, so it is a need to study this disease in Iranian patients by identifying clinical description and ERG findings, and then suggesting a study for performing genotype–phenotype correlations and to discover their genetic pattern.

In this study we are going to evaluate and review the clinical description and ERG finding of Iranian LCA patients and also determining positive predictive value of ERG in confirming clinical diagnosis.

Methods

Two-hundred fifteen cases of infants with low vision were referred to electrophysiology ward of Farabi Eye Hospital from May 2004 to November 2005 for diagnosis of the causes of low vision.

All of them were evaluated under anesthesia (EUA) and after excluding anterior segment, vitreous body and retinal problems as a cause of low vision, ERG tests were done under anesthesia.

The symptoms, signs, family history, and systemic problems were recorded. Refraction, best corrected visual acuity (BCVA) (in patients older than 4 years), slit lamp examinations, funduscopy and ERG tests were performed.

At first, clinical diagnosis of LCA was guessed then a separate definitive diagnosis in all cases was made by ERG (photopic and scotopic) to confirm clinical diagnosis and evaluate positive predictive value of this test. The clinical and electrophysiological examination was performed by a single examiner.

An extinguished ERG was considered for the diagnosis of LCA, while achromatopsia is characterized by absent photopic and normal scotopic responses, and negative ERG occurs in congenital stationary night blindness (CSNB) with visual dysfunction.

The criteria for clinical LCA diagnosis were absence of any lesions in cornea, anterior chamber, lens, vitreous body or retina, except mild pigmentary changes of fundus that can explain low vision with an extinguished or very low amplitude ERG confirming the diagnosis.

All the patients received optical or rehabilitative care related to their situation.

Descriptive and analytical statistics were performed to the obtained dataset and positive predictive value was determined by dividing the number of ERG-confirmed patients to clinical diagnosed ones.

Results

The clinical diagnosis of LCA was made in 37 cases out of 215.

Mean age of LCA patients was 27.43 months (range, 1-120 months), 14 cases were male and 17 cases were female. Positive family history was seen in 74.2% of cases. Parents were relative in 87.1% of cases.

The most common symptom was low vision (41.9%) and nystagmus (38.7%). Three cases (9.7%) were referred due to strabismus.

Full ocular examination and also ERG test were performed in all patients after anesthesia (EUA). Following ERG, a confirmative diagnosis were made in 31 cases, best corrected visual acuity was at least light

perception in most of cases, but in few of them, especially in older ones (older than 4 years), it was counting finger or more. Measurable grating acuity was not clearly obtainable in any of the children.

Emmetropia, hyperopia and myopia were seen in 8 (25.8%), 17 (54.8%) and 2 cases; respectively (Table 1).

Table 1. Clinical ocular findings

Signs and symptoms	cases	%
low vision chief complaint	13	41.9
Nystagmus	12	38.7
Strabismus	3	9.7
Photophobia	1	3.2
Low vision and photophobia	2	6.5
Hyperopia	17	54.8
Myopia	2	6.5
Normal fundus	10	32.3
Abnormal fundus	21	67.9

Fundus was normal in 10 cases (32.3%) and mild abnormality was observed in 21 cases (67.7%) in which mild retinal pigment epithelium (RPE) changes at periphery was the most common finding.

Two cases had history of convulsion and one case was mentally retarded. Prematurity was observed in one case and deafness, polydactily and renal abnormalities were seen in another case that might be considered as Bardet Biedel syndrome.

