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CASO CLÍNICO

Hereditary Hyperferritinemia-Cataract Syndrome: A Case Report

Síndrome Hereditária Hiperferritinemia-Catarata: Caso Clínico

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ABSTRACT

Hereditary hyperferritinemia-cataract syndrome is an autosomal dominant genetic disorder that is characterized by high serum ferritin levels without iron overload and early-onset cataracts. The authors describe the case of a 26-year-old woman with hyperferritinemia (1153.3 ng/mL, reference range 11.0 - 306.8 ng/mL), with no other abnormalities in iron metabolism, associated with cataracts diagnosed at the age of three. The diagnosis was confirmed by genetic testing with detection of a heterozygous variant in the *FTL* gene (c.-168G>T). It is important to recognise hereditary hyperferritinemia-cataract syndrome to avoid unnecessary medical procedures.
Keywords: Cataract/genetics; Hyperferritinemia; Iron Metabolism Disorders/congenital

RESUMO

A síndrome hereditária hiperferritinemia-catarata é um distúrbio genético autossómico dominante caracterizado por valores de ferritina sérica aumentados sem sobrecarga de ferro e por cataratas de início precoce. Os autores descrevem o caso de uma mulher de 26 anos com hiperferritinemia (1153,3 ng/mL, valor de referência 11,0 - 306,8 ng/mL), sem outras alterações na cinética de ferro, associada a cataratas diagnosticadas aos três anos de idade. O diagnóstico foi confirmado por estudo genético com a identificação de uma variante em heterozigotia no gene *FTL* (c.-168G>T). O reconhecimento da síndrome hereditária hiperferritinemia-catarata é importante para que seja possível evitar a realização de procedimentos médicos desnecessários.
Palavras-chave: Catarata/genética; Distúrbios do Metabolismo do Ferro/congénito; Hiperferritinemia

INTRODUCTION

Ferritin is a water-soluble protein that plays a key role in iron metabolism participating in iron detoxification and iron storage. Ferritin consists of 24 protein subunits of two different types: H-ferritin (heavy chain) and L-ferritin (light chain) that are encoded by genes located on chromosomes 11 and 19, respectively.[1] H- and L-ferritin have different functions, H-ferritin is responsible for iron storage and carries the ferroxidase activity needed to sequester iron while L-ferritin has a regulatory function with the presence of acidic groups that facilitate iron oxidation and hydrolysis.[2]

Iron homeostasis is mediated by iron-responsive elements (IREs) that are found within mRNA and by iron regulatory proteins (IRPs) that are cytoplasmic mRNA-binding proteins. A single functional IRE is found in the 5'-untranslated region (UTR) of mRNAs for the H and L-ferritin subunits, while multiple IREs are present in the 3'-UTR of the mRNA for the transferrin receptor. There are two iron regulatory proteins, IRP1 and IRP2, which are both capable of sensing cellular iron status and interacting with the IREs. Under conditions of intracellular iron depletion, both IRPs can bind IRE with high affinity and this interaction prevents translation of ferritin and eventually decreases ferritin protein levels. When iron concentration is high, IRP1 changes its conformation and loses its RNA-binding activity and activates its function as a cytosolic aconitase, an enzyme in the Krebs cycle. On the other hand, IRP2 is targeted for degradation by the proteasome. In the absence of a bound IRP, the ferritin transcript is readily translated, while the transferrin receptor transcript is rapidly degraded.[1]

Hereditary hyperferritinemia-cataract syndrome (HHCS), also known as Bonneau-Beaumont syndrome, arises from various point variants or deletions in the 5'-UTR of the *FTL* gene located in chromosome 19q13.3-q13.4, involving the IRE sequence. Mutations of the IRE element cause inhibition of the IRE-IRP interaction, with concomitant upregulation of FTL synthesis and accumulation of L-ferritin chains unrelated to the body's iron status.[3,4]

The authors describe the case of a 26-year-old woman with hereditary hyperferritinemia-cataract syndrome. This disorder is relatively harmless and can be misdiagnosed with other potential causes of hyperferritinemia. It is important to recognize it to avoid unnecessary medical procedures.

