

Clinicopathological diagnosis and treatment of juvenile hemochromatosis

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To the Editor: Hereditary hemochromatosis (HH) is a late-onset autonomic disease characterized by enhanced intestinal absorption of iron and iron overload, which may lead to liver cirrhosis, cardiomyopathy, diabetes, arthritis, and skin pigmentation. In 1996, Feder *et al*^[1] cloned the gene responsible for HH (*HFE*) and reported that 85% of HH patients were homozygous for the C282Y mutation in the *HFE* gene. This was subsequently termed type 1 HH. Other inherited forms of HH exist that are non *HFE*-related, an example of which is juvenile hemochromatosis (JH); two genotypes that induce JH have been reported thus far. One JH genotype involves the hemojuvelin gene (*HJV*), which was cloned from a Greek family with JH by Papanikolaou *et al*^[2] and is known as type 2A HH. The other involves the human antimicrobial peptide (*HAMP*) gene, which encodes hepcidin and is termed type 2B HH.

JH is a rare autosomal recessive disorder that typically occurs in the first to third decades of life. Its symptoms are more acute and severe than those of classic hemochromatosis. The primary goal of therapy is iron depletion to normalize the body's iron stores and to prevent or decrease organ dysfunction.

A 31-year-old man who presented with polyuria, arterial hypertension, and transaminasemia for 8 years, and increased skin pigmentation for 2 years, was admitted. He was initially diagnosed with liver dysfunction and diabetes at age 23. Since then, he was treated with insulin and liver protection therapy, but the effects were not good. When he was admitted to our hospital, he complained of progressive sexual impotence. Laboratory test results revealed remarkable hyperglycemia with glycosuria (13.2 mmol/L) and biochemical liver damage: glutamyl transpeptidase (GGT) 140 U/L, aspartate transaminase (AST) 113 U/L, and alkaline phosphatase (ALP) 162 U/L.

His serum ferritin concentration was 8729.2 ng/mL, with a transferrin saturation of 112.4%.

To determine the cause of the liver dysfunction, a liver biopsy was performed, which showed ballooning degeneration of hepatocytes. Portal lymphocytic infiltrates were present, with variable periportal inflammatory activity (interface hepatitis). Bridging necrosis was observed [Figure 1A]. Furthermore, fibrous septa and regenerative nodule formation were observed by reticulin stain [Figure 1B]. The Ishak scores for inflammation and fibrosis were 13 and 5, respectively. Iron staining (Perls' Prussian blue stain) showed diffuse extensive iron deposition in all hepatocytes, Kupffer cells, macrophages, biliary epithelial cells, and vascular endothelial cells [Figure 1C]. Iron was distributed according to a decreasing gradient from periportal to centrolobular areas.

We detected mutations in the *HFE*, *HAMP*, *TFR2*, *SLC40A1*, and *HJV* genes in the patient and in his parents, but only two mutations in *HJV* were identified. The patient was heterozygous for two mutations in *HJV*: a premature termination mutation (962G>A and 963C>A; C321X) and a mutation in the signal peptide (18G>C; Q6H). His father had the same mutations in the *HJV* gene, while his mother had one heterozygous mutation in *HJV* (9G>C; E3D).

Due to the slightly lower hemoglobin level (121 g/L), treatment with iron chelators was initiated. Intravenous deferoxamine (2.5 g/d–3.5 g/d) biweekly was administered for approximately 3 years until the serum ferritin decreased to a normal level. At the same time, he was treated with insulin and liver protection therapy. His serum ferritin apparently decreased to a normal level and his AST nearly decreased to a normal level. The skin hyperpigmentation completely disappeared after a 4-month treatment with deferoxamine. The elevated glucose and loss of libido appeared to be unaffected.

