INTERNAL MEDICINE

□ CASE REPORT □

A Novel Phenotype of a Hereditary Hemochromatosis Type 4 with Ferroportin-1 Mutation, Presenting with Juvenile Cataracts

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Abstract

Hereditary hemochromatosis (HH) is an inherited disorder usually seen in Northern Europeans, which results in iron overload syndrome. A few cases have also been reported in Japan. We herein report a Japanese man presenting with fever, arthritis, liver dysfunction, and hyperferritinemia who was diagnosed with type 4 HH. He was heterozygous for the 1520A>G (His507Arg) mutation in the ferroportin-1 gene (*SLC40A1*). He had a familial cataract as an infant, but hereditary hyperferritinemia cataract syndrome was excluded. This is the first report of type 4 HH with juvenile cataracts and suggests that there is an association between hyperferritinemia and early cataract formation.

Key words: hereditary hemochromatosis type 4, ferroportin, juvenile cataracts, hereditary hyperferritinemia cataract syndrome

(Intern Med 55: 2697-2701, 2016)
(DOI: 10.2169/internalmedicine.55.6565)

Introduction

Hereditary hemochromatosis (HH) is a hereditary disorder of iron metabolism (HDIM) characterized by systemic organ damage caused by iron deposition, mainly in the liver and spleen. HH is classified into four main types depending on the underlying genetic mutation: *HFE* (type 1), *hemojuvelin* (type 2A), *hepcidin* (type 2B), *transferrin receptor-2* (type 3), and *ferroportin* (type 4) (1). These mutations are thought to cause the dysregulation of hepcidin, leading to iron overload. HH, especially type 1, is not uncommon in Western countries, but only a few cases have been reported in Japan.

Hereditary hyperferritinemia cataract syndrome (HHCS) is another type of HDIM caused by a mutation of the iron response element in the ferritin light chain (*FTL*). It is distinct from HH and is characterized by hyperferritinemia and juvenile cataracts. In contrast to HH, patients with HHCS have a favorable prognosis; they do not experience iron deposition in the liver or spleen, do not require phlebotomy, and only require cataract surgery if their vision is impaired (2). We herein present the first report of a Japanese patient with HH and juvenile cataracts. In addition, we discuss the role of ferritin in cataract formation.

Case Report

A 42-year-old Japanese man was admitted to our hospital with complaints of continuing liver dysfunction and hyperferritinemia (>3,000 ng/mL). Three years before admission, he had complained of fever, polyarthralgia, and an atypical skin rash and was found to have liver dysfunction and hy-

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Received for publication September 14, 2015; Accepted for publication January 6, 2016

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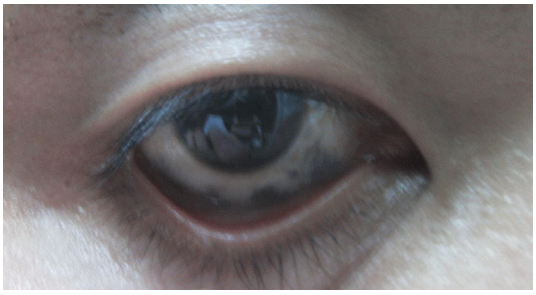
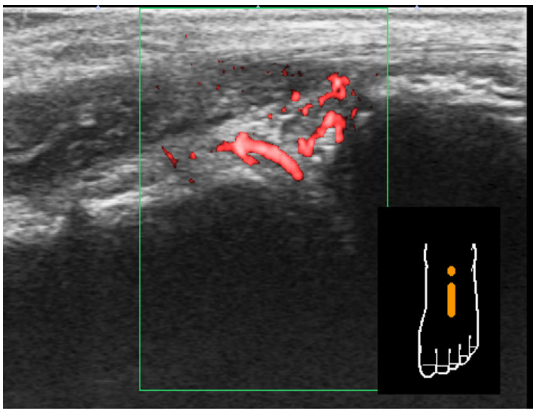


Figure 1. **Pigmentation in the bulbar conjunctiva. The patient's bulbar conjunctivae were bluish brown.**



