Reference number to be mentioned by correspondence : AG/CR200663

Hyperferritinaemia not always a sign of iron overload

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Abstract

The level of serum ferritin normally parallels the concentration of storage iron within the body. In the absence of chronic diseases elevated serum ferritin levels will lead to the diagnosis congenital haemochromatosis. However, there are genetic disorders with high ferritin levels without any sign of iron overload. A case history of a patient suffering from cataract at young age and high ferritin levels is described. Because his mother and his three sons also had cataract at young age and high ferritin levels the diagnosis hereditary hyperferritinaemia-cataract syndrome (HHCS) was made. The diagnosis was confirmed by detection of one of the mutations responsible for the syndrome. (Acta gastroenterol. belg., **2007**, 70, **360-362**).

Key words : hyperferritinaemia, iron overload, cataract, hereditary, HHCS.

Introduction

A large body of evidence indicates that the level of serum ferritin parallels the concentration of storage iron within the body. Ferritin is an acute phase protein and hyperferritinaemia can be present in cases of chronic inflammatory processes, Still's disease, liver diseases and polymetabolic syndromes. In the absence of these diseases and abnormalities elevated serum ferritin levels are indicative for increased iron stores and require further investigations and therapy. In the majority of cases this will lead to the diagnosis congenital haemochromatosis. This disease is characterized by increased levels of total body iron. The first diagnostic clue is the transferrin saturation in the blood, which has to exceed 50%. The family history usually is positive. The disease is easily detectable via genetic analysis of the Cys282Tyr and His63Asp mutations in the HFE gene. However, absence of the mutations does not exclude haemochromatosis in all cases. Two novel genetic disorders have been discovered with high ferritin levels. One is haemochromatosis type 4 (ferroportin disease) an impairment in macrophage iron recycling and iron absorption due to loss-of-function mutations in the SLC11A3 gene not characterised by the known mutations in the HFE gene (1,2). Another genetic disorder with high ferritin levels is described in the following case history.

Case-history

A 38 year old man visited the outpatient clinic because of abdominal complaints, chronic fatigue, and diminished physical condition. His medical history revealed a congenital bilateral cataract for which he was operated on at the age of 27. Physical examination revealed no abnormalities. Extensive laboratory investigations showed no abnormalities, livertests and blood chemistry were normal. The serum ferritin level, however, was 1376 µgram/l (normal value 30-400 µgram/l). Serum iron level was 9 µmol/l (normal value 12-29 µmol/l), and the saturation was 18%. There were no signs or symptoms indicative of chronic inflammatory processes, the CRP value and the ESR were normal. The abdominal complaints were caused by the irritable bowel syndrome.

The patient looked up his symptoms on the internet and was convinced he suffered from congenital haemochromatosis. However, genetic analysis did not show the well-known mutations and an MRI scan of the liver did not show signs of iron storage.

Repeated history, and moreover a family history revealed several family members who had undergone cataract surgery at young age. His mother underwent bilateral cataract surgery at young age, and his three sons were operated for bilateral cataract at the age of 6, 9, and 11 years respectively (see table). These findings lead to the diagnosis of the hyperferritinaemia-cataract syndrome.

Genetic analysis was done. A mutation was detected in the iron responsive element (IRE). This was a substitution of G → C at position 32 of the IRE. This confirmed the diagnosis hereditary hyperferritinaemia-cataract syndrome (HHCS).

Discussion

Iron is toxic, therefore, its cytosolic concentration is regulated by the transferrin receptor and storage in ferritin. Ferritin is composed of three different subunits (L, H, and G). Intracellular ferritin is composed of L- and H- subunits, serum ferritin of L- and G- subunits. HHCS is caused by mutations in the L-ferritin gene on chromosome 19. The mutations in the iron regulatory element

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Submission date :
Acceptance date :

Table 1. — **Details on laboratory parameters in the patient and his three sons**

