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Cataract Manifestation in Some Rare Inherited Diseases: A Narrative Review

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ABSTRACT

A congenital cataract is characterized by the opacity of the lens caused by genomic mutations. In this review, we discuss the correlation between genotype and phenotype of cataract formation in children with congenital abnormalities including Ayme-Gripp syndrome, Cockayne syndrome, Lowe's syndrome, Smith syndrome, and Vici syndrome.

Keywords: *Congenital cataract, clinical manifestations, inherited syndrome.*

INTRODUCTION

A cataract is a condition of cloudiness in the eye lens that occurs due to various intrinsic and extrinsic factors. This disease caused visual disturbances, especially in seeing objects precisely and in detail.(1) In clinical practice, cataracts can be found in the form of congenital cataracts, acquired cataracts, or age-related cataracts.(2) Cataracts develop due to structural or functional disturbances of lens proteins, resulting in an opacity. These events could happen as a result of stressors that occur both before and after birth. A significant proportion can be caused by mutations in some genes that encode lens proteins.(3)

OBJECTIVES

This paper aims to present an overview of the previous research and opinions about cataract formation, diagnostic assessment, and clinical therapy for inherited diseases. In this review, we also briefly discuss the correlation between genotype and phenotype of cataract formation in children with the focus of the discussion on molecular etiology of the disease.

SEARCH STRATEGY

In this article, we performed a search for the keywords "cataract", "pediatric cataract", "congenital cataract", "juvenile cataract", "genetic factor", and "inherited disease" on PubMed and Google Scholar databases (from January 2001 to December 2020). We mainly selected recent publications, but we also considered older critical articles. After selecting the search results and reviewing the article abstracts, we added proper papers with available full text into Mendeley® citation manager. After

that, we have conducted a literature review with a total of 31 articles.

RESULTS

CATARACT

Cataract is defined as the clouding of the crystalline lens caused by a significant variation in the refractive index of the lens at distances close to the wavelength of the transmitted light. This change in refractive index can be caused by changes in the structure of the lens cells, changes in the protein constituents of the lens, or a combination of both. Cataracts are commonly associated with some micro disturbance of the lens structure. This disease also become the most common risk factor of blindness in both children and the elderly around worldwide.(4)

Blindness due to cataracts globally is a more common situation in populations with low socioeconomic status and developing countries. Cataract disease is classified into various types based on its morphology and time formation. There are three types of cataracts based on the morphological classification: subcapsular, nuclear, and cortical cataracts. In addition, this disease is also classified as age-related cataracts, Childhood cataracts, and Secondary cataracts. Age-related cataract was the most common type of cataract that formed in individuals after 50 years of age. Childhood cataracts were an opacity of the eye lens which is divided into congenital cataracts (present at birth) and juvenile cataracts (developing after childbirth) as a manifestation of genetic conditions, congenital disorders, or intrauterine infections. Secondary cataract was abnormalities due to eye trauma, disorders due to other eye diseases such as glaucoma or infection, disorders due to the toxicity of certain drugs or medical treatment (for example, corticosteroids and radiation exposure), or conditions due to associated systemic diseases.(5)

CONGENITAL CATARACT

A congenital cataract is a heterogeneous disease that occurs due to genetic etiology and environmental factors. This disease can occur separately or in association with other systemic disorders that occur in an individual child.(4) Currently, more than 115 genes have been reported as the cause of cataracts and continue to grow along with advances in cytogenetic analysis methods.(6)

Congenital cataract was the most significant causes of decreased vision or optical disturbances in children, characterized by unilateral or bilateral lens clouding without any precipitating factors. Inherited congenital cataracts have been reported to be formed after some changes in specific genes, either in crystalline structures, transmembrane transport proteins (including gap junction proteins and chaperons), or genes related to the development of transcription factors and the lens cytoskeleton. These abnormalities can be detected by various diagnostic techniques like targeted next-generation sequencing (NGS) and genome-specific cytogenetic analysis. Typically, mutations that cause severe damage to the protein will lead to congenital cataract formation, whereas milder variants only will increase the risk factor to become senile cataracts in the old ages.(7,8)

A meta-analysis study reported that approximately 2.4 out of 10,000 children in worldwide were born with congenital cataracts with varying degrees and patterns of lens opacity as its clinical manifestations.(9) In another study, the prevalence of children with cataract disease was reported to occur on 1-15/10,000 births. The underlying etiologic factors were genetic disorders, metabolic disorders, ocular trauma, and some were still idiopathic.(10)

