HEREDITARY HYPERFERRITINEMIA-CATARACT SYNDROME

Orkide Kutlu[1], Şamil Ecirli[1], Abdullah Sakın[2], Faik Sağlam[3], Abdulkadir Baştürk[1]
[1]*Okmeydanı Training and Research Hospital, Clinic of Internal Medicine, Istanbul*
[2] *Kanuni Sultan Suleyman Training and Research Hospital, Clinic of Internal Medicine, Istanbul*
[3] *Konya Training and Research Hospital, Eye Clinic, Konya*

ABSTRACT

Hereditary hyperferritinemia-cataract syndrome (HHCS) is a very rare autosomal dominant genetic disorder resulting in the increase of ferritine light chain (L-ferritine) caused by a mutation of the regulatory gene. There is no known clinical findings other than cataracts. Herein, we report a female patient diagnosed with cataract at the age of 25 and hyperferritinemia at 50 years old. After excluding gastrointestinal and hematological reasons leading to ferritin increase, the case was diagnosed with HHCS and simultaneous Hashimoto's disease, in addition to the existence of conditions in her family history. By accurately diagnosing hyperferritinemia without iron overload or inflammation and a family history of hereditary cataracts, prognostic factors can be well-monitored avoiding invasive procedures like liver biopsies and /or phlebotomies.

Keywords: *Hyperferritinemia, hereditary, bilateral cataracts.* **Nobel Med 2017; 13(2): 80-82**

HEREDİTER HİPERFERRİTİNEMİ-KATARAKT SENDROMU

ÖZET

Herediter hiperferritinemi-katarakt sendromu, ferritin hafif zinciri sentezini düzenleyen gen mutasyonuna bağlı kontrolsüz bir şekilde ferritin hafif zincir sentezi artışı ile sonuçlanan otozomal dominant kalıtılan genetik bir bozukluktur. Sendromda kataraktan başka bilinen klinik bulgu yoktur. Burada 25 yaşında katarakt teşhisi alan ve hiperferritinemi etyolojisi saptanması amacı ile merkezimize yönlendirilmiş bir hastada ferritin yüksekliği yapacak gastrointestinal ve hematolojik sebepleri dışladıktan sonra (aile öyküsü ile birlikte) herediter hiperferritinemi-katarakt sendromu teşhisi koyduğumuzu ve eş zamanlı olarak Hashimoto tiroiditi saptadığımızı bildirmek istedik. Hiperferritinemisi olan fakat demir yükü veya inflamasyon bulguları olmayan ve ailesel geçişli katarakt öyküsü olan hastalara uygun tanı konulmakla gereksiz invaziv (kc biopsisi, flebotomi gibi) işlemlerden sakınmak ve prognoz tahminini iyi yönde yapmak mümkün olacaktır.

Anahtar kelimeler: Hiperferritinemi, herediter, bilateral katarakt. **Nobel Med 2017; 13(2): 80-82**

INTRODUCTION

Hereditary hyperferritinemia-cataract syndrome (HHCS) is a very rare autosomal dominant genetic disorder resulting in the increase of ferritine light chain (L-ferritine) in patients without iron overload leading to elevated ferritin and early onset of bilateral cataracts, and an estimated prevalence is about 1/200,000. The ferritin light polypeptide (FTL) regulating L-ferritine located in the 19q13 region emerges in the gene in connection with 5' non-coding region mutation. This region is known as iron responsive elements (IRE) and impacts two cytoplasmic protein syntheses called iron regulatory proteins (IRP). In the event of iron deficiency, IRP gains high affinity to IRE and thus inhibiting ferritin synthesis. In patients with HHCS, the interaction between IRE and IRP decreases due to the mutation; and as a result, L-ferritine synthesis increases in connection with the reduction of negative control. L-ferritin increases in an uncontrolled manner independent of the iron overload. The syndrome was first seen and became known in medical science via two Italian families in 1995; however, it still remains completely unclear. There are no known clinical findings other than cataracts. Patients determined to have hyperferritinemia may incorrectly be diagnosed with hemochromatosis, and iron deficiency may develop rapidly with unnecessary phlebotomies.[1,2]

CASE

A 52-year-old woman was admitted to the internal medicine outpatient clinic with the complaints of weakness, headaches and widespread body aches and with a history of cataract diagnosed at 25 years of age. She had been exposed to a cataract operation 5 years earlier. During routine hospital visits two years ago, elevated ferritin was determined in the patient. In the tests performed in a state hospital, the following results were obtained: Hemoglobin (Hb), 10.37 g/dL (12-16 g/dL); mean corpuscular volume (MCV), 73.93 fL (80-99 fL); red cell distribution width (RDW), 16.09% (11.5-15.5%); serum iron, 16 ug/dL (60-180 ug/dL); total iron binding capacity (TIBC), 442 ug/dL (155-300 ug/dL); and ferritin >2000 ng/mL (4.5-204 ng /mL). The physical examination showed that blood pressure (BP) of 110 /80 mmHg, 1-2/6 degree systolic murmur in the cardiac auscultation and vitilligo marks were present. The eye examination revealed that the lens on the right eye was operated, and a capsular cataract was present in the left eye (Figure 1,2). In tests we performed, the following results were obtained: Hb, 9.6 g/dL; MCV, 70 fL; RDW, 17.3%; ferritin, 1184 ng/mL; thyroid stimulating hormone, 10.21 uIU/ml (0.35-5 uIU/ml); free thyroxine, 0.83 ng/dL (0.7-1.5 ng/dL); anti-thyroid peroxidase antibodies (anti-TPO)>600 IU/mL (0-35 IU/mL); and anti-thyroglobulin (anti-TG), 464.3 IU/mL (0-40 IU/mL). Such findings as total protein, albumin, international normalized ratio (INR), sedimentation rate, anti-nuclear antibodies (ANA), C-reactive protein (CRP), rheumatoid factor (RF), hemoglobin electrophoresis and liver magnetic resonance imaging were determined to be within normal limits. In the genetic study needed in terms of hemachromatosis, no C282Y and H63 mutations were found. L-thyroxine replacement therapy was decided to be given to the patient.

