

Hereditary Hyperferritinaemia-Cataract Syndrome

Classical presentation for differential diagnosis

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Abstract

Hereditary Hyperferritinaemia Cataract Syndrome (HHCS) is a genetic disease caused by the mutation in ferritin light chain (FTL) gene and is of autosomal dominant inheritance. It presents with early onset of cataract and high serum ferritin. Cataracts are the predominant clinical abnormality in this syndrome. The excess of L-ferritin accumulates into the lens leading to cataracts.

We report two families with the HHCS. Four members of the first family were affected and confirmed by DNA analysis to carry the mutation c.40A>G. In the second family two members were affected with HHCS, confirmed again by DNA analysis to carry the mutation of c.32G>T. These two mutations are both recognised as causative mutations in HHCS. We also report on the importance of recognizing this syndrome during the early stage of investigating patients with high serum ferritin levels to avoid potential mismanagement.

Introduction

Hereditary Hyperferritinaemia Cataract Syndrome (HHCS) is a rare autosomal dominant genetic disease. It was first described independently by Bonneau and Girelli in 1995[1]. The syndrome is caused by a mutation in the iron responsive element (IRE) of L-ferritin located on chromosome 19. There have been 31 reported mutations since the first reported case in 1995, four of which are deletions and the remainder involving single nucleotide transition [2].

The only significant clinical abnormality in HHCS is cataract formation. The cataract morphology in the syndrome is distinctive, described as sunflower-type or breadcrumb-like [3]. There is accumulation of small crystalline aggregates of L-ferritin. The severity of the visual impairment and the level of the ferritin levels correlated with the type of mutation. HHCS with mutations at position 40 and 41 had severe cataract compared to cases at position 32 which lead to a mild cataract formation [4].

The latter mutation is reported less than the former, where five cases in France by Hetet et al [5], further two cases in France by Martin et al [6], three cases in Israel [7], one in Britain by Lachan et al [8] and one case in Australia [9] have been reported.

Family One

A 38 year old lady referred to the Haematology department at the Princess Alexandra Hospital with an elevated ferritin for further investigations of Haemochromatosis. She initially presented to her General Practitioner (GP) with feeling generally unwell and fatigued.

The investigations initiated by her GP showed a normal full blood count (FBC), renal profile and liver function test (LFT) were all within normal range, but she had a grossly elevated ferritin level of 1500 µg/L.

The investigations arranged in our department confirmed the presence of hyperferritinaemia of 852 µg/L, but the serum iron and transferrin saturation were in the normal range 14.4 mmol/L and 18 % respectively.

The HFE gene test for haemochromatosis was normal with homozygosity for the wild type HFE 282C and the wild type HFE 63H. The patient was found to have low folate of 1.0 µg/L and low vitamin B12 of 142 ng/L, and both were corrected with appropriate supplements.

As her symptoms of tiredness and hyperferritinaemia persisted further consultation was arranged when it was found that there was a personal and family history of corrective surgery for early onset cataract.

As a result of this information HHCS was suspected and investigation was initiated using DNA amplification and sequencing of the human L-ferritin gene.

Results

Our patient (LC) was found to be heterozygote with c.40A>G transversion by DNA sequencing FTL5' untranslated region.

Her father (KC) was also found to be heterozygote with c.40A>G transversion and two of her offspring's nine year old girl (CC) and three year old boy (FC) at the same point of c.40A>G transversion.