ERG corroborated the clinical diagnosis of LCA in 83% of the cases ([31]/[37]), ERG changes in our patients showed severe abnormalities in all cases. In more than 90% of cases the ERG was absolutely flat and unrecordable. These cases were the ones with very low visions. All the patients with abnormal fundus (pigmentary changes) and positive parents consanguinity, and younger than 6 months, were in the group with unrecordable ERG. ERG was recordable but with low amplitude in 3 cases (about 10%) in which fundus examination was normal (Figures 1-4).
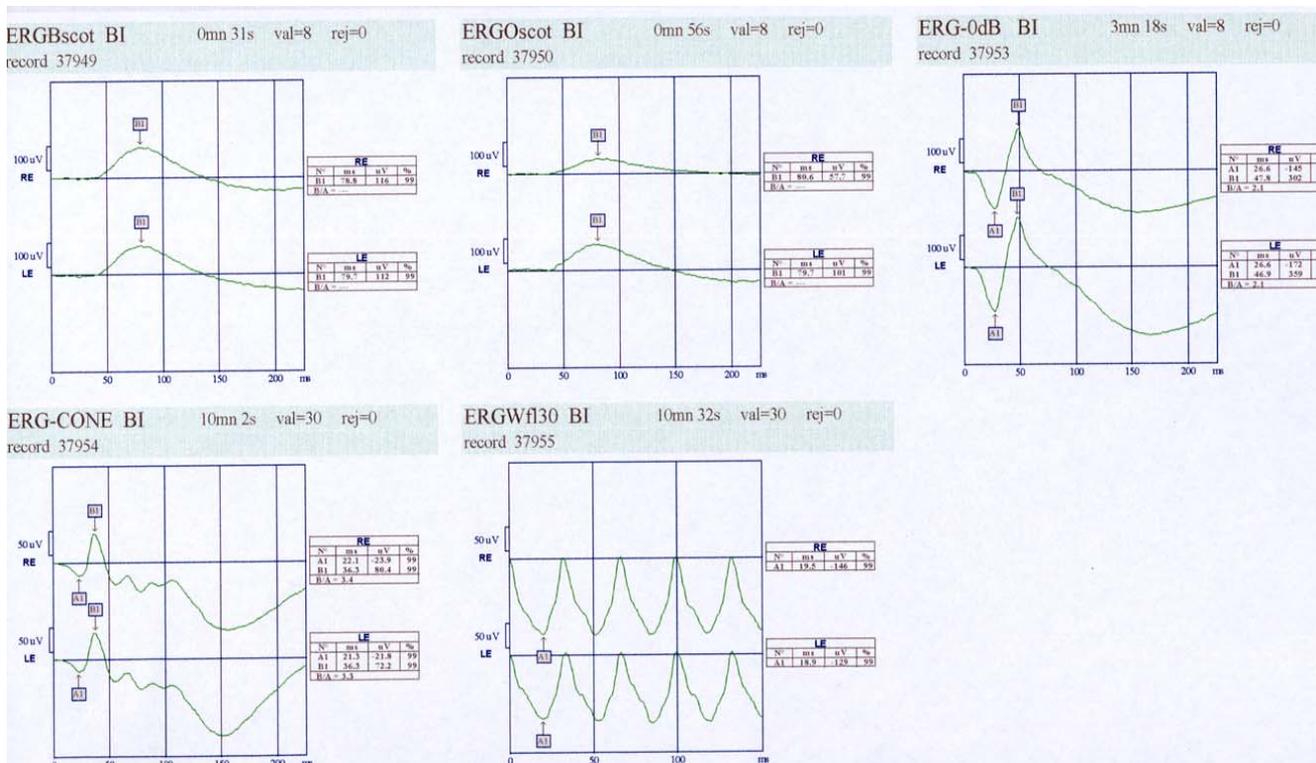

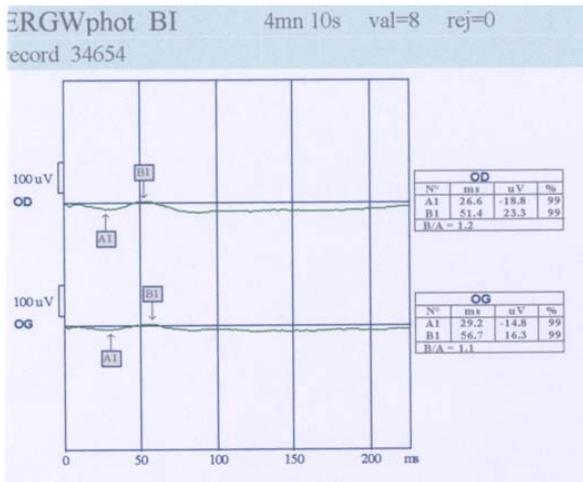**Figure 1.** Normal scotopic and photopic and flicker ERG in a normal person

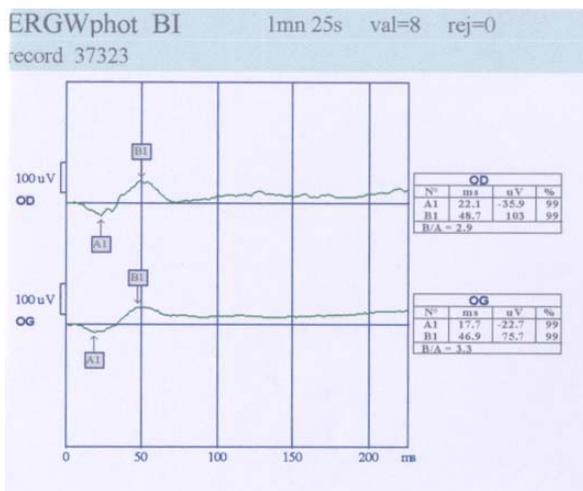**Figure 2.** Very low amplitude a and b waves in one of the cases with normal fundus and presenting nystagmus