Early diagnosis of hereditary cataracts will be very essential for patients and their families to underlie individualized genetic counseling and testing. The aim is to allow optimal child development during the

early period of life and help patients and their families plan future prognosis. (3)

Early surgery and advanced correction in ophthalmology are essential to optimize visual acuity, maximize vision potential, and prevent amblyopia. Surgery in congenital cataracts is safer and more beneficial if performed at the age of 6 months or older. It is purposed to monitoring postoperative complications and optimize visual acuity. Although surgical management has been declared the best treatment for cataract cases, multidisciplinary approaches such as the collaboration of an ophthalmologist with pediatricians, orthoptists, and genetic counselors are also expected to provide a much better outcome.(11)

INHERITED DISEASE RELATED TO CATARACT MANIFESTATION

Aymé-Gripp syndrome

The Ayme-Gripp Syndrome (AYGRP) is an established character by brachycephaly, an intellectual disability, sensorineural hearing loss, cataracts, cardiac anomalies, neurodevelopmental disorder, and skeletal limitation.(12) The pathogenic Mutation Annotation Format (MAF) of "C.161c > T, C.206C > G, CYP27A1" was discovered by transcription family factors in the N-terminus region and reported to be harmful by various in silico methods. MAF could be found in lens fiber cells during lens development, and homozygous MAF mutant mice proved defective differentiation of lens fiber cells, including crystallins. Whole-exome sequencing, with or without preliminary linkage analysis has reported some type of new cataract genes that has significant roles in PI3K/AKT/mTOR signaling, cholesterol production, or another pathomechanism within the last three years.(13)

By using comprehensive genomic testing, isolated pediatric cataracts were caused by 35 abnormalities in over 52 genes. Major inheritance was recorded caused by just 15 of these genes. Meanwhile, the minor inheritance was caused by just 7 of them. Cataracts in Ayme-Gripp Syndrome were mostly reported in the first year of life, but there are also findings that there are no problems in the eyes after seven years of age. Several studies reported that bilateral cataracts in this syndrome should be corrected surgically in two stages to prevent some secondary complications such as amblyopia, aphakia glaucoma, and complete blindness.(14)

Cockayne syndrome

Cockayne syndrome (CS) is a rare disease, first described by Edward Cockayne in 1936. Most of CS cases (75%) are related to the mutant gene (5q11), and 25% of patients are associated with the mutant ERCC8 or CKN2 gene (10q12). Both encode CSA and CSB proteins involved in DNA repair.(15) Changes caused by mutations can lead to the accumulation of damaged DNA, leading to cellular aging and change of cell growth. Therefore, the patient's death was interpreted as demyelination of the central and peripheral nervous system, leading to dysphagia, long-term chronic aspiration, multiple lung inflammations, and eventually extensive diffuse alveolar damage (16) In this sense, the causes of congenital cataracts are varied. Before considering certain types of genetic diseases, it is necessary to rule out the possibility of maternal infection during pregnancy. In addition, we should also investigate inborn errors of metabolism, such as galactosemia, which sometimes causes cataracts at birth. A careful clinical examination is essential to distinguish between congenital solitary cataracts and congenital cataract syndrome. There are two main categories in cataract syndrome: single gene disease and chromosomal disease (17).

According to previous studies, every baby with postnatal developmental delay, microcephaly, and the following two conditions: continuous cold hands and feet, bilateral hearing disturbance, photosensitive skin, tremor, joint contracture, and extreme weight loss, cataracts, and distinctive facial

morphology should be suspected of CS case. By using these criteria, the doctor can improve the clinical recognition rate of CS to approximately 90%.(18)

CS patients with complete bilateral cataracts require a multidisciplinary approach involving pediatrics and genetics. The total bilateral posterior capsule is the most common type of congenital cataract lesion in this syndrome. In addition, children with CS can also attend with enophthalmos, retinal dystrophy, strabismus, and nystagmus which would aggravate the vision loss. There is no implantation of intraocular lenses because patients with systemic diseases have a more intense inflammatory process and are at risk of complications such as glaucoma. Bilateral total cataract with posterior capsule metaplasia is common in patients with systemic syndrome.(19)

