

## CASE REPORT

## Hereditary hyperferritinaemia-cataract syndrome and differential diagnosis of hereditary haemochromatosis

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Hereditary hyperferritinaemia-cataract syndrome (HHCS) is a rare differential diagnosis of hereditary haemochromatosis. It should be suspected in patients with raised ferritin levels, but no evidence of iron overload, and in the absence of mutations in the HFE gene. Awareness of this condition prevents unnecessary liver biopsies and allows accurate genetic counselling since HHCS is an autosomal dominant disorder. The danger of treating these patients by phlebotomy in the same manner as those with hereditary haemochromatosis is highlighted.

A 41 year old man presented to his general practitioner with a two month history of a sore mouth. There was no history of mouth ulcers, bleeding gums, gastrointestinal symptoms, or arthritis. He did not have diabetes mellitus or immune deficiency. He was found to have congenital cataracts at the age of 4 years and he had a malignant melanoma completely excised from his back four years previously. His mother had also had congenital cataracts that had been removed recently. He was on no regular medication, was a non-smoker, and drank 21 units of alcohol a week.

On examination he had an opacity in the red reflex from both eyes suggestive of cataract. There were no mouth ulcers or other oral signs and the rest of his physical examination was also normal. He was investigated with a full blood count, serum ferritin, random blood glucose, and oral swab for culture and sensitivity. The only abnormality identified on these tests was a raised serum ferritin level (1642 µg/l; normal range 18–310). A diagnosis of hereditary haemochromatosis was considered and further investigations were performed. These included transferrin saturation, repeat serum ferritin, serum iron, liver function tests, liver imaging, and HFE mutation analysis. His serum iron level was 13.3 µmol/l, total iron binding capacity was 73.8 µmol/l, and transferrin saturation was 18% (normal range 15%–55%). The repeat serum ferritin levels were also raised (1623 µg/l). His liver function tests were normal and hepatic computed tomography showed no evidence of iron overload. He tested negative for the two common HFE gene mutations, C282Y and H63D. A liver biopsy was not performed due to the associated risks and lack of evidence for iron overload.

The combination of congenital cataracts and hyperferritinaemia without evidence of iron overload or inflammation was suggestive of hereditary hyperferritinaemia-cataract syndrome (HHCS). The patient was screened for a mutation in the iron responsive element (IRE) of the L-ferritin gene on chromosome 19. He was found to be heterozygous for a G to T change at nucleotide position +32 in the IRE of this gene. This mutation has been identified previously in a French family with HHCS and is also known as the “Paris 2” mutation. This result confirmed the diagnosis of HHCS in the

## LEARNING POINTS

- Persistent hyperferritinaemia in the absence of inflammation is not pathognomonic of hereditary haemochromatosis.
- Early suspicion of hereditary hyperferritinaemia-cataract syndrome (HHCS) can prevent unnecessary liver biopsies and hepatic imaging.
- The diagnosis of HHCS can be confirmed by genetic testing.
- Confirmation of the diagnosis of HHCS can prevent unnecessary phlebotomy, which can rapidly precipitate severe iron deficiency anaemia in these patients.
- HHCS is an autosomal dominant disorder whereas hereditary haemochromatosis is an autosomal recessive condition.
- HHCS and hereditary haemochromatosis are caused by mutations in different genes.
- HHCS should be considered in anyone presenting with early onset cataracts and hyperferritinaemia with or without a family history of similar problems.

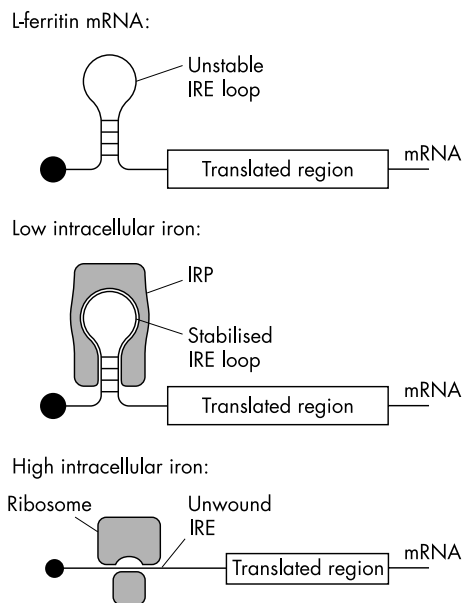
patient. The patient was advised that he did not need phlebotomy because he had no evidence of iron overload. He was also told that his children were at 50% (one in two) risk of being affected with this condition and could be offered genetic testing at an appropriate age.

## DISCUSSION

Hereditary hyperferritinaemia-cataract syndrome is a rare autosomal dominant disorder that has been identified in 25 families to date. Three families with this condition have previously been reported from this country.<sup>1–3</sup> It is caused by mutations in the IRE of the L-ferritin gene on the long arm of chromosome 19.<sup>3–4</sup> The pathogenesis of this condition can be understood through a description of the control of cellular iron stores at a molecular level.

Iron is transported in the blood as transferrin; it is taken up by cells via a transferrin receptor where it is stored as the protein ferritin. There are two forms of ferritin called H-ferritin (heavy) and L-ferritin (light). They perform similar functions, but are transcribed from separate genes on different chromosomes. The production of L-ferritin is regulated at the level of ribosomal translation of mRNA as opposed to transcription of genomic DNA. This is a common

**Abbreviations:** HHCS, hyperferritinaemia-cataract syndrome; IRE, iron responsive element; IRP, iron regulatory protein



**Figure 1** Schematic representation of translational regulation of L-ferritin production from its mRNA showing the location of the iron responsive element (IRE) and the interaction with ribosomes and iron regulatory proteins (IRPs) at times of iron depletion and excess.

method of genetic regulation, but diseases resulting from errors in this process have only recently been described.<sup>5</sup>

The translational regulation of L-ferritin production is illustrated in fig 1. Within the cell L-ferritin levels are regulated by cytoplasmic proteins that detect cellular iron called iron regulatory proteins (IRPs). If cellular iron is scarce the IRPs bind to the IRE of the L-ferritin mRNA and forms a hairpin loop due to complementary base pairing. The IRE loop is stabilised by the bound IRPs and this prevents the ribosome from attaching to the mRNA. Translation of the L-ferritin mRNA is thus inhibited by low cellular iron. Conversely, if cellular iron levels are high the IRPs dissociate from the IRE loop, which allows translation of L-ferritin mRNA to proceed so that cellular iron can be stored. Thus low levels of cellular iron inhibit the production of L-ferritin and high levels of cellular iron increase its production by regulating the translation of its mRNA into protein.

In HHCS various mutations in the IRE loop reduce its stability or prevent the binding of the IRPs. These mutations result in the translation of the L-ferritin mRNA in an unregulated manner resulting in the massively increased ferritin levels that characterise this disorder. Different mutations affect the binding affinity of the IRE to IRPs to

differing degrees; this accounts for much of the variation in disease severity.<sup>6</sup> Individuals with the same mutation may also have wide differences in ferritin levels and cataract severity.<sup>7</sup> The condition is autosomal dominant since a mutation in only one allele is required to raise ferritin levels; the alleles are transcribed equally, but translated unequally.

The bilateral nuclear cataracts are caused by a direct effect of L-ferritin accumulation in the lens<sup>8</sup> and may develop at a young age rather than being congenital. Apart from visual impairment there are no other symptoms<sup>4</sup> and no treatment is required except for symptomatic cataract removal. Treatment as for hereditary haemochromatosis with phlebotomy is contraindicated as it can rapidly precipitate severe iron deficiency anaemia.

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