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Leber congenital amaurosis: a case report and review of the literature

Amaurose congênita de Leber: relato de caso e revisão da literatura

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KEYWORDS:

Retinal Dystrophies; Amaurosis; Congenital Dystrophies; Retinal Degeneration.

ABSTRACT

Leber congenital amaurosis (LCA) is an early-onset hereditary retinal dystrophy that becomes apparent in the first year of life and is characterized by severe visual impairment. Currently, 14 gene mutations that are associated with this phenotype have been identified and the transmission is autosomal recessive. We report a case of a 17-year-old male patient complaining of severe low visual acuity in both eyes since childhood, but a diagnosis had not been made. The patient did not have a family history of severe visual acuity. The family history was revealed that his parents were first cousins (consanguineous union). Fluorescein angiography, optical coherence tomography, electroretinography, and genetic testing were performed, which confirmed LCA diagnosis. Currently, studies on gene replacement therapy with promising results exist; however, they do not yet include all variants.

PALAVRA-CHAVE:

Distrofias da Retina; Amaurose; Distrofias Congênitas; Degeneração da Retina.

RESUMO

A Amaurose Congênita de Leber (ACL) é uma distrofia retiniana hereditária de início precoce, do nascimento ao 1º ano de vida, caracterizada por deficiência visual severa. Atualmente estão identificados 14 genes cujas mutações se associam a este fenótipo e a transmissão é de modo autossômico recessiva. Relatamos um paciente do sexo masculino de 17 anos com queixa de baixa acuidade visual (BAV) severa desde a infância em ambos os olhos, sem diagnóstico e sem antecedentes familiares de baixa acuidade visual severa. Da história familiar destaca-se o fato dos pais serem primos consangüíneos de primeiro grau. Foi realizado angiofluoresceinografia (AGF), tomografia de coerência óptica (OCT), eletrorretinograma (ERG) e teste genético, confirmando o diagnóstico de amaurose congênita de Leber. Atualmente existem estudos com reposição de terapia genética com resultados promissores, mas que ainda não contemplam todas as variantes.

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INTRODUCTION

Leber congenital amaurosis (LCA) is the term for a group of hereditary early-onset retinal dystrophies characterized by moderate to severe visual impairment that becomes apparent in the first months of life. Visual acuity, if assessed, ranges from 20/200 to no light perception and is rarely better than 20/200[1].

In most cases, transmission is autosomal recessive, although, some cases are described with dominant transmission. Currently, 14 gene mutations associated with this phenotype have been identified.

During the first months of life, these patients develop nystagmus, high hyperopia, enophthalmos, their photomotor reflexes are often diminished or absent, and Franceschetti's oculo-digital sign is common. Cataracts and keratoconus[2] may appear later in life. The following criteria are used in published studies to characterize patients with LCA: (1) Blindness or severe LVA in the first six months of life or first year of life[3,4]; (2) Absent or very reduced electroretinography (ERG)activity (photopic and scotopic)[2,4-6]; (3) Fundus of the eye appears normal or with minimal pigmentary changes[5] and/or moderate arteriolar narrowing[2,5]; and (4) Absence of other multisystemic or retinal disorders[4,6].

The findings in the fundus of the eye during the first months of life are normal or with minimal changes, which makes diagnosis difficult. ERG examination is the key to establishing the diagnosis[2]; little or no activity is detected in the retina, which indicates low visual function. It is common for patients to develop other changes in the retina over time, such as vascular attenuation, optic nerve atrophy (especially after the first year), pigmentary changes such as bone spicules, granular or colobomatous macular involvement, and pigmented nummular lesions at the posterior pole and in the periphery[5].

In some cases, LCA is related to central nervous system complications, such as developmental delay, epilepsy, and impaired motor skills. Because LCA is relatively rare, the frequency of associated central nervous system complications is still unknown[5]. The differential diagnosis includes congenital stationary night blindness, achromatopsy, infantile retinitis pigmentosa, Joubert syndrome, Zellweger syndrome, and infantile Refsum edisease[3].

