Review Article

Capsula Eburnea

CATARACT IN CHILDHOOD: NEW FRONTIERS

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SUMMARY

Cataracts can be defined as any opacity of the crystalline lens. Congenital cataracts are particularly serious, since they have the potential to inhibit normal visual development in infants, ultimately leading to permanent blindness. However, most hereditary cataracts are associated with mutations of certain protein-coding genes responsible for maintaining the transparency of the crystalline lens. Therefore, diagnosis should be made as early as possible in order to implement a timely treatment plan to prevent the disabling effects of this disease.

Introduction

Congenital cataract is a lens opacity already present at birth, while the term infantile cataract refers to any opacity that arises during the first year of life. It is estimated that congenital cataracts occur in 0.6-6 of 10.000 live births. Worldwide, 20 million children under 16 years of age are affected by cataracts, and 200.000 (15%) among these are severely visually impaired or blind [1,2]. There are numerous possible causes for congenital cataracts: they can be idiopathic, caused by intrauterine infections (such as rubella, toxoplasmosis, chickenpox and herpes simplex), drugs (steroids, vitamin D and antibiotics), physical agents (radiation), or metabolic disorders (galactosemia, galactokinase deficiency, hypocalcemia and hypoglycemia), or be associated with eye diseases (microphtalmos, aniridia, Peter's anomaly and endophtalmitis) or systemic diseases (chromosomal anomalies, Lowe syndrome, Alport syndrome, Weill-Marchesani syndrome and Bardet-Biedl syndrome) (see Table I).

Genetic etiology

Currently about 60 genetic loci are implicated in the formation of congenital cataracts; of these, over 22 have been associated with mutations of specific genes [3,4], including 10 crystallin genes: αA-crystallin (*CRYAA*), αB-crystallin (*CRYAB*), βA1-crystallin (*CRYBA1*), βA4-crystallin (*CRYBA4*), βB1-crystallin (*CRYBB1*), βB2-crystallin (*CRYBB2*), βB3-crystallin (*CRYBB3*), γC-crystallin (*CRYGC*), γD-crystallin (*CRYGD*) and γS-crystallin (*CRYGS*) [5,6]. Two of the genes, BFSP1 and BFSP2, encode structural proteins, [7]; while four of them, alpha3-GJA3, alpha8-GJA8, MIP and LIM2, encode membrane proteins [8,9]; three further genes, HSF-4, PITX3 and MAF, encode growth and transcription factors [10]; finally, proteins that modify chromatin (*CHMP4B*), ephrin receptor EphA2 (*EPHA2*) and Nance-Horan syndrome (*NHS*) are also implicated in cataract formation [11]. All these genes contribute to the production of proteins needed to maintain a certain balance to ensure that the

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crystalline lens remains transparent and avascular. We now know that a correct protein folding depends not only on its amino acid composition, but also on the assistance of other proteins, known as molecular chaperones. These play a fundamental role in restoring the three-dimensional protein structure. The αA-crystallin belongs to the molecular chaperone family [12]. The proteins belonging to this family act by binding to hydrophobic residues from the target protein. Their action is thus two-fold: by binding to hydrophobic residues, the chaperones prevent the latter from interacting with other such residues from nearby proteins in an attempt to avoid contact with water and therefore impeding the formation of insoluble aggregates; they also prevent the hydrophobic residues of the protein from aggregating prematurely and causing impaired synthesis [13,14]. Crystallin genes encode about 90% of the water-soluble structural proteins of the crystalline lens (accounting for 30% of its mass) and therefore play an important role in the lens transparency [15]. Gap junction proteins are needed to maintain the lens avascular, due to their ability to allow the metabolically active epithelia to regulate the intracellular communication and transport processes. Around 30% of patients with congenital cataracts have crystallin gene mutations [4], and a large portion display gap junction protein alterations [16,17]. Kumar et al. [18] found two novel mutations in

Idiopathic	Unknown
Intrauterine Infections	Rubella, Toxoplasmosis, Chickenpox, *Herpes simplex*
Physical Agents	Radiation, Laser photocoagulation
Drugs	Steroids, Vitamin D, Antibiotics
Trauma	Various
Metabolic Disorders	Galactosemia, Galactokinase deficiency, Hypocalcemia, Hypoglicemia
Other Eye Diseases	Microphtalmos, Aniridia, Peter's anomaly, Endophtalmitis, *Cornea guttata*, Prematurity, Persistent hyperplastic vitreous humor
Isolated Genetically Determined Conditions	Autosomal dominant, Autosomal recessive and X-linked diseases
Associated With Systemic Diseases	• *Chromosomal anomalies:* Trisomy 21, Turner syndrome, Trisomy 13, Trisomy 18, Cri Du Chat Syndrome, Translocations (3;4 and 2;14) • *Mitochondrial anomalies:* Complex 1 deficiency • *Craniofacial syndromes:* Cerebro-oculo-facio-skeletal syndrome • *Renal pathologies:* Lowe syndrome, Hallerman-Streiff-Francois syndrome • *Skeletal disorders:* Smith-Lemli-Optiz syndrome, Conrad syndrome, Weill-Marchesani syndrome, Bardet-Biedl syndrome, Rubenstein-Taybi syndrome • *CNS diseases:* Zellweger syndrome, Meckel-Gruber syndrome, Marinesco-Sjogren syndrome, Batten disease • *Heart pathologies:* Hypertrophic cardiomyopathy • *Skin diseases:*. Cockayne syndrome, Rothmund-Thomson syndrome, Atopic dermatitis, Ichtyosis, Ectodermal dysplasia • *Dental pathologies:* Nance-Horan syndrome, Lenz syndrome

Table I: Possible causes of congenital cataract.