CASE REPORT

A 26-year-old woman was referred to the internal medicine clinic due to high serum ferritin levels and suspected hemochromatosis. The patient was born at term, and the pregnancy was unremarkable. Her history showed cataracts diagnosed

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when she was only three years old and she presented normal growth and psychomotor development. It was found that the patient had high serum ferritin levels.

The family history revealed that the patient's 62-year-old father and 33-year-old brother also presented with early-onset cataracts and high ferritin levels, and both had already undergone cataract surgery. Also, other family members from the father's side had early-onset cataracts and high ferritin levels, including a 39-year-old cousin and a 56-year-old aunt. The patient also knew that her grandfather and great-grandmother, both from her father's side, had early-onset cataracts but were never assessed for hyperferritinemia (Fig. 1). From her mother's side there were no family members with early-onset cataracts or high ferritin levels.

Blood tests showed high ferritin levels with no other abnormalities in iron metabolism (Table 1); blood count, liver function and inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) were normal. Moreover, viral hepatitis and human immunodeficiency virus (HIV) were excluded as potential causes of hyperferritinemia. Genetic testing for hereditary hemochromatosis (*HFE* gene) was performed and was negative. Abdominal ultrasonography and magnetic resonance imaging were normal with an estimated hepatic iron concentration of 18 µmol/g (normal concentration up to 36 µmol/g) in the latter.

Ophthalmological evaluation with slit-lamp examination revealed sutural and nuclear cataracts in both eyes (Fig. 2 and 3). Visual acuity was 5/10 on the right eye and 8/10 on the left eye.

After a review of the clinical case, hereditary hyperferritinemia-cataract syndrome (HHCS) was established as a diagnostic hypothesis. Genetic testing was performed with detection of a heterozygous variant in the IRE region of the ferritin light chain gene (*FTL* gene - c.-168G>T, classified as pathogenic). At the time of writing, the patient's father and brother were waiting for the genetic test for HHCS and the remaining family members did not want to be tested.

DISCUSSION

Hereditary hyperferritinemia-cataract syndrome is a rare autosomal dominant genetic disorder with an estimated prevalence of < 1/1 000 000.[4] The clinical manifestations are early-onset bilateral cataracts associated with hyperferritinemia without iron overload, and the cataracts are the only recognizable phenotypic manifestation. This disorder's cataract morphology is described as central and peripheral crystalline flecks in a radial pattern.[5] Although L-ferritin may accumulate harmlessly in other tissues, low protein turnover and containment by the capsule may cause ferritin crystals to accumulate within the eye's lens, disrupting light transmission. It is thought that the clinical severity of HCSS is correlated with the position of the *IRE* mutation.[4]

Since there is no iron overload, phlebotomy is not recommended and the only treatment needed is cataract surgery when patients suffer from visual impairment. Therefore, HHCS is considered a relatively harmless disease.

Most clinicians are not familiar with this disease. Since hemochromatosis is a relatively common disorder associated with hyperferritinemia, it could lead to misdiagnosis of HHCS. Hemochromatosis presents with high serum ferritin and high transferrin saturation levels, unlike HHCS that presents only with hyperferritinemia. Patients with HHCS who undergo phlebotomy rapidly develop iron deficiency anemia without significant change in ferritin serum levels.[1] Family history of hyperferritinemia and cataracts are important indicators of HHCS. The diagnosis is confirmed by genetic testing of the *FTL* gene.[6] Genetic counseling should be offered to the affected individuals so they can be informed about the chances of their future offspring being affected by the syndrome. In this case, the patient has a 50% risk of having an affected child with each pregnancy.

