Case Reports and Reviews

Short Communication



The Difference Between Hereditary Hyperferritinemia- Cataract Syndrome and Crystallin Gene Mutations

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Abstract

Cataracts are characterized by the loss of transparency of the crystalline lens which result in impaired vision. Genetic abnormalities are important causes of congenital and early-onset cataracts. Two distinct mechanisms are involved in early cataract. The first is mutations in crystallin genes and the second is mutations affecting the regulation of ferritin synthesis. Hereditary hyperferritinemia-cataract syndrome (HHCS) is an autosomal dominant disorder characterized by elevated serum ferritin concentrations and bilateral cataracts without systemic iron overload. It results from mutations in the iron-responsive element (IRE) in the 5' untranslated region of the ferritin light-chain gene (FTL).

The mutations in crystallin genes can disrupt lens protein stability and transparency. Understanding these distinct molecular mechanisms is essential for accurate diagnosis, genetic counseling and clinical management.

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Keywords

Cataract, hereditary hyperferritinemia-cataract syndrome, and ferritin light-chain gene.

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Introduction

The crystalline lens is a transparent, avascular structure that focuses light onto the retina. Its transparency depends on the organization of lens fiber cells and the high concentration of specialized structural proteins known as crystallins. These proteins are classified into three major groups: α-crystallins, β-crystallins and γ-crystallins.

Crystallins maintain lens transparency through their structural and molecular properties. α-Crystallins also act as molecular chaperones that helping prevention of the aggregation of damaged or misfolded proteins. Mutations affecting crystallin genes may disrupt protein stability, solubility and result in hereditary cataracts [1–7].

Another genetic disorder associated with cataract formation is hereditary hyperferritinemia-cataract syndrome (HHCS). Unlike crystallin-related cataracts, HHCS results from abnormal regulation of ferritin synthesis caused by mutations in the iron-responsive element of FTL messenger RNA [1–3].

HHCS is a rare autosomal dominant genetic disorder characterized by elevated serum ferritin concentrations and bilateral cataracts without systemic iron overload.

The syndrome was described in 1995 in families presenting with hyperferritinemia and congenital or early-onset cataracts [1,2].

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Discussion

HHCS is caused by mutations in the iron-responsive element (IRE) located in the 5′ untranslated region of the ferritin light-chain gene (FTL) on chromosome 19.

The iron regulatory proteins (IRPs) bind to the IRE in FTL messenger RNA when intracellular iron availability is low. This interaction inhibits translation and prevents excessive ferritin production. In HHCS, mutations disrupt the interaction between IRPs and the IRE. Therfore, translational repression is impaired and L-ferritin synthesis increases of the iron requirements [2,3,8]. The development of cataracts in HHCS can be summarized as following. A pathogenic mutation occurs in the IRE of FTL messenger RNA this result in impairing the binding of iron regulatory proteins to the IRE. L- ferritin production increases leading to elevated serum ferritin concentrations. This is caused by disruption of the translational regulation of FTL. Excess ferritin accumulates in the lens and forms crystalline deposits.These deposits interfere with light transmission, resulting in lens opacity and cataract formation [3,9]. Ferritin is an iron-storage protein, and its synthesis is regulated by cellular iron availability. The molecular regulation of ferritin translation is part of the broader iron-homeostasis system described by Hentze and colleagues [8]. The patients typically have normal iron stores so distinguishing HHCS from hereditary hemochromatosis is confirmed [3,10].

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The term crystalline cataract describes the appearance or structure of lens opacities. It does not necessarily mean that the cataract is caused by a mutation in a crystallin gene.

On the other hand, the explanation of crystalline cataract will be discussed later. The crystalline are essential proteins responsible for maintaining lens transparency and refractive properties. Mutations in crystallin genes can cause congenital, juvenile or other forms of hereditary cataracts [4–7].

