Case Report

Juvenile Hemochromatosis due to a Homozygous Variant in the HJV Gene

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Hemochromatosis type 2 or juvenile hemochromatosis is a severe type with an early onset, hypogonadism and cardiomyopathy being the most common symptoms at presentation and organ failure before age 30 [5, 6]. To date, more than one hundred cases of juvenile hemochromatosis have been reported with a prevalence of 1 in 5-6 million people worldwide [7, 8]. The hemouvelin (HJV) gene is located in the chromosome 1q21.1, which encodes a protein involved in the iron metabolism. Hemojuvelin is a bone morphogenic protein coreceptor and acts as a modulator of hepcidin expression, a peptide that regulates the entry of iron into plasma [9]. Seventy-nine variants have been reported so far in the HJV gene (https://www.hgmd.cf.ac.uk/ac/index.php).

1. Introduction

Hereditary hemochromatosis (HH) is a disorder that causes excess iron absorption and its deposition in many organs. Progressive iron accumulation during decades result in illnesses such as liver fibrosis and cirrhosis, cardiomyopathy, diabetes, hypogonadism, hypothyroidism, arthropathy, and skin pigmentation [1]. Iron depletion by therapeutic phlebotomy or chelation therapy reduce morbidity and mortality [2].

The HFE, HJV, HAMP, TFR2, and SLC40A1 genes have been identified as causative of HH types 1, 2a, 2b, 3, and 4, respectively. All of them have an autosomal recessive inheritance, except for type 4 with autosomal dominant inheritance [3, 4].

HH type 2a or juvenile hemochromatosis (OMIM 602390) is a severe type with an early onset, hypogonadism and cardiomyopathy being the most common symptoms at presentation and organ failure before age 30 [5, 6]. To date, more than one hundred cases of juvenile hemochromatosis have been reported with a prevalence of 1 in 5-6 million people worldwide [7, 8]. The hemouvelin (HJV) gene is located in the chromosome 1q21.1, which encodes a protein involved in the iron metabolism. Hemojuvelin is a bone morphogenic protein coreceptor and acts as a modulator of hepcidin expression, a peptide that regulates the entry of iron into plasma [9]. Seventy-nine variants have been reported so far in the HJV gene (https://www.hgmd.cf.ac.uk/ac/index.php).

2. Case Report

A child of Spanish origin with a familial history of iron overload and consanguineous parents was checked for ferritin, and he presented with hyperferritinemia since 3 years of age. Aged 8, he was diagnosed with hemochromatosis, presenting hyperferritinemia (777 ng/ml; normal range 30–400), high serum iron concentration (380 μg/dl; normal range 50–120), and high saturation of transferrin...
Magnetic resonance imaging (MRI) of the abdomen was performed (Figure 1), and liver iron was quantified as indicated in https://www.sedia.es/calculadora-fe/.[10] If the value is greater than 79 μmol/g, it is compatible with high overload, and if it is greater than 85 μmol/g, it is confirmatory of high overload. The patient showed a severe hepatic iron overload, 99.10 μmol/g equivalent to 5.56 mg/g. Other liver tests were normal except for two punctual determinations of ALT/SGPT: abdominal ultrasound, no significant findings observed; ALT/SGPT, 26–46 U/l (normal range 9–39); AST/SGOT, 29–39 U/l (normal range 10–50); AF, 195–333 U/l (normal range 141–460); and GGT, 10–16 U/l (normal range 8–61). A study of Gilbert’s disease due to intermittent hyperbilirubinemia (values 0.5–1.7 mg/dl; normal range 0.2–1.2 mg/dl) was recently requested, and the homozygous presence of the (TA) 7/(TA)7 polymorphism compatible with Gilbert’s syndrome has been detected in the patient.

