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CLINICAL OBSERVATIONS IN HEPATOLOGY

Raised Serum Ferritin Concentration in Hereditary Hyperferritinemia Cataract Syndrome Is Not a Marker for Iron Overload

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Hyperferritinemia and bilateral cataracts are features of the rare hereditary hyperferritinemia cataract syndrome (HHCS; OMIM #600886). HHCS is an autosomal dominant condition caused by mutations which increase expression of the ferritin light polypeptide (*FTL*) gene. We report a patient with HHCS who was misdiagnosed and treated as having hemochromatosis, in whom a heterozygous c.-160A>G mutation was identified in the iron responsive element (IRE) of *FTL*, causing ferritin synthesis in the absence of iron overload. This report demonstrates the need for clinical awareness of HHCS as a cause of hyperferritinemia in the absence of iron overload and provides a possible diagnostic schema. (HEPATOLOGY 2014;59:1204-1206)

Case Report

A 43-year-old Caucasian man was hospitalized following exposure to formaldehyde. His hemoglo bin, serum iron concentration, total iron binding capacity (TIBC), and transferrin saturation were within the laboratory reference ranges but his serum ferritin concentration was elevated (1650 μg/L; reference range 25-300 μg/L). Serum transaminase activities, copper, ceruloplasmin, and lead concentrations were normal. A liver biopsy showed normal liver architecture and no evidence of iron overload. There was no history of alcohol abuse. He did, however, have a family history of hemochromatosis in a pattern suggestive of autosomal dominant inheritance (Fig. 1A) and a personal history of bilateral rheumatoid factor negative arthritis affecting his ankles and knees which had resolved spontaneously after 6 months and of bilateral cataract removal the previous year. A diagnosis of hemochromatosis was made on the basis of the strong family history and the presence of persistent hyperferritinemia despite the absence of evidence of iron overload. Venesection (450 mL) was performed monthly for 6 months but was stopped when the patient became symptomatic with a microcytic, iron deficient anemia in the absence of any other source of bleeding; at this time his hemoglobin was 10.0 g/dL (12.5-17.5 g/dL), transferrin saturation 4% (20%-55%) while his serum ferritin remained elevated at 1,728 μg/L. Venesection was stopped; he was treated with iron supplements until he was iron replete; his serum ferritin concentrations remained elevated throughout.

HFE mutation screening for p.(C282Y) and p.(H63D) showed that the patient was p.(H63D) heterozygous. This genotype is unlikely to be associated with *HFE*-hemochromatosis. Ferroportin (*SLC40A1*) coding and splice site sequence was wild-type.[1] A heterozygous c.-160A>G mutation was identified in the IRE within the 5′ untranslated region (5′-UTR) of *FTL*, in the patient and his mother (Fig 1B). Bioinformatic analysis (http://ccbg.imppc.org/sires/index.html) predicted that the mutant messenger RNA (mRNA) will not form the regulatory IRE "hairpin" structure (Fig 1C). These results confirmed a diagnosis of HHCS. Subsequent investigation showed that the inheritance of hyperferritinemia in this family

Abbreviations: HHCS, hereditary hyperferritinemia cataract syndrome; IRE, iron responsive element; TIBC, total iron binding capacity.

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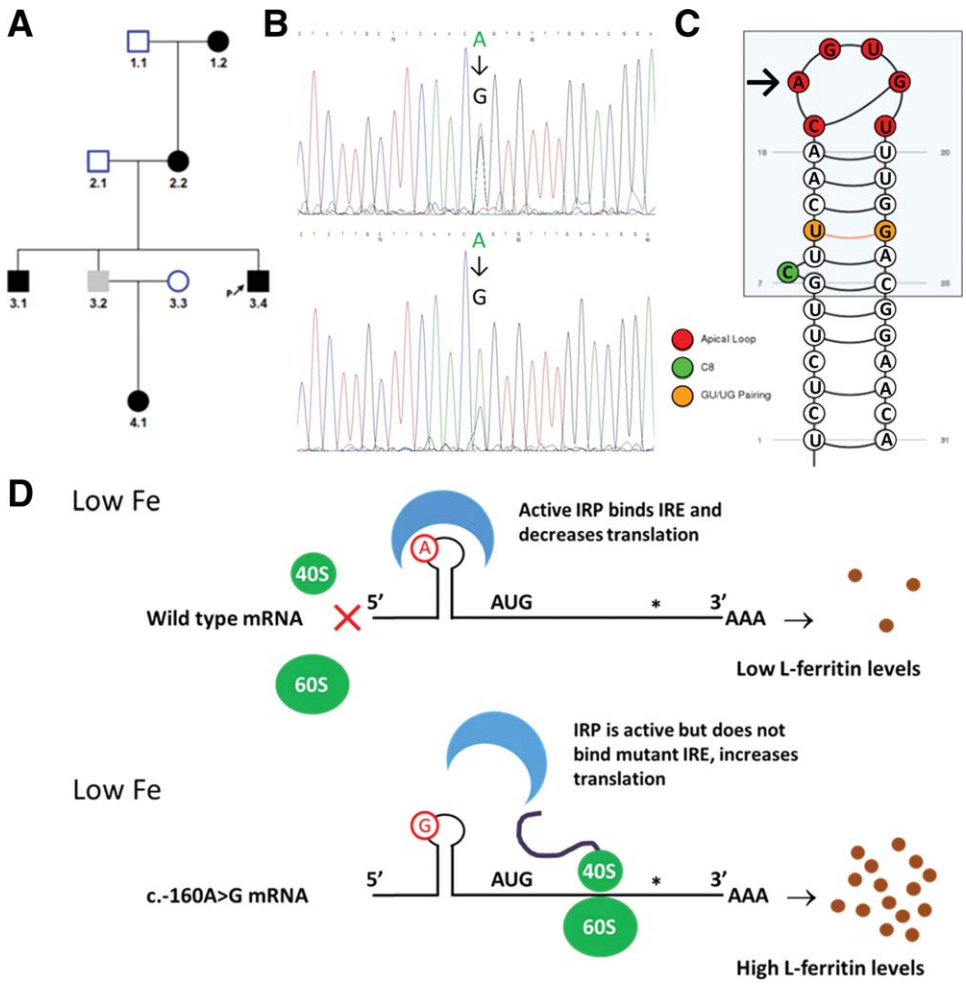