CRYGC (R48H) and G5A8 (L281C). The pathogenicity of these mutations has yet to be confirmed by further studies.

Importance of early diagnosis and treatment

The most frequent clinical sign of congenital cataract is leucocoria. However, it can also be diagnosed during the red reflex test shortly after birth (this is an examination technique used to detect alterations in lens transparency). In absence of leucocoria, the following symptoms may indicate the presence of cataracts: heterotropia (especially common in unilateral cataracts) and nystagmus (usually arising at around 2-3 months of life in patients with bilateral cataracts). Another possible symptom to keep in mind is the oculo-digital sign of Franceschetti, a phenomenon in which the child with a reduced visual acuity rubs his or her eyes in an attempt to induce a retinal light response by mechanical stimulation. Any of these symptoms should lead to the suspicion of impaired vision, not necessarily due to cataracts: therefore a differential diagnosis is essential, especially if leucocoria is present. A full medical history should be obtained, and a thorough eye examination under anesthesia performed in order to reach a preliminary diagnosis and detect any further eye abnormalities, such as: corneal opacity, glaucoma, persistent hyperplastic primary vitreous, chorioretinitis, Leber's amaurosis, foveal or optic nerve hypoplasia, rubella retinopathy etc. Diagnostic techniques useful to this end, when deemed necessary, include the electroretinogram, evaluation of visual evoked potentials, ultrasound scans and laboratory tests for detecting connatal infections [19,20]. Without a doubt, in most cases the treatment of choice is the surgical removal of the crystalline lens accompanied by, where opportune, intraocular lens (IOL) implantation. However, in children with early-stage galactosemic cataracts, a galactose-free diet may be considered. Unfortunately, surgery is the more difficult option due to the anatomy of the eye in children, who have a more curved cornea and smaller corneal diameter (making postoperative predictions harder), thinner and more vascularized sclera, thicker and more vascularized iris, and lastly, a smaller lens diameter, with a thinner and more elastic anterior capsule, along with a softer and more elastic lens tissue (that is difficult to aspirate). Two surgical techniques are currently being used for cataracts in children: lensectomy (through a pars plana incision) [21] and phacoemulsification (with trabecular aspiration) [22]. Surgical timing is of utmost importance, and needs to be carefully assessed taking into account whether the cataract is uni- or bilateral, the opacity partial or total, or whether the manifestation is associated with a syndrome meaning that even surgical treatment would not lead to any visual improvement. A delay in treatment could lead to deprivation amblyopia, followed by nystagmus. Indeed, with the visual development occurring at an early age, the lack of appropriate external stimuli during this period can cause irreversible damage to ocular structures. For an advanced unilateral cataract, surgery should be performed urgently and followed by aggressive anti-amblyopic treatment. Prognosis is in fact good when the surgery is performed within the fourth or fifth week of life, but in cases where the cataract is diagnosed after the 16th week of life, surgical treatment is superfluous since the amblyopia will be refractory to treatment by this time [22,23]. For advanced bilateral cataracts, urgent surgery (within the first 4-5 weeks of life) is also essential to prevent deprivation amblyopia [24]. Simultaneous bilateral surgery can be performed, or in cases with asymmetric severity between the eyes, priority should be given to the more severely affected one. No surgery is required for partial bilateral cataracts. In uncertain cases, it is recommended to wait and monitor the development of the opacity and visual deficit, and eventually intervene if they deteriorate. Finally, for partial unilateral cataracts, close observation and non-surgical management, involving dilation or occlusion of the unaffected eye with frequent check ups, are recommended (see table II). It is also important to choose the right time for the IOL implant. Implantation usually takes place immediately and in all cases for unilateral cataracts, while for bilateral cataracts, the decision varies depending on individual anatomy, presence of any further ocular or systematic abnormalities etc. Better and safer outcomes can be ensured by performing the IOL implant after the first year of life, since the majority of refractive changes take place within the first 18 months of life [25,26]. The

incidence of complications after cataract surgery is higher in children than in adults; these include posterior capsule opacification (inevitable if posterior capsulorhexis is not performed), secondary pupillary membrane formation, especially in cataracts associated with chronic uveitis, lenticular epithelial proliferation, glaucoma and retinal detachment, although rare and usually with a late onset [27,28]. Although considerable progress has been made in the treatment of congenital cataracts, functional results can be disappointing due to the possibility of developing serious and irreversible amblyopia. For this reason, in aphakic correction it is important to evaluate the age at onset and laterality, with the eventual application of eye glasses, contact lenses, IOL implants or occlusion therapy also by means of atropine penalization. When an IOL is implanted, a small amount of hyperopia is desirable; this will usually, in time, correct itself to emmetropia.

Conclusions

Congenital cataract is a disease with devastating effects for a child's life, since it causes a reduction of visual acuity that can be irreversible if not treated, or if treatment is delayed. For this reason, an early diagnosis plays a key role in preserving the child's eyesight, with treatment timing being equally important. Thanks to emerging knowledge on certain genes involved in the pathogenesis of this disease, in the future it will be possible to implement newborn screening programs.

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Advanced Bilateral Cataract	Urgent surgical intervention (within the first 4-6 weeks of life)
Advanced Unilateral Cataract	Urgent surgical intervention
Partial Bilateral Cataract	Observation and monitoring; if visual deterioration occurs, surgery is required
Partial Unilateral Cataract	Observation and non-surgical management of the unaffected eye

Table 2: Protocols for the treatment of congenital cataracts.

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