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CASE REPORT

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Novel homozygote variant in the HJV gene leading to juvenile hemochromatosis: a case report

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ABSTRACT

Hereditary hemochromatosis (HH) is an autosomal recessive metabolic disorder. Mutations in different encoding genes, mostly HFE, lead to iron overload in different organs of the body. We herein report a case of HH caused by a novel variant in the HFE2 (HJV) gene. A 27-year-old man was admitted to the internal medicine ward of Shahid Rahimi Hospital in Khorramabad, Iran, on 6/6/2018. He first sought medical care for impotence and was diagnosed with increased serum iron. He ceased follow-up and was referred to our center with advanced symptoms of hemochromatosis, including central hypogonadism, heart failure, and ascites. The genetic test revealed that he was homozygote for a variant defined as c.950G>A (p.Cys317Tyr) in exon 4 of the HJV gene. The patient's symptoms improved following medical intervention. At a 4th year follow-up, he was alive and his clinical status was stable.

Keywords: Hemochromatosis; Familial hemochromatosis; Iron overload; Genetic hemochromatosis.

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Introduction

Hereditary hemochromatosis (HH) is a commonly diagnosed autosomal recessive metabolic disorder among Caucasians. HH results from mutations in different encoding genes responsible for controlling the hepcidin/ferroportin axis, leading to reduced hepcidin and iron overload in different organs of the body (1). Most cases of HH are linked to the HFE gene, while non-HFE-related HHs rarely occur due to mutations in HFE2 (HJV), TFR2, HAMP, and SLC40A1 genes (2). Juvenile hemochromatosis has been classified as types 2A and 2B, which arise from mutations in the HJV and HAMP genes, respectively. Hepcidin regulation is linked to the pathogenesis of both type 2A and 2B HH. Type 3 HH is an autosomal recessive condition caused by TFR2 gene mutations. It was the first hemochromatosis diagnosis linked to a gene mutation apart from the HFE gene. Type 4 HH, also known as ferroportin disease, is an autosomal dominant condition that has been attributed to SLC40A1 gene mutations. Contrary to HFE HH, individuals suffering from ferroportin disease commonly exhibit low to normal transferrin saturation and iron overload in macrophages, primarily from the liver, spleen, and bone marrow (3). Type 3 HH leads to an iron overload similar to HFE hemochromatosis, and, consequently, may present with abnormal liver function, diabetes, hypogonadism, cardiomyopathy, or arthritis (24). Typical onset occurs during adulthood, but inheritance of both TFR2 and HFE mutations are known to lead to an earlier onset of the disease.

HH might be symptomless or present with a wide range of clinical manifestations based on the organs affected. The initial presentations of the disease occur mostly in the fourth to fifth decades of life (4). In type 2A, however, which is caused by mutations in the HJV

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gene, severe iron loading and organ failure occur before 30 years of age (5). Herein, we present a case of HH in a young man caused by a novel variant in the HJV gene. This work is written according to CARE guidelines (6).

Case report

Patient information

A 27-year-old man was admitted to the internal medicine ward of Shahid Rahimi Hospital in Khorramabad, Iran, on 6/6/2018 due to generalized abdominal pain. Months earlier (10/23/2017), the patient had visited another medical center because of impotence, where in his laboratory tests increased levels of serum iron were noticed (serum iron=242 mcg/dL). He attended phlebotomy sessions but later ceased follow-up. On the current admission, he also complained of exertional dyspnea, intermittent chest pain, dry mouth, and swelling of the lower limbs. His past medical and drug history were unremarkable. Regarding the familial history, the patient mentioned that his brother had died of hemochromatosis at a young age.

Clinical findings

On physical examination, skin hyperpigmentation was noticed. In the cardiovascular examination, tachycardia, a distended jugular vein, as well as a systolic murmur at the left sternal border were detected. Abdominal examination revealed splenomegaly and ascites. Moreover, a +1 pitting edema was found in the patient's lower extremities below the knees.

Diagnostic assessment

Samples of the patient's serum and ascites were taken and sent to the hospital laboratory. The results showed central hypogonadism, impaired liver function tests, and insufficient vitamin D level. See Table 1 for further laboratory findings. His electrocardiogram showed low QRS voltage and poor R-wave progression. Cardiac echography revealed an ejection fraction of 20% and signs of restrictive cardiomyopathy (RCM). On the abdominopelvic ultrasound, free intraperitoneal fluid, decreased liver parenchymal echo, and a spleen measuring 81×142 mm were reported.