The genes CRYAA and CRYAB encode α A-crystallin and α B-crystallin, respectively. The α- crystallins function is a molecular chaperone that helping in maintaining protein stability and preventing the aggregation of damaged or misfolded proteins. Pathogenic variants can impair these functions and contribute to cataract formation [5,6].

Some CRYAB variants are also associated with muscle disorders, demonstrating that crystallin proteins can have functions beyond maintaining lens transparency [5].

The β- crystallins contribute to the structural organization and optical properties of the lens. Genes such as CRYBB1 and CRYBB2 encode members of this protein family.

Mutations in β-crystallin genes can affect protein stability, solubility and modulation of the interactions with other lens proteins. The end result of mutataion is hereditary cataracts [4–6].

The γ- crystallins are important for maintaining the refractive properties and transparency of the lens. Mutations in genes such as CRYGC and CRYGD can cause congenital or early-onset cataracts by altering protein stability and solubility [4–6]. Crystallin-related cataracts generally develop through the following sequence. A pathogenic variant occurs in a crystallin gene resulting in abnormal folding and stability of the protein. This result in protein aggregation and structural changes of lens transparency. Light scattering increases which result in cataract formation [4–7]. Ferritin plays a central role in cellular iron storage and protection against iron-mediated oxidative damage. It consists of heavy and light subunits encoded by FTH1 and FTL respectively. Ferritin synthesis is regulated by the interaction between iron regulatory proteins and iron-responsive elements in messenger RNA. This system allows cells to adjust ferritin production according to iron availability [8,10].

In HHCS, the mutation affects the regulatory IRE in FTL messenger RNA rather than the coding sequence of a crystallin protein. This results in increased ferritin synthesis and accumulation in the lens [8,10,11].

The primary difference is that HHCS results from abnormal regulation of ferritin synthesis, whereas crystallin-related cataracts result from genetic alterations affecting structural lens proteins [1–6].

HHCS should be considered in individuals with early-onset bilateral cataracts and persistently elevated serum ferritin concentrations without evidence of iron overload.

The diagnostic evaluation including measurement of serum ferritin which is elevated with normal iron serum level. The ophthalmological examination show a characteristic shape of lens capacities. The genetic testing for Identifies pathogenic variants in the IRE region of FTL. The family history helps to identify the pattern of inheritance as an autosomal dominant variant. [3,8,10].

Cataracts associated with HHCS commonly present as bilateral, multiple, small, white, crystalline or pulverulent opacities. The opacities may resemble tiny flecks or crystalline deposits and sunflower-like patterns have also been described.

The location and severity of the opacities can vary among affected individuals. The cataracts may progress over time, and some patients eventually require cataract surgery [3,9].

In suspected crystallin- related cataracts, genetic testing may identify pathogenic variants in genes such as CRYAA, CRYBB2, or CRYGD [3–6]. Mostly these cases are clinically suspected by symptoms of the patient as gradual blurring of vision is the first symptom can be seen. Then progressive reduction in visual clarity. Glare and photophobia with increased sensitivity to bright lights and sunlight. Another important thing is complaining from halos around lights and seeing rings around light sources particularly at night. Also, difficulty in seeing clearly in dim illumination. Another ophthalmic problems are detected as changes in spectacle prescription and monocular diplopia which means double vision in one eye.

Conclusion

Hereditary hyperferritinemia-cataract syndrome and crystallin-related hereditary cataracts are distinct genetic conditions that cause lens opacity through different molecular mechanisms.

HHCS results from mutations in the iron-responsive element of FTL messenger RNA, leading to increased L-ferritin synthesis and ferritin accumulation in the lens. Its characteristic clinical findings are bilateral cataracts and elevated serum ferritin without systemic iron overload.

In contrast, mutations in crystallin genes such as CRYAA, CRYBB2, and CRYGD affect the structure, stability or function of lens proteins and can cause hereditary cataracts.

Understanding these differences is essential for accurate diagnosis, genetic counseling, and appropriate clinical management

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