Pediatric Ferroportin Disease

Gonzalo Galicia-Poblet,* Ester Cid-Paris, *Nerea López-Andrés, *Alba Losada-Pajares, †Juan-Carlos Jurado-López, ‡Maria-Isabel Moreno-Carralero, and §Maria-Josefa Morán-Jiménez

Hereditary hemochromatosis is a rare iron overload disease caused by mutations in the genes involved in iron homeostasis, the most frequent being HFE-hemochromatosis. The classic phenotype of hemochromatosis is elevated transferrin saturation and serum ferritin, and progressive iron deposits mainly in parenchymal cells of the liver. The non-HFE hemochromatosis is caused by mutations in other genes: transferrin receptor 2 gene (TFR2), hemoglobin and hepccidin genes (HJV and HAMP), and ferroportin gene (SLC40A1) causing ferroportin disease (FD), the most common form of non-HFE hemochromatosis (1,2) (Table 1).

A 9-year-old girl was referred by the pediatrician because of elevated ferritin and transaminases. She was clinically asymptomatic and the first diagnosis was the iron overload (55 ± 30 μmol/g) (Fig. 1D) and slight hepatic fatty infiltration, but a low signal intensity persisted in the bone marrow.

The patient had the mutation c.484_486delGTT (p.Val162-del) in the exon 5 of SLC40A1 gene in heterozygosis, confirming the diagnosis of FD (Fig. 2B). This mutation was also found in her father and her 6-year-old brother. No other pathogenic mutations were found in the genes studied.

The hepatic and iron parameters of the patient’s brother were studied in December 2011 and no alterations were found except for elevated serum ferritin, 202 ng/mL (7–140), which increased to 293 ng/mL in August 2013. An MRI in January 2014 revealed a mild iron overload in the liver (55 ± 30 μmol/g). Serum ferritin was 359 ng/mL in May 2014 and therapy of venesections was begun (5 mL/kg body weight).

DISCUSSION

FD is an autosomal dominant disorder caused by mutations in the gene coding for ferroportin, the only known exporter of iron. Mutations in the SLC40A1 gene are heterogeneous and cause loss of function or classical FD (type 4A) and gain of function or nonclassical FD (subtype 4B). The loss of function is a result of impaired iron trafficking, caused by altered cell-surface expression of ferroportin or altered iron egress. The gain of function is a result of resistance of ferroportin to hepcidin, caused by alteration of the hepcidin-binding site. Hepcidin is a hormone regulator of iron metabolism, which modulates iron export by binding to ferroportin, inducing its internalization and subsequent degradation (3).

The 2 subtypes of FD are characterized by hyperferritinemia and iron overload; the most prevalent, the classical form with normal or low plasma iron and transferrin saturation, and accumulation of iron mainly in macrophages (type 4A), and the nonclassical form with classic HFE-hemochromatosis phenotype, high transferrin saturation, and parenchymal cell iron accumulation (type 4B) (Table 1) (1,2). MRI is a noninvasive tool to diagnose, classify, and follow up these 2 forms of FD without performing liver biopsy (4).

The phenotypic expression of FD is variable, even in patients harboring the same mutation. It is suggested that pathological, acquired, or genetic factors (such as metabolic syndrome and excessive alcohol consumption that probably decrease hepcidin expression) may affect clinical expression. The clinical expression of FD is less severe than other types of hemochromatosis, concerning iron overload and clinical features (Table 1). A review of studies on large cohorts of patients and families with FD reports a high penetrance of FD, rarely associated with fibrosis, except for nonclassical form with a higher risk of fibrosis and more severe hepatic iron overload (5).
TABLE 1. Characteristics of hemochromatosis

| Subtypes of hemochromatosis | Gen (inheritance) | Age of onset | Biochemical features | Clinical expression | Iron overload/iron deposition | Pathogenesis |
|-----------------------------|------------------|--------------|----------------------|---------------------|--------------------------------|--------------|
| HFE hemochromatosis (type 1) | HFE (AR)         | Adulthood    | Increased plasma iron and ferritin concentrations, increased transferrin saturation | Fatigue, skin pigmentation, arthropathy, liver damage/cirrhosis, endocrine dysfunctions, cardiomyopathy | Variable/parenchymal | Decreased hepcidin expression |
| Juvenile hemochromatosis (type 2A) | HJV (AR)         | Childhood to youth | The same as HFE hemochromatosis | Cardiomyopathy and hypogonadism are more prevalent, liver damage | Severe/parenchymal | Inhibition of hepcidin expression |
| Juvenile hemochromatosis (type 2B) | HAMP (AR)        |             | The same as HFE hemochromatosis | Fatigue, arthropathy, endocrine dysfunctions | Variable-severe/parenchymal | Decreased hepcidin expression |
| TFR2 hemochromatosis (type 3) | TFR2 (AR)        | Youth adulthood | Increased plasma iron and ferritin concentrations, normal to low transferrin saturation | The same as HFE hemochromatosis | Mild/macrophagic | Decreased iron export from macrophages |
| Ferroportin disease (classical FD or type 4A) | SLC40A1 (AD)    | Any age | The same as HFE hemochromatosis | Fatigue, arthropathy, endocrine dysfunctions, liver damage | Mild/parenchymal | Resistance of ferroportin to hepcidin |
| Ferroportin disease (nonclassical FD or type 4B) |             |             | The same as HFE hemochromatosis | Fatigue, arthropathy, endocrine dysfunctions, liver damage | Mild/parenchymal | Decreased iron export from macrophages |

Patients in this study have the classical form of FD. AD = autosomal dominant; AR = autosomal recessive; FD = ferroportin disease.

FIGURE 1. MRI T2* (GRE TR120, TE 21, flip angle 20°) of the upper abdomen of the patient’s father (A and B) and patient (C and D). (A) MRI in March 2007, before apheresis treatment, revealed iron overload (not standardized criteria for iron quantifying at that moment); (B) MRI in June 2012, after apheresis treatment, liver iron content 60 μmol/g, calculated according to the protocol from the University of Rennes (normal value <36); (C) MRI before apheresis treatment, liver iron content 250 μmol/g and spleen and bone marrow signals are low because of iron deposition; (D) MRI after 12 sessions of apheresis treatment, liver and spleen signals are normal, liver iron content 60 μmol/g, and bone marrow hypointense signal persists. MRI = magnetic resonance imaging.
FD has been reported worldwide in individual cases and in families, normally in middle-aged patients and also in children between 2 and 17 years, carrying a mutation in heterozygous state in the SLC40A1 gene. The allelic variant described in the present family, c.484_486delGTT (p.V162del) in the SLC40A1 gene, causes the classical form of FD. This mutation has been previously reported in adults in families from Italy, Greece, United Kingdom, Sri Lanka, and France, the youngest being 18 years old (5–7).

This document emphasizes that besides the importance of diagnosis and treatment of iron overload disease, it is also valuable to detect genetic defects particularly in cases that do not have classical HFE mutations. A family genetic study should be made and the carriers of the pathological mutation monitored, especially children.

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