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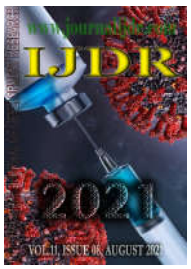

RESEARCH ARTICLE OPEN ACCESS

LEBER CONGENITAL AMAUROSIS: A INTEGRATIVE REVIEW

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ABSTRACT

Leber's Congenital Amaurosis (LCA) is an autosomal recessive eye disease, representing the most severe dystrophy of the retina, in which a genetic defect causes significant functional impairment in the retinal photoreceptors. It was first described in 1869 and is currently responsible for about 20% of cases of blindness in school-age children and for the involvement of 4.5 million people worldwide, with inbreeding populations or in isolated communities where the frequency disease increases considerably. In addition to the severe loss of visual acuity since birth, these patients have a variety of other eye disorders, such as photophobia, nictalpia and keratoconus, as well as several anomalies of the retina, such as chorio-retinal degeneration and atrophy, maculopathy and pseudopapiledema of the optic disc. It is also possible to find changes in the central nervous system associated with the LCA, such as developmental delay and impaired motor ability. Thus, using data from the literature, this review work aims to clarify the main diagnostic methods and most effective forms of treatment today.

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INTRODUCTION

Leber Congenital Amaurosis (LCA) is among Hereditary Retinal Dystrophy (HRD), a group of disorders in which a defective gene leads to dysfunction or death of photoreceptors. LCA is the most severe retinal dystrophy, leading to early blindness in childhood (Alkharashi and Fulton 2017). The disease has a high impact on society as it represents more than 5% of all retinopathies and corresponds to approximately 20% of children attending schools for the blind, also causing non-ophthalmologic changes (den Hollander, Roepman et al. 2008). It has a mostly autosomal recessive character, and so far 23 types of genes responsible for triggering the disease have been identified, 4 of which are the most relevant (Elderberry 2014; Alkharashi and Fulton 2017). The diagnosis of LCA in children is challenging and usually performed from six weeks of life, based on the ophthalmologic alterations observed, such as itinerant eye movements and mild peripheral pigmentary retinopathy and genetic tests that identify up to 23 genes responsible, especially the types RPE65, CEP290, GUCY2D and CRB1 (Chacon-Camacho and Zenteno 2015; Chung DC and Traboulsi EI 2009). Regarding the treatment of Leber's Congenital Amaurosis, there are difficulties involved due to its wide diversity of genetic mutations, and RPE cell transplantation, gene replacement and pharmacological therapy represent the three main intervention approaches in Leber Congenital Amaurosis (Ahmed E and Loewenstein J 2008).

MATERIALS AND METHODS

This is a descriptive and retrospective bibliographic study, containing information from the literature from 1992 to 2020, portraying the evolution of diagnoses and therapy. A search of scientific articles was carried out in the PUBMED, LILACS and MEDLINE databases, gathering and comparing the different data found in the sources of consultation in order to select papers pertinent to the objective. The following Health Sciences Descriptors were used: "Leber Congenital Amaurosis"; "Hereditary ophthalmopathies"; "Retinian Diseases/CN"; "Ophthalmopathies/GE AND mj: "Retina"; "Keratoconus AND congenital leber amaurosis"; "Congenital amaurosis of leber AND retinian dystrophy"; "Congenital amaurosis of leber AND retina"; "Congenital amaurosis of leber AND gene therapy". At the end of the review, 18 articles were selected to construct an article that addresses the various aspects pertinent to the theme, addressing the etiology, epidemiology, clinical manifestations,

and especially the diagnosis and treatment of Leber's Congenital Amaurosis.

RESULTS AND DISCUSSION

Natural history of the disease: Theodore Leber, a German, was the first ophthalmologist to describe the disease in 1869, which reported patients with profound loss of vision at birth or after a few days of life, nystagmus, slow pupillary response, and pigmentary retinopathy; Later, Franceschetti and Dieterle added to Leber's description the absence or decrease of electrical responses in electroretinography (Heher, Traboulsi et al. 1992). In 1957, Waardenburg observed an association of LCA with cataract and keratoconus and in the same year, the predominant lyomeanrecessive nature of the LCA was established by Alstom and Olson, and in 1963 Waardenburg, along with Schappert-Kimmijser, reported the genetic heterogeneity of the disease (Ahmed and Loewenstein 2008). Soon after, in 1963, Henkes and Verduin described aplasia, dysplasia and degeneration as the three pathological processes that could lead to a manifestation of LCA, in addition to pigmentation, retinopathy, amauerotic pupils and involuntary sensory eye movement, severe visual loss at or near birth date, and severe reduction or abolition of electrical responses in electroretinography (Ahmed and Loewenstein 2008).