Figure 3. Lower than normal amplitude a and b waves but relatively good ERG in a case with photophobia
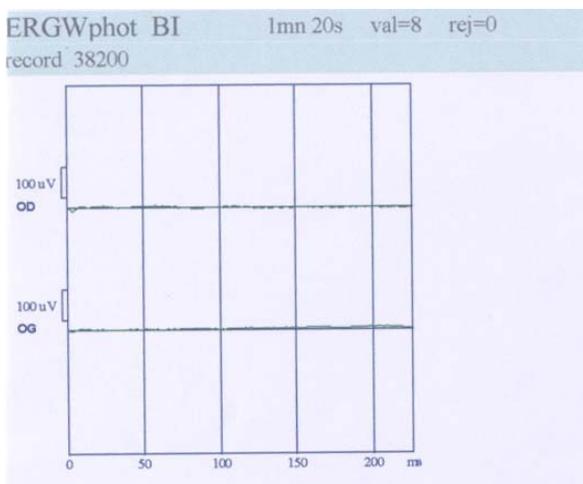

Figure 4. Absolutely flat ERG in many of cases

Discussion

LCA is the most common retinal cause of visual dysfunction in infants and children;[5-8] it is characterized by early poor vision, oculodigital sign, roving eye movements, sluggish pupillary responses and high hyperopia.[8-10]

The differential diagnosis of congenital blindness can be challenging. Differentiating these various entities is especially important because some are progressive, some are stationary and some are confined to the eye, but others are systemic. Future potential therapies with gene replacement are disease-specific. Therefore, the exact retinal diagnosis is important and will probably be more important in the near future.[5]

Five early onset retinal diseases without syndromic features that need to be ruled out in the differential diagnosis of LCA are complete achromatopsia, incomplete achromatopsia, CSNB, incomplete CSNB, and albinism. Clinical examinations especially refractive errors can help for diagnosis.[11,12] Diagnostic mean to these six diseases is the ERG test.[13]

As our results show, low vision chief complaint is seen in 41.9% of cases and with respect to the age of patients, any visual inattention should incite parents and ophthalmologists to the problem. Visual impairments are mentioned in more than 50% of cases in several reports.[6,9,11]

Edwards WC and colleagues explained many fundus changes in these patients, but most of these changes, as retinal pigment epithelial (RPE) atrophy, vascular attenuation and bone corpuscular pigments appeared in later stages;[14] Chew E and colleagues have reported yellow flecks in some of their cases.[15] Our results show mild RPE changes in about 68% of cases, but these alterations were not so considerable and characteristic and we do not suggest ophthalmologists to rely on fundus changes for LCA diagnosis.

The second most prevalent referring sign of our series is nystagmus (38.7%), Cibis Gw and colleagues explained the importance of ERG test in congenital idiopathic nystagmus to rule out LCA.[13] We think any early onset nystagmus in pediatric age should be regarded as a suspicious pathology pointing to LCA. Hyperopia, although not specific for LCA, is a considerable finding in this disease.

In Wagners and colleagues' results and in ours too, hyperopia is encountered in 54.8% of cases.[17] We suggest this sign as a decisive one in borderline cases with abnormal but not totally extinguished ERG.

High percentage of family history and consanguinity points to autosomal recessive genetic pattern in our series and other reports;[2,11] of course recent advances in genotyping technologies[2] have allowed the introduction of comprehensive and affordable screening procedures to determine causual genetic variations, resulting in precise molecular diagnosis of disease. Flat or unrecordable ERG is seen in more than 90% of our cases and recordable but low amplitude is encountered in about 10% of cases. In a study by Schappert-Kimminjser et al, of 112 ERGs, 68 were totally flat, 42 showed small photopic response when stimulation light was in high intensity and only two cases showed a small scotopic response,[11] that is relatively compatible with our results.

This is the first report of LCA in Iranian population with ERG test under general anaesthesia. One of the limitations of this study is that flash Visual Evoked Potentials (VEP) was not done in all cases including LCA patients, to rule out probable visual pathway lesions. Another limitation is lack of genotyping technologies to show the precise diagnosis and genetic patterns of the disease. But in overall we think history taking and careful ocular examination under general anaesthesia and ERG test performed in all low vision infants referred to us could differentiate the LCA from other causes, and suggest EUA and ERG test in any infant with low vision.

Conclusion

The incidence of LCA in low vision children in our study in Iran is nearly similar to other studies. ERG helped in firmly establishing the presence or absence of global retinal dysfunction in the majority (83.7%) of LCA patients. It can differentiate these cases from other cases with poor vision in infantile age but for determining the prognosis and possible treatments, genetic testing is recommended.

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