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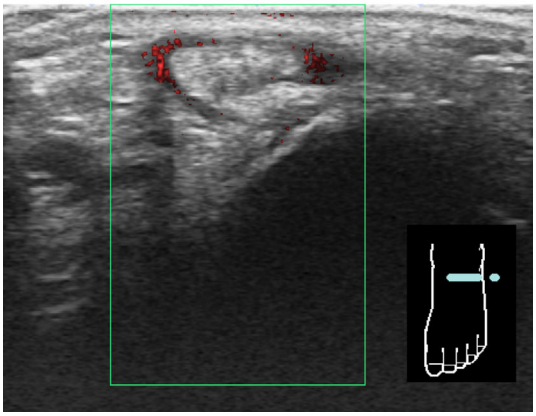

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Figure 3. **Tenosynovitis in the left transverse tarsal joint and left flexor digitorum longus muscle. Joint sonography showed an abnormal grayscale and power Doppler signal in A) the left transverse tarsal joint and B) the left flexor digitorum longus muscle, indicating tenosynovitis.**

perferritinemia. He was tentatively diagnosed with adult-onset Still's disease (AOSD) and was treated with moderate doses of prednisolone and tacrolimus for immunosuppression. Prednisolone treatment was decreased to 10 mg by the time of his admission. He had a history of childhood cataracts, cervical vertebral syndrome, left osteonecrosis of the femur, and diabetes mellitus. His father also had childhood cataracts, liver dysfunction, and diabetes mellitus. The patient smoked 5-20 cigarettes a day for 20 years and drank two bottles of beer a day. On physical examination, his bulbar conjunctivae were bluish brown (Fig. 1), and cataracts were detected in both eyes. He had no skin rash but had mild arthritis in the left ankle and foot. Gallium scintigraphy showed uptake in multiple joints (Fig. 2). Joint sonography showed an abnormal grayscale and power Doppler signal in the left transverse tarsal joint and the left flexor digitorum longus muscle, suggestive of active tenosynovitis (Fig. 3). Hematological examination revealed no abnormalities, with a red blood cell count of 4.31×10^{12}/L and an Hb concentration of 14.2 g/dL.

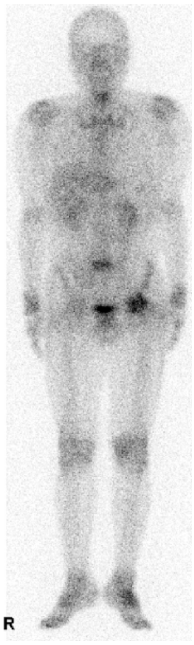

Figure 2. **Multiple areas of uptake seen on gallium scintigraphy. Gallium scintigraphy showed uptake in multiple joints.**

Blood tests revealed mild elevation of aspartate aminotransferase at 65 IU/L (normal range: 12-30 IU/L), alanine aminotransferase at 101 IU/L (7-27 IU/L), elevation of serum iron concentration to 273 μg/dL (80-170 μg/dL), elevation of serum ferritin concentration to 3,751 ng/mL (30-400 ng/mL), and a transferrin saturation of 93% (20-50%; transferrin saturation was calculated by dividing the serum iron concentration by the total serum iron binding capacity). Total bilirubin and serum albumin concentrations were normal at 0.7 mg/dL and 4.6 g/dL, respectively. Hepatitis B surface antigen and C antibody findings were negative, and C-reactive protein levels were not elevated. A bone marrow examination was hypocellular, and there was no evidence of abnormal differentiation or maturation of blood cells, or of hemophagocytosis. Abdominal contrast-enhanced computed tomography and magnetic resonance imaging showed abnormal signals suggestive of iron deposition throughout the liver and spleen (Fig. 4).

Further inquiry revealed that the patient and his father both had a history of childhood cataract, and his father had also had liver dysfunction and required phlebotomy. Conse-