Genetic assessment

First, a hemochromatosis strip assay, which covers 12 mutations in the HFE gene, 4 mutations in the TFR2 gene, and 2 mutations in the FPN1 gene, was requested for the patient, but none of the common hemochromatosis mutations were identified. On 8/19/2018, another genetic testing was requested and it was reported as follows: Whole exome sequencing and variant data analysis of the patient revealed a homozygous variant in exon 4 of the HFE2 (HJV) gene (NM_213653.3) defined as c.950G>A (p.Cys317Tyr). To date, the c.950G>A variant in the HFE2 (HJV) gene has not been published as a mutation, nor has it been reported as a benign polymorphism. This variant is not found in Iranome databases, Genome Aggregation Database (gnomAD), Exome Aggregation Consortium (EXAC), and the NHLBI Exome Variant Server. In silico prediction programs (Mutation Taster, PROVEAN, Polyphen, and CADD) support this variant's probable pathogenicity. Furthermore, the c.950G>A variant seems to be located in a functional domain of the protein. Therefore, based on the currently available information and according to the ACMG guidelines, this variant was classified as a likely pathogenic variant [Lab reference: D95915-2/961067203].

Table 1. The patient's laboratory data

Test	Patient value	Reference range
Serum sample		
WBC	6.3 $\times 10^9$/L	4.4-11.3
HGB	15.5 g/dL	14.0-17.5
MCV	81 fl	80-100
MCH	36.2 pg	27.5-33.2
MCHC	35 %	33.4-35.5
PLT	116 $\times 10^9$/L	150-450
Serum iron	172 mcg/dL	60-170
TIBC	267mcg/dL	240-450
Ferritin	333 mcg/L	24-336
FBS	76 mg/dL	≤99
TSH	1 mIU/L	0.5-5.0
T3	0.8 nmol/L	0.92-2.76
T4	6.8 µg/dL	5.0-12.0
FSH	1.4 mIU/mL	1.5-12.4
Testosterone	0.1 nmol/L	10-35
25(OH)D3	29 ng/mL	30<
ALP	270 IU/L	Less than 350
AST	95 IU/L	10 – 40
ALT	85 IU/L	10 – 40
Albumin	4.2 g/dL	3.4 to 5.4
Ascites sample		
WBC	425/µL (PMN:20)	<500
Albumin	1.73 g/dL	3.5<
LDH	139 SU	<400
Protein	2.6 g/dL	0.3-4

WBC=white blood cell; RBC=red blood cell; HGB=hemoglobin; MCV= mean corpuscular volume; MCH =mean corpuscular hemoglobin; MCHC =mean corpuscular hemoglobin concentration; PLT =platelet; TIBC=total iron-binding capacity; FBS=fasting blood sugar; TSH=thyroid-stimulating hormone; FSH=Follicle-stimulating Hormone; ALP=alkaline phosphatase; AST=aspartate aminotransferase; ALT=alanine aminotransferase; PMN=polymorphonuclear leukocyte; LDH=lactate dehydrogenase

Therapeutic intervention

For the management of the patient's heart failure, digoxin 0.25 tablets every other day, captopril 25 mg tablets twice daily, and carvedilol 6.25 tablets twice daily were administered. Spironolactone in a 25-mg tablet twice daily and furosemide in a 40-mg tablet twice daily were used for both cardiac involvement and ascites. Lactulose syrup three times daily, domperidone 10 mg tablets twice daily, and metronidazole 250 mg injections were also administered for ascites. Calcium-D tablets daily and pantoprazole 40-mg injection twice daily were also prescribed. These medications were administered during the patient's hospitalization (about four weeks).

Follow-up and outcomes

Following the aforementioned therapeutic interventions, the patient's clinical status improved significantly. During hospitalization, a great body of clinical and para-clinical evidence was in favor of JH; however, the definite genetic diagnosis had not yet been reported. The patient was discharged on 7/2/2018 with a prescription for his cardiological medication and calcium-D tablets. Weekly phlebotomy sessions were also scheduled to avoid iron overload. The second genetic assay was reported after the patient's discharge (8/19/2018) and confirmed the diagnosis of JH. The patient continued to attend regular follow-up sessions. In the last follow-up on 10/13/2022, he had adhered to the therapeutic regimen and his symptoms were controlled. Figure 1 illustrates the timeline of events for the present case.