CASE REPORT

A 17-year-old male student, E.F.D., complained of low visual acuity (LVA) in both eyes (OU) since early childhood. He reported involuntary eye movement (nystagmus) that began at six months of age when he was assessed and the hypothesis of Leber congenital amaurosis diagnosis was raised, but no additional tests were performed besides fundoscopy. He reported photophobia, visual difficulties at school, and some degree of learning deficit (using enlarged prints and sometimes rubbing the eye with fingers to see clearly). The patient had no family history of blindness or LVA. On examination, the patient exhibited bilateral horizontal nystagmus, corrected visual acuity of 20/200 in both eyes (OD: +2.50; S = −0.75 C 900° and OS: +3.50; S = −1.00 C 750°), biomicroscopy without abnormalities, intraocular pressure (IOP) of 10 mmHg in OU. Fundoscopy of OU showed macular coloboma and areas of pigmented epithelium hyperplasia in the coloboma area and in the periphery of the four quadrants (Figure 1).

Complementary diagnostic tests were requested, which are listed in the figures below.

DISCUSSION

LCA is the most severe childhood hereditary dystrophy and its main feature is severe LVA at birth or in the first year of life. The diagnosis is made at approximately two years of age, when the symptoms of patients become apparent to parents, as in the case described above.

All patients with LCA have severe low vision or near blindness. Severe LVA is reported in all studies reported in the literature. The most common refractive error is hyperopia[7], including in this case. The main symptoms are oculo-digital pressing, enophthalmos, strabismus, nystagmus, and photophobia[1,3,4,8].

Fundoscopy findings have been described as normal or minimally altered in the early stages, with subsequent occurrence of changes of extremely variable appearance. The main test for the early diagnosis of LCA is ERG activity, which is absent or almost absent, even without changes in the fundus of the eye. A delay in neuropsychomotor development associated with LCA has been questioned and may result solely from sensory deprivation caused by the disease.

A proposal for gene replacement therapy for LCA has been studied for years. The medication voretigene neparvovec-rzyl (Luxturna) has been recently