Unfortunately, we couldn't do the genetic analysis in our case. Although we failed to reveal the reason, elevated ferritin was determined to be present in the close relatives of our case; in two daughters, a sibling and a child of the sibling. Ferritin values in the daughters at the ages of 30 and 27 were 980 and 1200 ng/mL respectively, and they had also been diagnosed with cataracts when both were at 12 years of age. While the third daughter and other four siblings of the patient were inaccessible, we assumed that the inaccessible relatives also had hyperferritinemia due to autosomal dominant genes. The sibling's daughter of the patient was found out to be under medical supervision due to elevated ferritin and to undergo phlebotomy at first, but the phlebotomies were discontinued later on.

DISCUSSION

In the case presented, hyperferritinemia connected to ferritin light chain mono polymers was observed. Since ferritin heavy chain is independently synthesized in chromosome 5, it is normal to see in this syndrome. Since the ability of ferritin to carry iron is connected to heavy chain, light chain can neither carry nor store iron. Therefore, no overload of iron is observed in such patients. At least 25 known mutation points have been identified in connection with the syndrome.[3]

Cataracts are the sole finding in HHCS. Ferritin is normally a protein expressed in the lens and accepted to have an antioxidant role. In the study carried out by Mumford *et al*. on the lenses of HHCS patients on which extra-capsular cataract extraction was performed, they showed up to ten times elevation in ferritin levels when checked.[4] Two mechanisms are considered in explaining the etiology in cataracts in HHCS. The first is that excessive L-ferritin production destroys iron homeostasis, and a change in L- and H- ferritin subunit rates may increase free iron, so reactive oxygen products cause oxidative damage in the lens. However, Levi *et al*. indicated that they found no increased iron evidence in the lenses of

Figure 1. Cortical cataract radial fusiform shape deposits behind the anterior capsule.

Figure 2. Cortical cataract starlike deposits behind the posterior of nucleus.

HHCS patients. As the second reason for cataract development, a decrease in lens protein solubility is held responsible. According to this hypothesis, ferritin, expressed in excess directly, deposits and creates opacity in insoluble aggregates. Cataract morphology is characteristic in the syndrome, and they are in the form of randomly positioned, rod-like crystal deposits growing slowly, especially in the lens cortex.[1]

In differential diagnosis, hereditary hemochromatosis (HH) should be considered in particular. HH is an autosomal recessive gene iron storage disorder associated with a defect in chromosome 6. C282Y mutation is determined in nearly 90% of patients and closely connected with HH. H63D is another mutation seen frequently in Caucasians and determined in 30% of patients.[5,6] Patients with HHCS are often confused and incorrectly assessed as HH, and due to inaccurately decided phlebotomies, rapid iron deficiency anemia develops.

While there are a number of different factors that could cause elevated ferritin, HHCS can easily be diagnosed through characteristic bilateral early onset of cataracts and a family history. By diagnosing HHCS, better prognostic outcomes may be obtained, and unnecessary phlebotomies can be avoided. Patients presenting with a characteristic story can be examined for IRE gene mutation to confirm the diagnosis. In situations where differential diagnosis with HH is considered, patients should first be genetically examined in terms of HH, and invasive procedures such as liver biopsies and phlebotomies thought to be therapeutic should be avoided. Patients should be examined accordingly in situations where coincidentally determined thyroid function pathologies may occur.

In conclusion, clinicians should suspect this syndrome especially in family members with early onset cataracts or high ferritin levels with no iron load. Individuals with unexplained ferritin levels should be referred to an ophthalmologist in terms of possibly asymptomatic.

*The authors declare that there are no conflicts of interest.

C **CORRESPONDING AUTHOR:** Orkide Kutlu Okmeydanı Eğitim ve Araştırma Hastanesi, Clinic of Internal Medicine, Istanbul orkidekutlu@windowslive.com

✔ **DELIVERING DATE:** 02 / 10 / 2015 • **ACCEPTED DATE:** 17 / 10 / 2016

REFERENCES

1. Craig JE, Clark JB, McLeod JL, et al. Hereditary hyperferritinemia-cataract syndrome: prevalence, lens morphology, spectrum of mutations, and clinical presentations. Arch Ophthalmol 2003; 121: 1753-1761.
2. Yin D, Kulhalli V, Walker AP, et al. Raised serum ferritin concentration in hereditary hyperferritinemia cataract syndrome is not a marker for iron overload. Hepatology 2014; 59: 1204-1206.
3. Brooks DG, Manova-Todorova K, Farmer J. Ferritin crystal cataracts in hereditary hyperferritinemia cataract syndrome. Invest Ophthalmol Vis Sci 2002; 43: 1121-1126.
4. Mumford A, Vullimy T, Lindsay J, Watson A. Hereditary hyperferritinemia-cataract syndrome: two novel mutations in the L- ferritine iron responsive element. Blood 1998; 91: 367-368.
5. Perruccio K, Arcioni F, Cerri C, et al. The hereditary hyperferritinemia-cataract syndrome in 2 italian families. Case Rep Pediatr 2013; 2013: 806034.
6. Gürsel O, Eker İ, Kürekçi AE. Demir metabolizmaları ve bozuklukları. Türkiye Çocuk Hast Derg 2015; 1: 71-77