Fig. 1. (A) Pedigree showing autosomal dominant inheritance of hyperferritinemia with cataracts. Solid symbol, affected; open symbol, unaffected, gray symbol, unknown; arrow, proband (P). (B) Sequence chromatogram of the *FTL* gene from the proband (upper panel) and his mother (lower panel), showing the heterozygous c.-160A>G mutation (arrow; Reference Sequence NM_000146.3). (C) IRE prediction of wild-type *FTL* mRNA showing the mutation site (arrow) in the apical loop which binds IRPs. Bioinformatic analysis of c.-160A>G mutant *FTL* did not predict an IRE. (D) Schematic diagram showing how the c.-160A>G mutation causes loss of normal IRE-IRP-mediated repression of *FTL* expression at low intracellular iron concentrations, causing unregulated L-ferritin synthesis, in the absence of iron overload, in HHCS.

coincided with the inheritance of bilateral cataracts (Fig. 1A).

Within cells, ferritin is comprised of 24 FTL and ferritin heavy polypeptide 1 (FTH1) subunits, forming a hollow sphere within which excess iron can be stored safely. When intracellular iron concentrations are low the requirement for iron storage is also low; iron responsive proteins (IRPs) bind IREs and so decrease translation of ferritin subunits. In HHCS, the IRE mutation reduces IRP binding and impairs the normal suppression of FTL translation at low intracellular iron concentrations, so serum ferritin concentrations are elevated in the absence of iron loading (Fig 1D).

Discussion

Serum ferritin concentration, in the absence of potential confounding factors such as inflammation, obesity, and cancer, is an indicator of body iron stores. Despite its widespread use as a clinical marker, the origins of serum ferritin remain incompletely understood. Serum ferritin mainly comprises truncated FTL subunits and surprisingly contains little iron, so it differs from intracellular ferritin. Serum ferritin is thought to be mainly secreted by macrophages, although hepatocytes and other cells may also contribute.[2] In HHCS, L-ferritin synthesis is uncoupled from cellular iron stores so that hyperferritinemia indicates unregulated L-ferritin synthesis, not iron overload. Although in HHCS L-ferritin may accumulate harmlessly in other tissues, this is not the case in the lens of the eye, where low protein turnover and containment by the capsule may retain ferritin synthesized within the lens; accumulated ferritin crystals may then disrupt light transmission.

HHCS is associated with bilateral cataracts, autosomal dominant inheritance, and hyperferritinemia unrelated to body iron stores. Although HHCS is increasingly recognized as a clinical syndrome, other published reports indicate that the diagnosis is often missed initially and only recognized following the adverse effects of venesection or chelation therapy with desferrioxamine.[3] This is well illustrated in the present patient in whom there were several missed opportunities for exclusion of hemochromatosis and diagnosis of HHCS. These include:

family screening (at presentation of the grandmother and mother as well as the patient); at interpretation of the liver biopsy histopathology result showing no iron overload; at rheumatological investigation of this young patient with rheumatoid factor negative arthritis. For the serum biochemical investigation of iron status, along with measurement of ferritin concentration, iron concentration, and TIBC for determination of transferrin saturation are always required. In this case, despite venesection and the development of iron deficiency, serum ferritin remained persistently elevated in the absence of iron overload. Hemochromatosis cannot be diagnosed on the grounds of hyperferritinemia without iron overload.

There are other causes of hyperferritinemia without evidence of iron overload, including alcohol abuse, obesity, inflammation, and occult malignancy. In those without these causes who are not homozygous for *HFE* p.(C282Y), a strong case can be made for ophthalmological investigation and screening for mutations in *SLC40A1* and the IRE of *FTL*. Clearly, an awareness of the existence of HHCS is essential but, until consensus guidelines covering this scenario are developed, screening as outlined above will avoid misdiagnosis of the syndrome and so prevent unnecessary liver biopsy and the consequences of unwarranted treatment.

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