Year of birth	1967	1992	1993	1996	normal values
Age at diagnosis	39	14	13	9	
Age of cataract	28	11	9	6	
Haemoglobin	8.5	7.5	8.0	7.8	8.9-10.7 mmol/l
Plasma iron	16.2	13.9	15.1	15.0	12-29 µmol/l
Transferrin	50.2	66.1	59.7	57.3	45-72 µmol/l
Iron saturation	32	21	25	26	20-55%
Ferritin	1541	1824	1469	1819	30-400 µmol/l

(IRE) in the 5' untranslated regions (UTR) of the transcript reduce binding affinity to the iron regulatory proteins (IRP's) and lead to constitutive upregulation of the protein in tissue and serum. There are several heterogeneous mutations in IRE. Due to the mutations production of L-ferritin becomes non-iron regulated and rises in the serum. Genetic sequencing easily shows these mutations in the IRE loop segment. C39U, A40G, C36G, A37G and C39T mutations are found. Serum ferritin levels vary substantially also within subjects sharing the same mutation (3).

Hyperferritinaemia does not always equal iron overload. The hyperferritinaemia-cataract syndrome was described for the first time in 1995 (4,5). The characteristics of HHCS are normal iron concentration in the blood, normal iron saturation, no signs of iron overload in tissues, presence of hyperferritinaemia and presence of bilateral cataract occurring at young age. The genetic basis of HHCS has been unravelled. More than 60 patients are described in the literature, mostly journals dedicated to ophthalmology, haematology or genetic research. Publications in the gastroenterological and hepatological literature are very sparse. Recently a family of patients with the HHCS was described for the first time in a journal dedicated to gastroenterology and hepatology (6). The authors named it a challenging diagnosis because generally the clinicians are not aware of the existence of this syndrome. Because internists and gastroenterologists can encounter the problem of hyperferritinaemia, it is important that these specialists are aware of this syndrome in order to avoid unnecessary investigations and therapy because of suspected iron overload.

HHCS is an autosomal dominant disorder and other members of the family will thus be affected. In HHCS serum ferritin levels exceed normal values by 10-20-fold without any evidence of iron storage. Cataract formation on young age is very prominent and critical for the diagnosis of HHCS. Without cataract no HHCS. Hereditary haemochromatosis, the most important reason for hyperferritinaemia, is autosomal recessive and thus the family history can be negative in many cases. In addition, cataract at young age is not a part of this disease.

HHCS has been described in many families in Italy, France, Spain, Australia, Canada, Germany, and the United States of America. Many families are of Italian, French or Spanish descent (7). This patient and his family is authentic Dutch.

Most patients described in the literature were treated as having haemochromatosis and received phlebotomies because of suspected iron overload. However, repeated phlebotomies will lead to iron deficiency anemia in patients with the HHCS (8). It is reported that severe iron deficiency anemia can be present despite the elevated ferritin levels (9).

Many people are heterozygous for the mutations in the HFE gene. A specific problem can occur if these mutations are present in a patient with the HHCS (8). Despite the fact that heterozygosity does not present with the clinical presentation of haemochromatosis the patients described underwent repeated phlebotomies and became anemic.

The eye lens contains L-ferritin levels which are 10-fold higher than in control lenses (10). The lens deposits are composed of crystals of L-ferritin (11). The cataract is not congenital but develops during childhood and requires surgery at young age. Cataract induction due to the G32A mutation is considered serious and leads to impairment of sight early in childhood (7). The mutation G32C also has been previously described (8,12,13). The mutation G32C leads to cataract at young age. This is the mutation detected in the patient. The patient's mother developed cataract at the age of 54 years, the patient in the case history was operated when he was 28 years. His three sons developed cataract at a very earlier age. It could be assumed that the phenotype of HHCS develops through consecutive generations leading to an earlier expression of the disease.

It is important to notice that isolated hyperferritinaemia with persistent normal transferrin saturation does not per se imply that there is iron overload. Especially if there is a history of "congenital" cataract the diagnosis HHCS should be considered. Once the diagnosis is confirmed via genetic analysis the patient should be reassured and further investigation and even therapeutic phlebotomy are contraindicated. The ophthalmologist will perform cataract surgery if necessary.

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