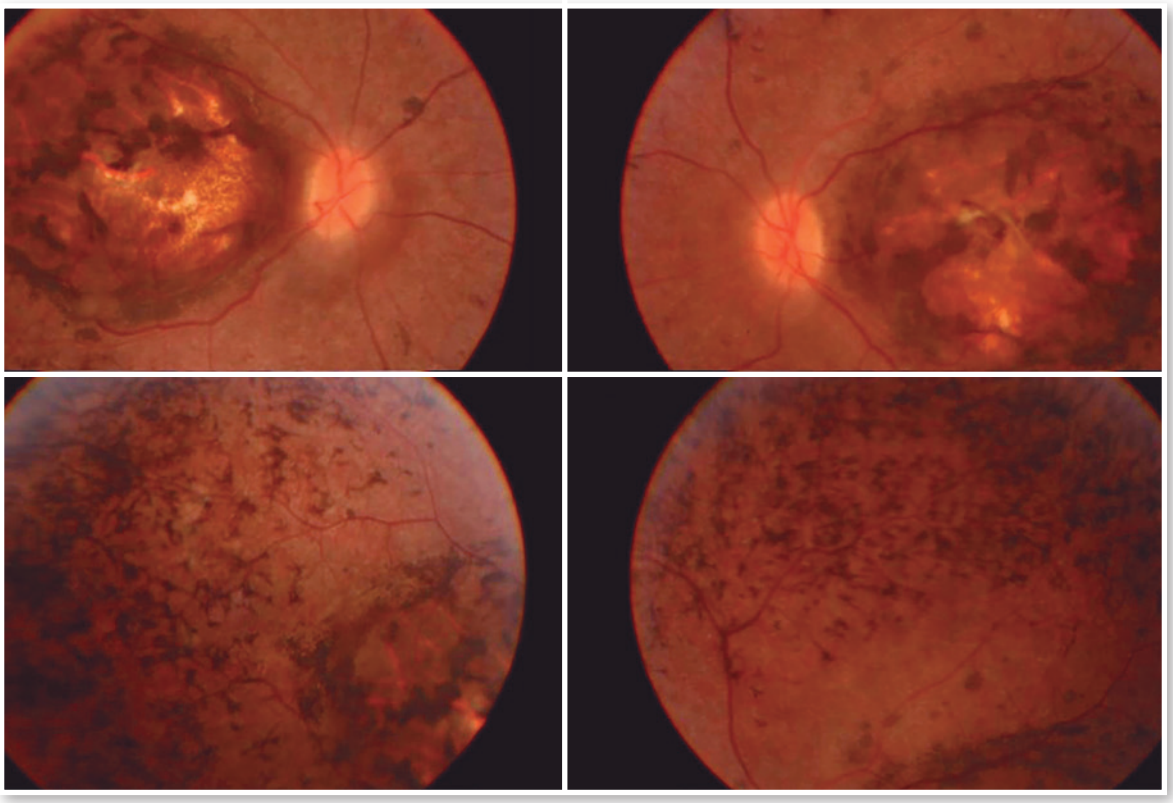

Figure 1. Retinography of both eyes showing macular coloboma with areas of retinal pigment epithelium hyperplasia in the coloboma area and middle periphery.

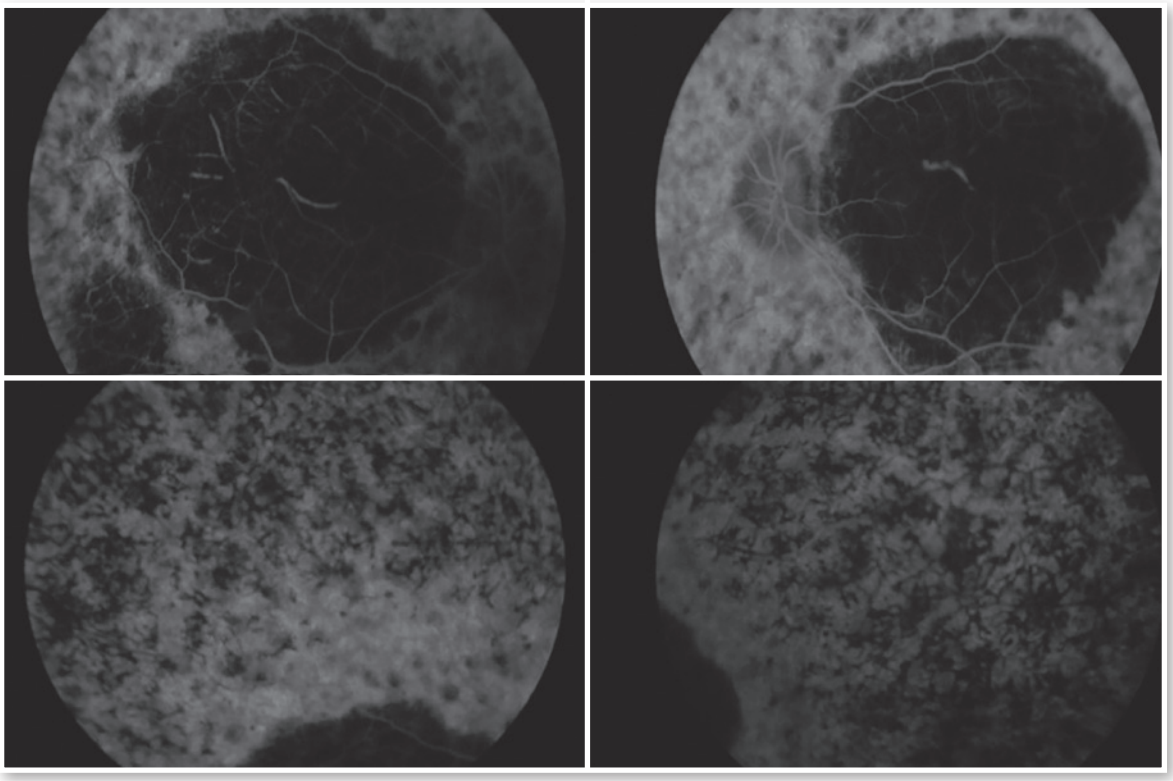

Figure 2. Fluorescein angiography with hypofluorescence by a blockage in the macular and peripheral areas, as well as mottled hypofluorescent areas in the periphery of the four quadrants, which did not change in the late phases of the examination.