Epidemiology: This rare retinal dystrophy (LCA) has a population frequency between 1:30,000 and 1:81,000 affecting approximately 4.5 million people worldwide, that is, an important form of congenital blindness. In addition, it has a high social impact covering more than 5% of all retinopathies, besides being responsible for approximately 20% of children attending schools for the blind (den Hollander, Roepman et al. 2008). It is noticed that, in conblood populations or in isolated communities, the frequency of the disease increases considerably, reinforcing the genetic burden that the disease carries with it (Chacon-Camacho and Zenteno 2015).

Etiology": Leber's Congenital Amaurosis presents a pattern of heredity, mainly autosomal recessive, but in rare cases, the autosomal dominant pattern can be found, and to date 23 responsible genes have been identified, especially the types RPE65, CEP290, GUCY2D and CRB1 (den Hollander, Roepman et al. 2008; Alkharashi and Fulton 2017). It is known that defects in the biochemical pathways of the retina and degeneration of photoreceptors with early death, associated with aplasia with abnormality in embryological development, constitute the three categories of disease in which THE can be classified (Ahmed and Loewenstein 2008).

Clinical condition: Patients with LCA present severe visual deficit at birth, which is detected around six weeks of life, due to oscillations in eye movement or absence of fixation of the gaze and, in addition, the presence of nystagmus, decreased pupillary response speed and an apparent background of the eye, which eventually evolved into a case of retinian inflammation (Chacon-Camacho and Zenteno 2015). Although in most cases gene mutations cause severe visual losses, there are some types that can have less impact on visual acuity, such as CRB1, LRAT or RPE65 gene mutations that provide visual acuity of 20/50, but these values tend not to remain stable (Chung and Traboulsi 2009). Thus, some patients have visual capacity that allows them to walk or even read in adulthood, while others lose the ability to read visual in a few years or even do not present it, reading only in Braille (Hufnagel, Ahmed et al. 2012).

Ophthamological changes: Initially, the retina has a normal appearance. Over time, however, several anomalies may develop, such as moderate attenuation of its vascularization, pseudopapiledema of the optic disc, maculopathy, bone spicule pigmentation, salt and pepper pigmentation, peripheral confluent yellow spots, retinal white spots, marbled retina, preserved periarteriolar pigmentepithelium, Coats reaction and macular coloboma (which in this case is not a true coloboma , but reflects a slight degeneration and corio-retinal atrophy centered on the photon) (Alkharashi and Fulton 2017). As for refraction defects, these are variable, and patients with Leber Congenital Amaurosis more commonly present hyperopia, but may present with high degrees of myopia and some children may still develop photophobia and nictalpia (Chacon-Camacho and Zenteno 2015). Other common findings to be found are keratoconus, which is usually associated with LCA and can further reduce visual acuity and cataract that is usually found in more severe LCA conditions (den Hollander, Roepman et al. 2008). It is common for patients to present Franceschetti's oculus-digital sign, a phenomenon that consists of pressing the eyeball into the orbit in search of possible luminous sensations, but is not pathognoconic of the disease (den Hollander, Roepman et al. 2008; Chacon-Camacho and Zenteno 2015).

Non ophthamological changes: Among the non-ophthalmologic alterations associated with LCA, the main disorder is mental retardation, which was reported in 52% of patients with the disease, but it is believed that these data are overestimated since, in most cases in which mental retardation was reported, no imaging of the cerebral parenchyma (Chacon-Camacho and Zenteno 2015) was performed. In addition, cases of olfactory dysfunction associated with the mutation of the CEP290 gene and stereotyped movements such as hand friction, hair touch and grimaces in patients with LCA (den Hollander, Roepman et al. 2008) have been described; Chacon-Camacho and Zenteno 2015).