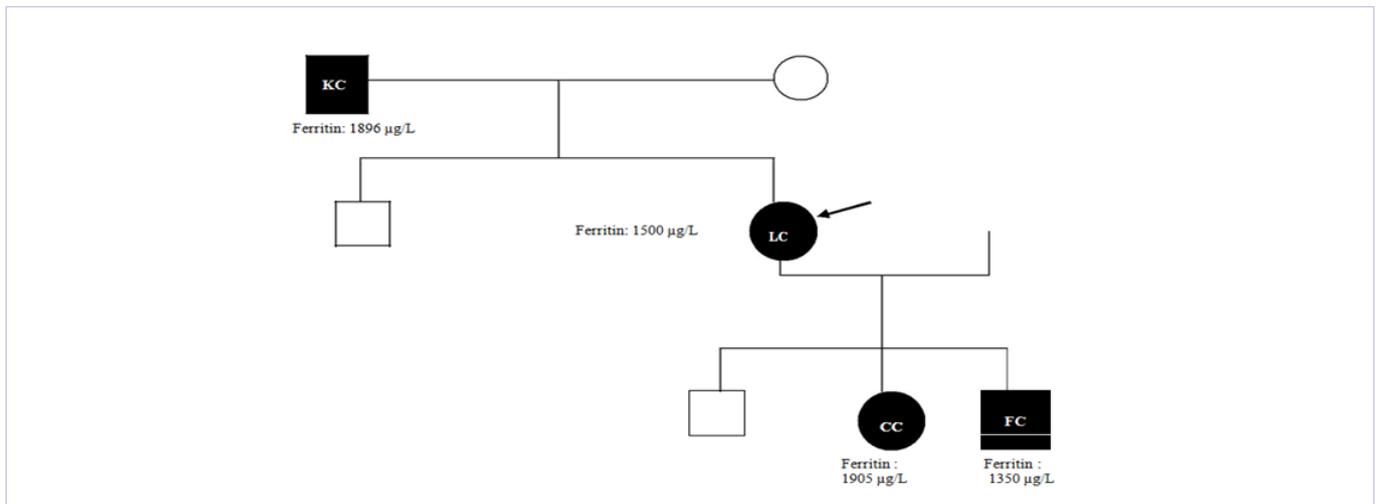


Figure 1: Pedigree of the family. Male is represented by square and female by circle. Arrow indicates the index patient. Affected members of the family are marked with filled symbols.

Family Two

A 50 year old lady was referred to the Haematology department at the Princess Alexandra Hospital with an elevated ferritin for further investigations of Haemochromatosis.

She had a routine blood test with her GP which showed a normal FBC, LFT's and renal profile. However, the ferritin was grossly elevated since 1997 with a level of 1563 µg/L in 2008.

The investigations in our department confirmed the presence of hyperferritinaemia of 1515 µg/L however; the transferring saturation and serum iron were both in the normal range 27 % and 16.9 umol/L respectively.

The HFE gene test for haemochromatosis was normal with homozygosity for the wild type HFE282C and the wild type HFE 63H.

The patient's medical history revealed bilateral cataract operations right eye in year 2000 and the left eye in the year 2007.

Family history revealed that the patient's son, father and two siblings all had cataracts. Her brother was being treated elsewhere for iron overload with venesections.

As a result of this information we arranged for DNA amplification and sequencing of the human L-ferritin gene for her and other family members. We also suspected that 3 her brother was incorrectly diagnosed and treated and therefore, we offered to investigate him in our department for possible HHCS.

Results

Our patient (OM) was found to be heterozygote with c.32G>T transversion by DNA sequencing FLT5 untranslated region. Her son (AM) was also found to be heterozygote with c.32G>T and so was her sibling (LM) at the same point of c.32G>T. Her brother (LM) was also found to be heterozygote with c.32G>T transversion by DNA sequencing FLT untranslated region. The Father (AM) of our patient was also tested and was found to be heterozygous for c.32G>T. All members of this family were tested for HFE gene which was negative haemochromatosis.