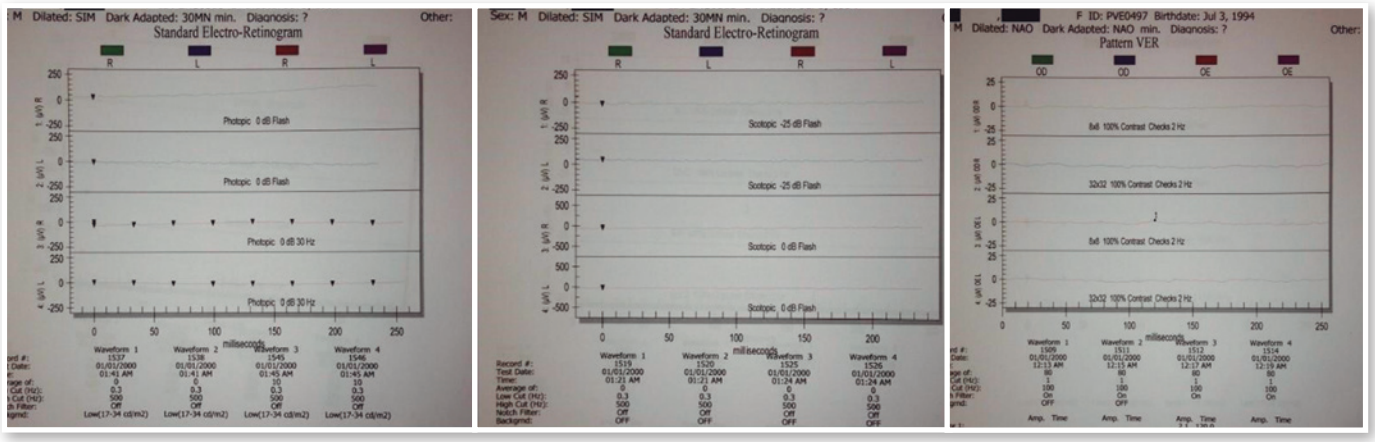

Figure 3. Electroretinography performed according to the protocol recommended by ISCEV showed no response record, in both the scotopic and photopic phases and in both eyes.