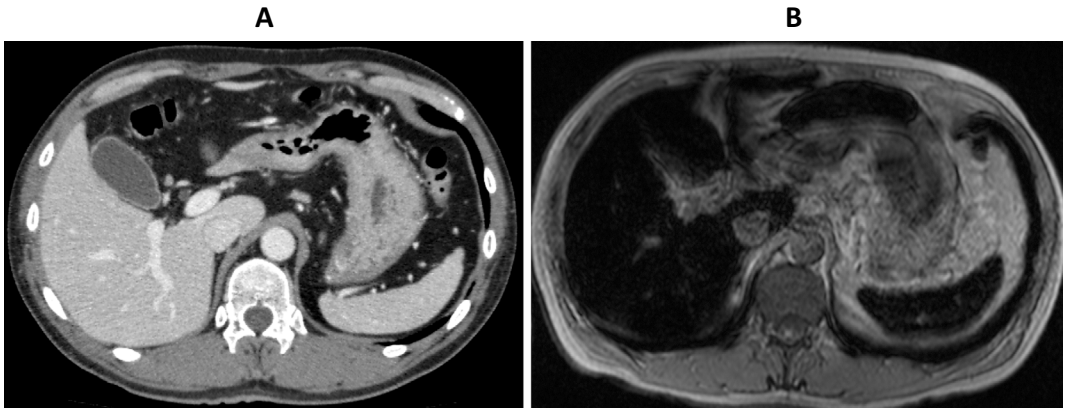

Figure 4. **Imaging evidence of iron deposition in the liver and spleen. A) Abdominal contrast-enhanced computed tomography and B) magnetic resonance imaging revealed abnormal signals, suggesting iron deposition throughout the liver and spleen.**

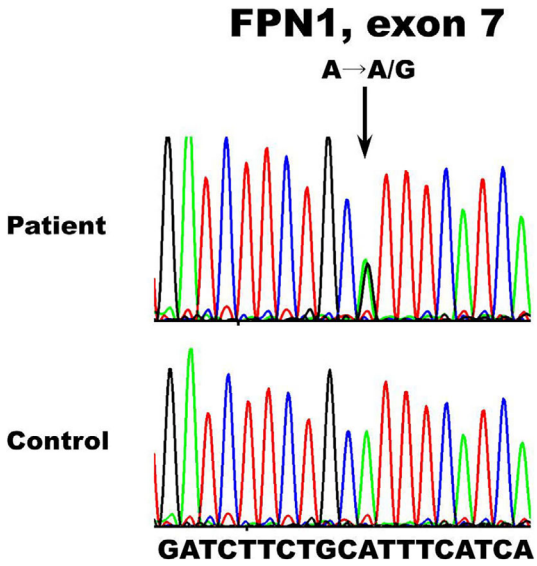

Figure 5. **Detection of a p.His507Arg mutation in ferroportin-1. The patient was found to be heterozygous for 1520A>G (His507Arg), which was detected after a sequence analysis of ferroportin-1 (*SLC40A1*).**

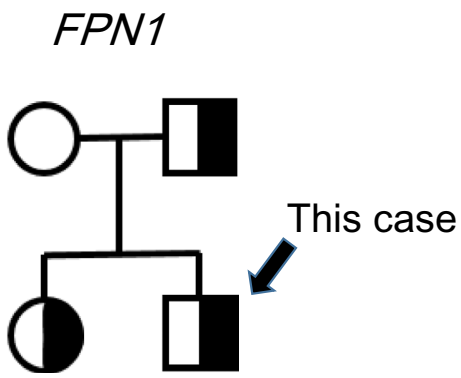

Figure 6. **Family pedigree of the mutation in ferroportin-1. The heterozygous mutation of ferroportin-1 was found in the patient, his father, and his sister.**

quently, HDIM was suspected, and the genes associated with iron metabolism were examined for mutations after obtaining informed consent and having our examination approved by the Kyoto University Ethics Committee Review Board. The patient was found to be heterozygous for 1520A>G (His507Arg) in the *SLC40A1* gene encoding ferroportin (Fig. 5). Some single nucleotide polymorphisms were also detected in introns, but they did not affect the amino acid sequence. The patient's father and sister also had the same mutation (Fig. 6), but its presence with or without juvenile cataracts was unknown. Further investigation using liquid chromatography coupled with tandem mass spectrometry found that the patient's concentration of hepcidin-25 was elevated at 132.5 ng/mL (8-32 ng/mL), and no mutations were found in *FTL*, thereby eliminating the possible diagnosis of HHCS. We therefore diagnosed this patient with type 4 HH, and are treating him with monthly phlebotomy.