Lowe's syndrome

Ocular Cerebral Lowe's Renal Syndrome (OCRL), also known as Lowe's syndrome, is a rare congenital disease that could be marked by a triad of organ system diseases: eye diseases (such as neonatal cataracts and mental illnesses), neurological disease (retardation), and kidney dysfunction.(20) OCRL is caused by the disturbance of the oculocerebrorenal (OCRL1) gene at the Xq2426.1 site. OCRL1 is the primary phosphatidyl inositol-bisphosphate (PIP2) hydrolase in human proximal renal tubule cells. PIP2 has several function such as regulating intracellular signal transmission, transport of ions and substances across membranes, regulating the actin cytoskeleton, transcription, and membrane transport.(21) PIP2 is primarily found in skin fibroblasts, but its amount was drastically reduced in Lowe syndrome patients.(22)

According to studies on women with Lowe's syndrome, 94% of them can be diagnosed by slit-lamp examination due to significant white to grey mottled opacities in all layers of the lenticular cortex.(23) Prenatal diagnosis is based on enzyme activity detected in chorionic villi at 9-11 weeks or amniotic fluid cells at 15-20 weeks. At birth, bilateral cataracts and hypotonic ocular involvement can be seen in congenital infection (rubella), peroxisome disease, mitochondrial disease, myotonic dystrophy, or congenital myopathy (ocular muscular encephalopathy).(24)

The patient's management includes PCO eye surgery, body rehabilitation, bicarbonate, potassium, and vitamin D supplements. Early cataract removal is essential to avoid amblyopia. A regular eye examination can detect glaucoma early, allowing early treatment with glaucoma medications or trabeculectomy surgery. Metabolic disorders can be diagnosed and treated earlier, decreasing the mortality rate and morbidity.(25)

Smith-Lemli-Opitz Syndrome

Smith Lemli Opitz syndrome (SLOS) is an autosomal recessive disease that was presented in 1964 by three researchers. SLOS is associated with mutations in the 7-dehydrocholesterol reductase (7-DHCR) gene, resulting in decreased cholesterol biosynthesis.(26) Gene mutations in SLOS are identified by targeted genotyping. The most common mutation (1/3 of alleles in the mutant population) detected is c.964 1G> C (IVS81G> C), which results in the insertion of 134 base pairs. Children with SLOS who also have high 7-dehydrocholesterol (7-DHC) / 8-dehydrocholesterol (8-DHC) and low serum cholesterol have many physical malformations, including cataracts.(27)

Congenital cataracts in SLOS are present in approximately 20% of cases and also develop in early age patients. The pathophysiology of postnatal cataract development in SLOS remains unclear. However, the reported cases of iris synechiae and capsular fibrosis by Donoghue S (2018) indicate that the development of cataracts may be accompanied by an inflammatory reaction (phacoanaphylaxis). The study also found that there may be a toxic effect in the lens

caused by an increase in 7-DHC levels. This condition leads the capsule to rupture spontaneously, so there can be no posterior capsule and liquefaction of the lens cortex.(28)

Vici Syndrome

Vici syndrome (VICIS) is a recessively inherited disorder characterized by agenesis of the corpus callosum, cataracts, cardiomyopathy, oculocutaneous hypopigmentation, and combined immunodeficiency. This syndrome is caused by a mutation on chromosome 18q12.3 that encodes P granule protein 5 (EPG5), an autophagy regulator.(29) Most EPG5 mutations are distributed throughout the EPG5 coding sequence and are specific to the individual family, making it difficult to establish precise genotype-phenotype correlations. However, based on the survival time analysis until death or censorship date, it can be determined that patients with homozygous EPG5 mutations died at the median age of 9 months, whereas patients with heterozygous EPG5 mutations at the age of 48 months.(30) Neuro-ophthalmological features included retinal hypopigmentation, developmental delay, lower than average b-wave amplitudes on ERG, and possibly misrouting at the optic chiasm similar to typical albinism. Most patients with Vici syndrome have bilateral congenital cataracts. There were also optic atrophy and retinal changes in some patients, and a small number of patients had ocular albinism. (31)

CONCLUSION

Cataract features in five inherited diseases on this study showed a similar manifestation as bilateral opacity in the eye. Even these cases are rare, early diagnosis and prompt treatment were very essential to get an excellent management result. Surgical management is still the main choice of treatment, so the success outcome of its therapy will be determined by the presence or absence of complications.

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