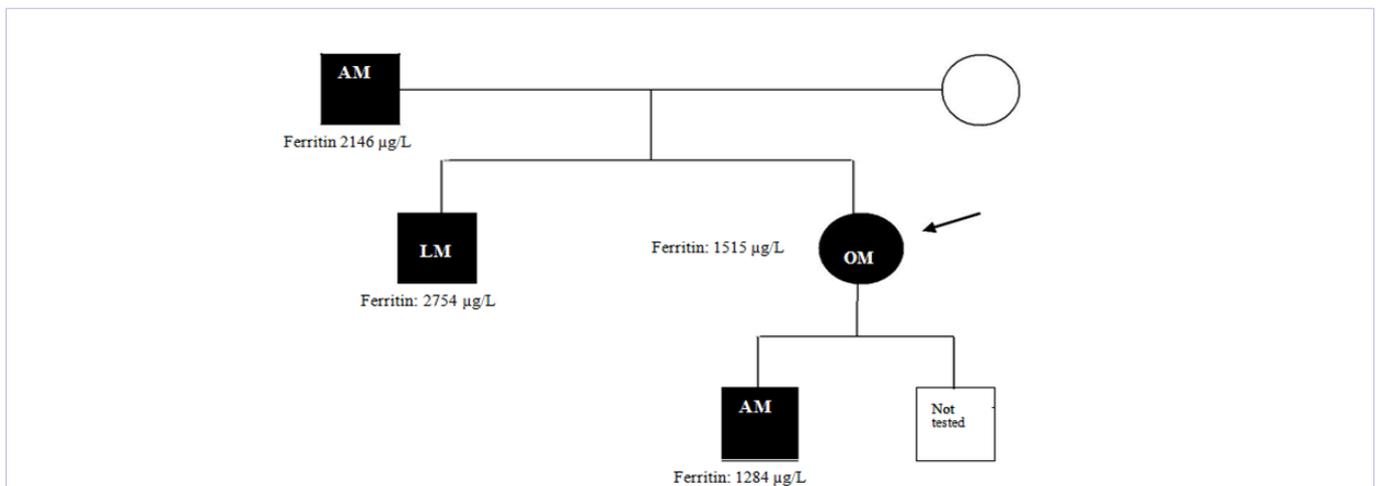


Figure 2: Pedigree of the family. Male is represented by square and female by circle. Arrow indicates the index patient. Affected members of the family are marked with filled symbols.

Discussion

The prominent feature of HHCS is bilateral cataracts, which has a distinctive morphology. The diagnosis should be entertained in cases of hyperferritinaemia with bilateral cataracts. The DNA analysis identifies the mutations in the IRE region. Conditions with iron overload similar to Hereditary Haemochromatosis (HH), and rarer disorders like atransferrinaemia and aceruloplasminaemia do not normally manifest with early onset of cataracts. Therefore, in the absence of cataracts should not be pursued. It is of paramount importance to diagnose HH as it is a treatable iron overload. In HHCS iron chelation should be avoided and treatment should aim to address the main presenting feature i.e. the cataracts.

The formation of the cataract in HHCS is postulated by two mechanisms. The first by the over expression of L-ferritin which leads to iron homeostasis disturbance and change in the L-to-H subunit ratio of ferritin composition which may increase free iron and reactive oxygen species with concomitant oxidative damage to the lenses [10].

However, the work by Levi et al. showed no evidence of increased iron in the lens of HHCS [11].

The second mechanism is to do with loss of lens protein solubility. This is postulated by direct formation of deposits or insoluble aggregates as a result of ferritin over expression. These ferritin rich deposits with crystals appearance have been reported as cataract in HHCS [12].

Serum Ferritin is a simple and readily available test for physicians and becoming among the routine examinations. Therefore, of the differential diagnosis in a healthy person with a normal transferrin saturation and serum iron HHCS should be entertained. The family history in such cases plays an important role in defining further paths of investigation which was obvious in these families.

Furthermore, individuals with HHCS should not undergo procedures like liver biopsy or and regular venesections performed in HH patients.

An affected member of the second family has been regularly venesected for his hyperferritinaemia, at his local hospital, which is not a necessity in this syndrome. The high levels of ferritin in this syndrome do not correlate with iron overload and further ferritin follow up are not necessary.

Acknowledgement

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