Diagnosis: Because Leber's Congenital Amaurosis is a rare disease, the difficulty in performing a comprehensive ophthalmologic examination in infants and the lack of characteristic findings make the diagnosis challenging, however, early detection of the disease is extremely important in order to achieve maximum benefit to the patient regarding vision and also to psychological and emotional issues caused by visual dysfunctions (Alkharashi and Fulton 2017). The diagnosis of the disease is made through the alterations detected in the fundus test and molecular genetic test. However, initially, the investigation is part of clinical manifestations, such as itinerant eye movements or nystagmus and precarious responses of pupillary light. On the background examination it is possible to observe disc pallor and mild peripheral pigmentary retinopathy and, in some cases, edema or pseudopapilloedema in the optic disc, stained retina, maculopathy or numular pigmentation (Teive, Trojan et al. 2004; Kumaran, Moore et al. 2017). The confirmation of ocular dystrophy is performed through molecular genetic testing, which is used for the evaluation of the main mutations found in the disease (Teive, Troiano et al. 2004). In retinal dystrophy, genetic tests are indispensable for the realization of definitive diagnosis and studies in the area of genetics have been of paramount importance for the emergence of better means of classifying and understanding the mechanisms of the disease, as well as for the scope of new advances in treatment (Alkharashi and Fulton 2017). It is noteworthy that when diagnosing the LCA, it is necessary to clarify and advise the child's relatives about the prognosis and progression of the disease, addressing aspects such as family inheritance and the evolution of visual dysfunctions (Alkharashi and Fulton 2017).

Differential diagnosis: The differential diagnosis of Leber's Congenital Amaurosis is complex and it is estimated that from the investigation process to the definitive diagnosis of the disease, patients with congenital blindness consult with about 7 ophthalmologists because there is a diversity of visual dysfunctions that have similarities with LCA, characterized by retinal dystrophy that results in a complete or partial loss of vision , which may mainly affect the eyes or be syndromes that have congenital blindness with systemic association (Hufnagel, Ahmed et al. 2012; Alkharashi and Fulton 2017). The main diseases that make the differential diagnosis with LCA are complete Achromatopsia, Incomplete Achromatopsia, Complete Congenital Stationary, Incomplete Congenital Stationary, Night Blindness, and Albinism, and these pathologies differ from Leber's Amaurosis by the degree of vision loss, the appearance of the bottom of the eye, and the presence or absence of colored vision (Ahmed and Loewenstein 2008; Alkharashi and Fulton 2017). Finally, the main syndromes that make the differential diagnosis with LCA are: Alstrom syndrome, Bardet-Biedl syndrome, Joubert's syndrome, Senior-Loken syndrome, Refsum's disease,

Abetalipoproteinemia, Batten's disease, Usher's syndrome, Saldino-Mainzer syndrome, L'Hermitt-Ductos syndrome, Zellwegers disease and Neonatal Adrenoleica dystrophy, and systemic manifestations related to each of them help elucidate the diagnosis (Ahmed and Loewenstein 2008; Alkharashi and Fulton 2017).

Treatment: The difficulty in the treatment of Leber's Congenital Amaurosis is due to its wide diversity of genetic mutations, as each mutated gene causes a distinct molecular abnormality resulting in different and specific therapeutic processes (Alkharashi and Fulton 2017). Among the therapeutic interventions available for Leber Congenital Amaurosis, photoreceptors or RPE cell transplantation, gene replacement, pharmacological therapy, retinal camera and stem cells represent the main approaches of therapeutic intervention in LCA (Coussa RG et. al. 2017). Retinal cell transplantation consists of the replacement of photoreceptors or RPE cells in order to restore retinal function, however, because it is an approach practiced recently, there are still some challenges to be faced, such as the difficulty in normal reestablishment of the retina when neuritis occurs after transplantation. Through this picture and in order to delay cell loss and protect native photoreceptors of the retina against inflammation, these photoreceptors are supported through retinal tissue transplantation (Ahmed and Loewenstein 2008). Pharmacological therapy consists of therapeutic targets based on knowledge about biochemistry and intervention-based mechanisms (Ahmed and Loewenstein 2008). The oral drug is called QLT 091001, which is currently entering phase III test, demonstrating to date safe and effective in children and the elderly with RPE65 mutations, and thus corresponds to the intervention most likely to succeed in retinal dysfunctions and early degeneration (Coussa RG et. al. 2017).