Discussion

Hepcidin regulates the cellular release of iron by interacting with ferroportin-1 (FPN), which acts as a receptor for hepcidin. The FPN-hepcidin complex at the cell surface is internalized into the cell and completely degraded in lysosomes (1). Type 4 HH is a disorder caused by dysfunction of FPN and is classified as either M-type or H-type. In M-type, iron deposits in macrophages and transferrin saturation (TSAT) remain low to normal, due to impaired iron transport. In contrast, H-type is characterized by iron deposition mainly in hepatocytes and splenocytes, and TSAT is elevated because of resistance to hepcidin-induced inactivation of FPN (2). Although not confirmed by liver biopsy, the present case was considered to be H-type because TSAT was found to be elevated. To the best of our knowledge, only three cases of type 4 HH (one M-type and two H-type) have been reported in Japan (3-5). This is the first Japanese case of p.His507Arg in *SLC40A1*. A case with the same mutation (H-type) has been previously reported in the United Kingdom, although the clinical course and presence with or with-

out juvenile cataracts is unknown (6). Both TSAT and serum ferritin concentration can vary in patients with an FPN mutation (7); for example, both M-type and H-type disorders can be found in the p.Arg88Gly, p.Gly204Ser, and p.Gly490Asp mutant groups (8, 9). These observations may reflect the subtle balance of hepcidin-FPN regulation along with variable expression levels of FPN.

A cataract is defined as the opacification of the ocular lens leading to a decrease in vision. Approximately 30% of congenital cataracts have a monogenetic cause with autosomal dominant transmission, and more than 40 cataract-associated loci have been documented, of which 25 represent identified genes (10). HHCS is an autosomal dominant disorder associated with hyperferritinemia and the onset of cataracts in early life, characterized by ferruginous cataracts without systemic iron deposition with a normal serum iron concentration and TSAT, and caused by mutations in the 5'-iron-regulatory element upstream of FTL mRNA which cause dysregulation of FTL biosynthesis. Thirty-seven mutations have been associated with HHCS since it was first reported in 1995 (11). Among disorders with hyperferritinemia, juvenile cataracts are not found with any other disorders except HHCS. As both the present case and cases of HHCS share common traits of hyperferritinemia and juvenile cataract, a similar mechanism may explain the early cataract formation. In HHCS, unbalanced formation of FTL causes free polypeptides to precipitate as crystallin inclusions in the lens stroma, leading to the formation of cataracts (11), while in cases of a mutation of IRE in FTH, tissue iron depositions without cataracts are observed (12). Physiologically, FTL facilitates iron-core formation, whereas FTH generates ferroxidase activity that appears to be essential for incorporation of iron into the protein shell (13). Therefore, FTL may be more pathogenic in cataract formation than FTH, because it can easily form iron-core aggregates. FPN can function as a regulator of ferritin for exit of iron from the cytoplasm, followed by the degradation of ferritin by proteasomes (14). In our case, hyperferritinemia due to upregulated FPN function and additional factors inducing aberrant ferritin subunit synthesis, such as predominant FTL or imbalance of FTL/FTH, may promote the accumulation of ferritin in the lens and lead to early cataract formation. In addition, although our patient was followed by only phlebotomy, iron-chelating therapy with deferoxamine and deferasirox is considered to be a risk factor for cataracts (15, 16), although the mechanism of pathogenesis has not been clarified.

Our patient had active polyarthritis, probably caused by iron overload. Arthropathy is not an unusual symptom in HDIM. In a previous report, 16% of patients with type 4 HH were found to have arthropathy (7), compared with 24% in type 1 HH (17) and 10% in HHCS (11). In type 1 HH, arthropathy is usually persistent, refractory to phlebotomy, and structurally irreversible, becoming more common with increasing age and ferritin concentration. Because ferritin is reported to function as a proinflammatory cytokine via an iron-independent PKC-ζ/NFκB-regulated signaling pathway in rat hepatic stellate cells (18), these processes may also be involved in both the genesis of arthropathy, as well as in fever and skin rash associated with hyperferritinemia. Furthermore, we postulate that the complications of cervical vertebral syndrome and osteonecrosis were not associated with type 4 HH, because the onset of these symptoms were within a year before admission after corticosteroid therapy.

Our patient had initially been diagnosed with AOSD and was treated with immunosuppressants for 3 years, until persistent fatigue, liver damage, hyperferritinemia, and the finding of a family history of liver disease and juvenile cataract led to the diagnosis of type 4 HH. For clinicians, it is important to suspect HDIM when liver damage and hyperferritinemia persist despite immunosuppression.

In conclusion, this is the first report of a Japanese individual with type 4 HH, heterozygous for 1520A>G (His507Arg) in *SLC40A1*, complicated by familial cataracts at infancy. This case may help to explain the association between hyperferritinemia and cataract formation.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank Daiki Kawabata for his technical assistance in the genetic analysis. DNA sequencing analysis was performed at the Medical Research Support Center, Graduate School of Medicine, Kyoto University.

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