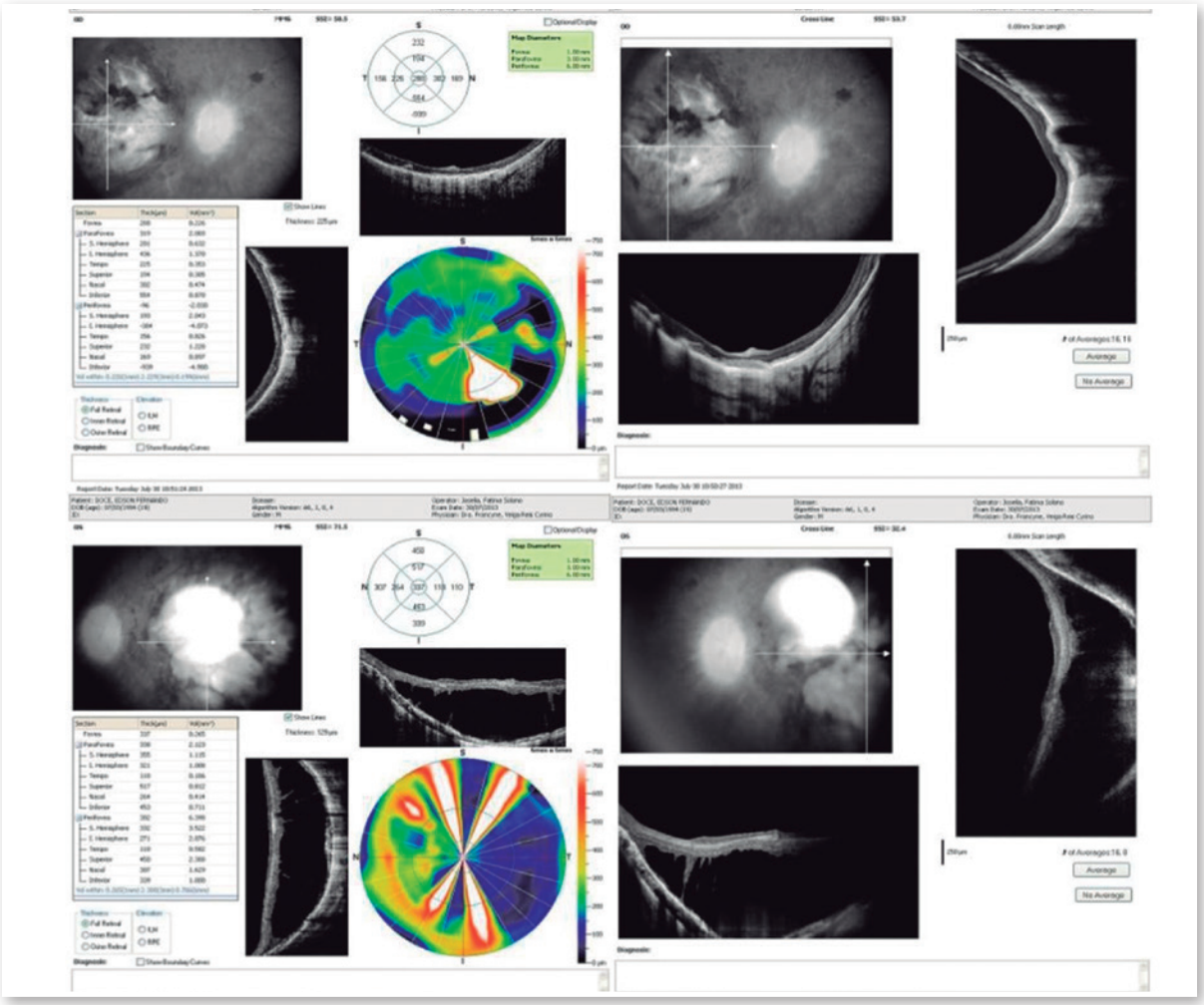

Figure 4. Optical coherence tomography showed diffuse atrophy of the retinal layers and retinal pigment epithelium in the right eye. In the left eye, extensive retinoschisis in the colobomatous area at the posterior pole was observed. Coloboma of the retina with pigment epithelium atrophy was observed in the right eye, with decreased central foveal thickness.

Figure 5. Result of genetic testing: retinopathy associated with the RDH12 gene (Leber congenital amaurosis 13).

approved by the Food and Drug Administration and is indicated for children and adults with confirmed retinal dystrophy caused by biallelic mutations of the RPE65 gene, i.e., mutations in both copies of a gene inherited from the father and mother. The therapy works by introducing a normal copy of the gene into retinal cells using an adenovirus that transfers it to the nucleus of defective cells. This allows cells to start producing the protein that converts light into an electrical signal that can be transmitted by the optic nerve, effectively restoring vision[9,10].

The therapy is applied only once in each eye with at least six days between surgical procedures. The most common adverse reactions of this treatment include conjunctival hyperemia, cataracts, and increased IOP. Approximately 1,000 to 2,000 people may have the mutation in the United States[9,10]. The genetic test did not show the mutation in the RPE65 gene in the case presented in this study. The detected variant was associated with the RDH12 gene, which is involved in the reduction of all-trans-retinal and its isomers (PMID: 15258582) and which, in this case, was inherited due to consanguinity of the parents (family variant).

In cases of hereditary dystrophies, genetic counseling is mandatory to reduce the possibility of transmission in the following generations. In the above-described case, the mutation will not be transmitted if the patient does not marry within the family. Unfortunately, to the best of our knowledge, no treatment has been reported for this variant; however, studies are underway and it will be possible to slow and even halt the progression of these debilitating conditions in the not too distant future.

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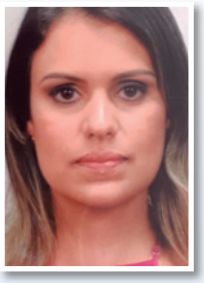

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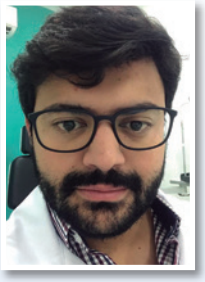

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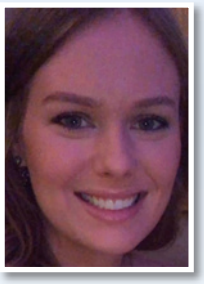

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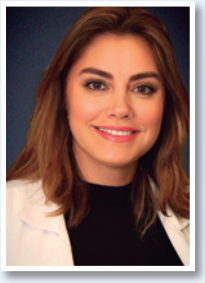

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