Genomic DNA was extracted from a peripheral blood sample. The analytical method for genetic study was the Ion AmpliSeq™ Technology (Life Technologies, Carlsbad, CA, USA). A targeted gene panel was used to sequence coding, splice site regions, and 5’ and 3’ untranslated regions of genes HFE, HJV, HAMP, TFR2, SLC40A1, FTL, and FTH1, whose reference sequences are NM_000410.3, NM_213653.3, NM_021175.3, NM_003227.3, NM_014585.5, NM_000146.3, and NM_002032.2, respectively. Torrent Suite 4.4 and Ion Reporter 5.2 softwares (Life Technologies) were used to analyze sequences and germline variants. Sequences were visualized in the Integrative Genomics Viewer (IGV-Human hg19). Sequences were reviewed and compared with the reference sequence by ClustalW2 software (https://www.ebi.ac.uk/Tools/msa/clustalw2/).

3. Discussion

The patient had the variant c.309C>G (p.Phe103Leu) in exon 3 of the HJV gene in homozygous state. These variants were inherited from his consanguineous parents. Moreover, this patient has the variant c.187C>G (p.His63Asp) in exon 2 of the HFE gene in heterozygous state. The variant c.309C>G in the HJV gene has been reported in a female patient in her thirties with iron overload in the liver and spleen[11].

The hematologist prescribed phlebotomies of 7 ml blood/kg bodyweight weekly with the aim to achieving a serum ferritin concentration 50–100 ng/dl and a transferrin saturation index <50%[12]. The patient tolerated this therapy well though the process in such a small child was difficult, not only because of difficulty of venous access or peripheral catheterization dislodgement but also because the child was nervous and because the intercurrent infections altered the scheduled therapy. The therapy was suspended at the end of March and July 2019 due to infectious processes that required antibiotic treatment. From August 2018 to June 2021, the patient underwent thirty-four phlebotomies, and he achieved partial iron depletion (Figure 2). In the last MRI performed in May 2021, no hepatic iron overload was observed (19.4 μmol/g equivalent to 1.1 mg/g). During this...
period, the hemoglobin remained in the range of 13–15 g/dl, the serum iron in the range of 156–317 μg/dl, the serum ferritin in the range of 89–777 ng/ml and, the transferrin saturation in the range of 56–96%. Currently, the patient continues undergoing phlebotomies therapy. Chelation therapy is not considered at present.

A cardiologist, endocrinologist, and gastroenterologist are attending the patient who has had no organ manifestations such as cardiomyopathy, arthropathy, hypogonadism, osteopathogenic medicine, thyroid abnormality, glucose intolerance, or abnormal liver function test, but has skin pigmentation.

Phlebotomy is the mainstay of therapy for hemochromatosis to prevent iron overload [12]. This is particularly critical during childhood in the heart, pancreas, and pituitary gland that would lead to multiorgan dysfunction. Iron chelation is a treatment to reduce iron overload; this therapy has also been reported to reverse end-stage heart failure and to improve hematological and clinical parameters in patients with juvenile hemochromatosis [13–15].

Juvenile hemochromatosis is typically diagnosed during childhood, but a milder phenotype and late onset has been reported in some patients; therefore, genetic testing for variants in the HJV gene should be proposed in all cases of clinical expression of iron overload [11, 16–20].

A genetic study for the currently proposed genes responsible for hemochromatosis is recommended in patients with a phenotype of iron overload and in those patients with a positive family history. The earlier the diagnosis is made, the sooner treatment can be started to prevent complications derived from the progressive iron deposit in the body.

**Ethical Approval**

The Research Ethics Committee of the Hospital Universitario 12 de Octubre, Madrid, Spain, approved the genetic study.

**Consent**

The patient’s parents were informed and gave their consent for the genetic study on their son. Written informed consent to perform the genetic analysis was according to the local guidelines (Ley de Investigación Biomédica 14/2007, Ley Orgánica de Protección de Datos y Garantía de Derechos Digitales 3/2018) and to the General Data Protection Regulation of the European Parliament and of the Council 2016/679.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Authors’ Contributions**

MBMR and JMVV diagnosed and treated the patient, followed up the therapy, and revised the manuscript; MIMC performed the genetic study; AMLM performed the radiological analysis and revised the manuscript; MJMJ and MM designed the genetic study, analyzed the genetic variants, and wrote the article.

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**References**