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Figure 1: Pathological features of biopsy of the liver of the patient. (A) Bridging necrosis was present (H&E, original magnification $\times 100$). (B) Fibrous septa and regenerative nodule formation (Reticulin staining, original magnification $\times 40$). (C) Diffuse extensive iron deposition in all hepatocytes, Kupffer cells, macrophages, biliary epithelium and vascular endothelial cells (Perls' Prussian blue staining, original magnification $\times 200$).

Liver involvement is a constant feature of HH, but the presence of cirrhosis at initial presentation is less common in JH and is only about 27%.^[3] Hepatocellular carcinoma has not been reported in JH, which is primarily because untreated individuals with JH die prematurely as a result of cardiac complications. It has been reported that, when patients present with JH, the incidences of hypogonadism and cardiomyopathy are 94.6% and 43.2%, respectively, and that these are the earliest and most frequent manifestations of JH.^[3] Different clinical manifestations could reflect the occurrence of the disease in a different environment or genetic background.

Laboratory data for JH is limited because documented cases of JH are rare. However, tests for serum ferritin (SF) concentration and transferrin-iron saturation (TS) should be performed. Several studies have demonstrated that the SF concentration provides a valuable correlation with the degree of iron stores in the body, and thus SF concentration has added value as a predictor of advanced fibrosis and cirrhosis in confirmed HH.

Liver biopsy plays an important role in the accurate assessment of iron deposition in JH patients. Furthermore, liver biopsy is currently the gold standard for the diagnosis of fibrosis and cirrhosis. Patients with elevated serum iron levels should be considered for liver biopsy if they have elevated liver enzymes or other clinical evidence of liver disease.

Iron deposition in the liver may affect parenchymal cells and mesenchymal cells. In HFE hemochromatosis, iron remains located at the biliary pole of hepatocytes. It is distributed according to a decreasing gradient from periportal to centrolobular areas, which is a typical pattern indicative of parenchymal iron overload. The histologic presentation of iron overload in JH is different and is responsible for marked iron overload of a mixed pattern with parenchymal predominance. The iron deposition in the patient with JH in our study was also of a mixed pattern, which showed diffuse extensive iron deposition in all hepatocytes, Kupffer cells, macrophages, biliary epithelial cells, and vascular endothelial cells. The Deugnier scores of parenchymal and mesenchymal iron deposition were 21 and 17, respectively. Due to the fast progression of iron deposition in JH patients, hepatocellular iron load may increase quickly and finally leading to the

redistribution of iron toward mesenchymal cells. Iron accumulates and triggers chronic liver damage that ends in hepatic fibrosis and cirrhosis. The Ishak scores for inflammation and fibrosis in our case were 13 and 5, respectively.

Mutations in the *HJV* gene are the most frequent cause of JH and may be found in either a homozygous or a compound heterozygous state. Various mutations in the *HJV* gene have been reported. The G320V amino acid change appears to be common in patients originating in Europe.^[2] However, the mutation found in our patient was different, as he was heterozygous for 2 mutations: a premature termination mutation (962G>A and 963C>A; C321X) and a mutation in the signal peptide (18G>C; Q6H). We searched two papers on only Chinese JH, and all of those patients had the same two mutations. Therefore, we speculated that these mutations may be hotspots in Chinese patients with JH and that these mutations could cause loss of function of hemojuvelin and impaired iron metabolism.^[4,5]

A study showed that deferoxamine treatment was as effective as normal phlebotomy treatment with weekly 500-mL blood removals. Due to the slightly lower hemoglobin level in our study, treatment with intravenous deferoxamine was also effective. Thus, deferoxamine treatment is an effective second-line treatment in those patients for whom regular phlebotomy cannot be performed.

In conclusion, liver biopsy has an important role in JH patients so that the degree of iron deposition and fibrosis can be accurately assessed. C321X and Q6H mutations may be hotspots in Chinese patients with JH. Iron parameters, cardiac function, sexual function, and liver function are more easily normalized by administration of iron chelators in combination with phlebotomy than phlebotomy alone.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his names and initials will not be published and due efforts will

be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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