With regard to gene replacement therapy, the goal is to restore normal vision functions and a certain level of proteins in the patient by introducing into the retina a copy of non-mutated genes, and it is important to highlight that it does not need to be performed before retinal degeneration (Ahmed and Loewenstein 2008). An example is the anti-oligonucleotide anti-sense treatment, which is responsible for significantly increasing CEP290 protein levels, thus rescuing a cyil phenotype present in fibroblasts derived from patients (Coussa RG et. al. 2017). In addition to these three approaches mentioned, a prosthesis was developed to act on retinas that do not have visual transduction cells, the retina camera, performing this photoelectric transduction through circuits, with the ability to convert visual information into electrical impulses, restoring vision through the normal pathways. (Ahmed and Loewenstein 2008). The retina laterary camera consists of a prosthesis called Argus II, developed to capture visual information through the interior of the retina, converting visual information into electrical impulses, thus restoring vision through the common pathways (Coussa RG et. al. 2017). Finally, stem cell therapy has been shown to be a therapeutic innovation in LCA with the advent of the use of patient-specific pluripotent types, which have the ability to expand, and can be placed in a culture medium and used as an unlimited source of retinal cells for the treatment of retinal degeneration (Dalkara D et. al. 2016). It is important to emphasize that researchers who study eye gene therapies and physicians who enroll patients in clinical trials related to LCA should recognize the current limitations of these therapies in order to adequately manage expectations and avoid disappointments (Casey GA et. al. 2020).

Gene therapy for the RPE65 form of Leber Congenital Amaurosis: To date, 23 genes have been associated with Leber Congenital Amaurosis, and the most studied, safest and most effective treatment is gene replacement therapy for RPE65 (Weleber, Pennesi et al. 2016; Kumaran, Rubin et al. 2018).

The mutation in the RPE65 gene affects vitamin A metabolism and causes the interruption of a cycle containing RPE65, which is responsible for the isomerization of the all-trans retinol that regenerates Retina 11-cis, causing a degeneration of the respective gene and photoreceptors and, consequently, vision (Weleber, Pennesi et al. 2016; Alkharashi and Fulton 2017).

Individuals with RPE65 mutations are good candidates for gene transfer therapy because retinal cell degeneration is slow, which provides a potential extended time window for intervention (Ashtari M et al. 2017). Moreover, in Leber Congenital Amaurosis caused by RPE65 mutations, the visual cortex can become responsive to visual input through unilateral ocular gene therapy, even after prolonged visual deprivation of up to 35 years (Ashtari M et. al. 2017). The mutation in the RPE65 gene affects vitamin A metabolism and causes the interruption of a cycle containing RPE65, responsible for isomerization of all-trans retinol regenerating Retina 11-cis (1, 16). Thus, there is a limitation to the response of photoreceptors and, later, a degeneration of retinal epithelial cells (Sengillo JD et. al. 2016; Alkharashi and Fulton 2017). It is important to highlight that the neurosensory cells of the retina are well preserved early in life in Leber Congenital Amaurosis caused by RPE65, this fact is of paramount importance for treatment, because in the theory of gene therapy, a relatively preserved RPE replaces the affected gene with a functioning wild RPE65 gene, by injecting a recombinant adeno-associated viral vector into the sub-retinian space (Alkharashi and Fulton 2017). This substitution occurs through an adeno-associated viral vector subretinal injection, which consists of delivering human DNA from RPE65 cells to retinal pigment epithelial cells, and to date, it is the only viral vector that has shown beneficial results in the treatment of Leber Congenital Amaurosis (Sengillo JD et. al. 2016; Pierce EA and Bennett J 2015). On the other hand, there are limitations in gene therapy for the form RPE65, since a major point of concern is the duration of the effect of gene therapy, because although the results had initially suggested improvements related to vision, patients continue to present structural loss and retinal degeneration (Sengillo JD et. al. 2016; Alkharashi and Fulton 2017).

CONCLUSION

In conclusion, although Leber's Congenital Amaurosis is a severe form of retinal dystrophy with genetic inheritance, it is still underdiagnosed and has its limitations regarding therapeutic options and diagnostic approach due to the wide variety of genetic mutations related to the disease. The vast majority of studies show recent advances in diagnosis through gene identification and molecular biology, because eye changes vary according to gene fines, and a specific treatment is required for each case. Despite the therapeutic difficulty due to the existence of a wide diversity of genetic mutations, numerous studies have been conducted and prove the efficacy of certain existing therapies such as photoreceptors or RPE cell transplantation, gene replacement and pharmacological therapy. Among the main therapies, the one that most demonstrates efficacy and safety is gene therapy, being the most studied in clinical trials. However, to date, no therapy is able to prevent the progression of retinal degeneration. Thus, it is extremely important to raise parents' awareness about the need to seek an ophthalmologist through any ocular manifestations, such as oscillations in eye movement or absence of eye fixation, nystagmus or decreased pupillary response rate, in order to perform an early therapeutic diagnosis and intervention, both of the LCA and other ophthalmologic dysfunctions of childhood.

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