Hereditary hyperferritinemia-cataract syndrome should be considered in the differential diagnosis of hyperferritinemia, especially in the presence of normal transferrin saturation. It is important to recognize this entity to avoid unnecessary and even adverse medical procedures in patients with HHCS.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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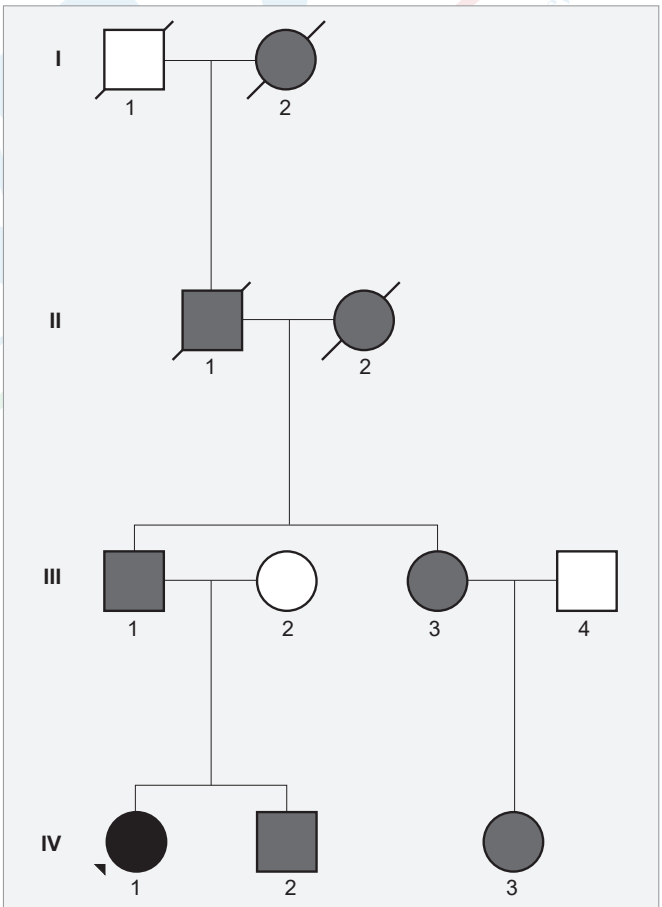

Figure 1 – Family tree. Squares indicate men, circles indicate women; slashed symbols indicate deceased individuals. Black-filled symbol indicate affected individual with HHCS; grey-filled symbols indicate suspected individuals.

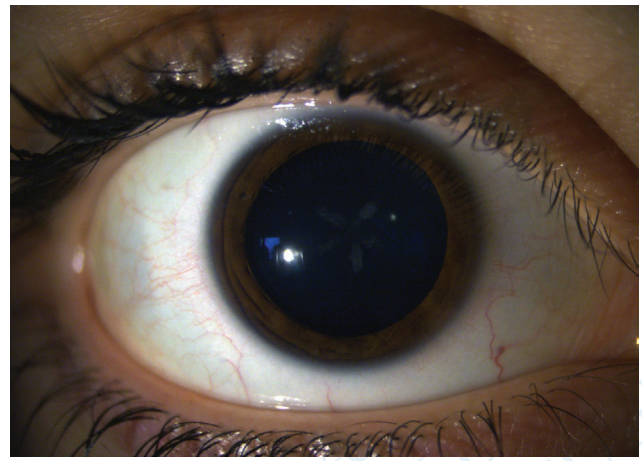

Figure 2 – Slit lamp examination of right eye

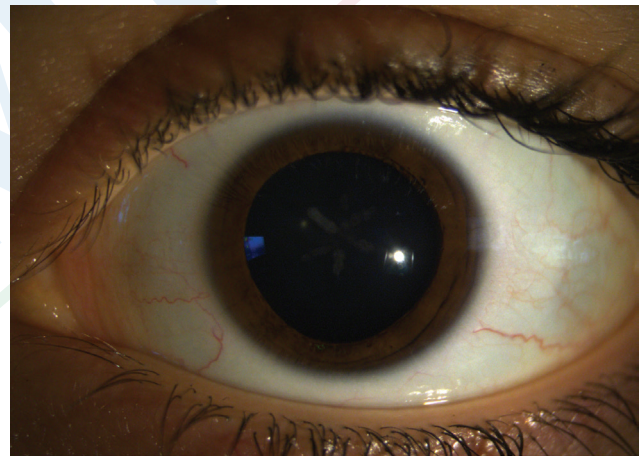

Figure 3 – Slit lamp examination of left eye

Table 1 – Iron study

Blood tests	Results	Reference range
Iron	20.2 µmol/L	9.0 - 30.4 µmol/L
Transferrin	300.0 mg/dL	200.0 - 360.0 mg/dL
Transferrin saturation	29.0 %	7.4 - 64.7%
Ferritin	1153.3 ng/mL	11.0 - 306.8 ng/mL