Discussion

Hemojuvelin is a product of the HJV gene, and it is engaged in the signaling pathway that regulates hepcidin (HAMP) expression and iron homeostasis. Pathogenic variants in this gene have been associated with hemochromatosis type 2A, also called juvenile hemochromatosis (JH) (7). JH leads to drastic iron overload and organ failure in patients before 30 years of age (5). The common complications of iron overload, including cirrhosis, cardiac involvement, endocrine failure, diabetes, arthropathy, and skin hyperpigmentation, are akin to those of adult-onset HH; however, hypogonadism and cardiomyopathy are the most frequent symptoms at presentation (8). Timely diagnosis is crucial, as in the absence of treatment, this condition can result in morbidity

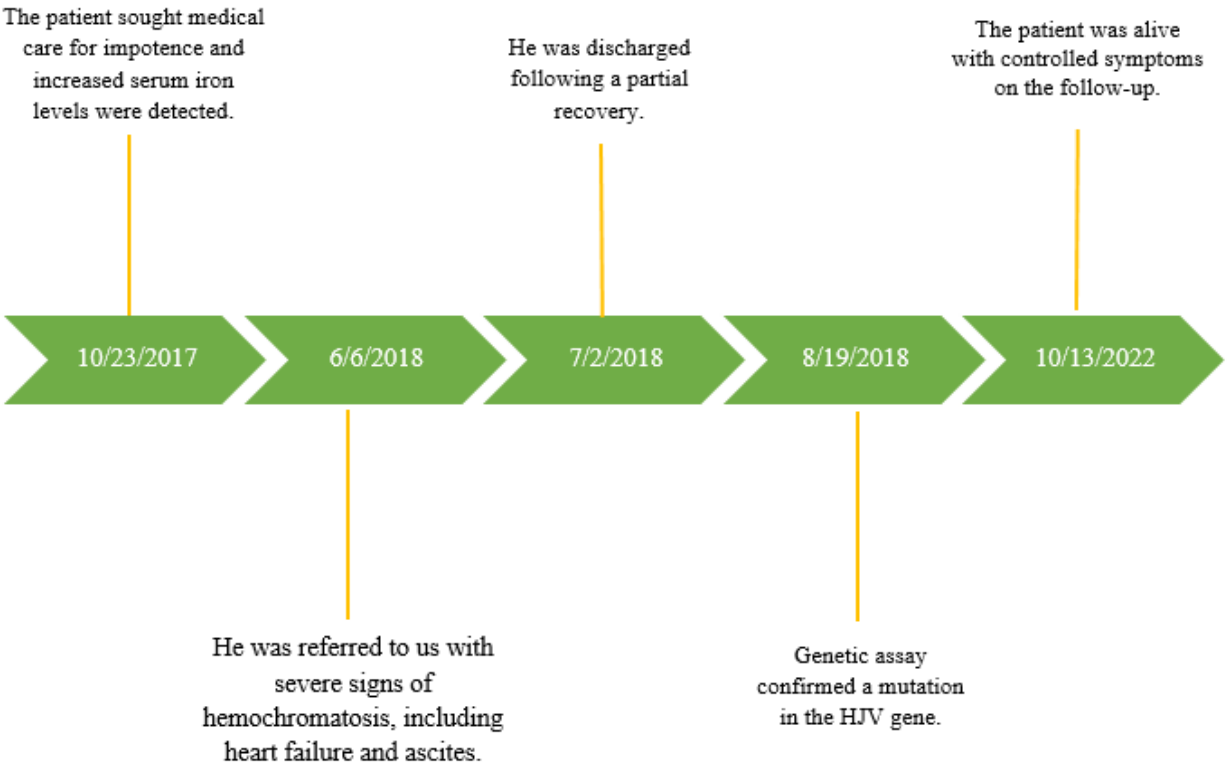

Figure 1. Timeline of the events for the present case

and even death (9). Heart failure and/or major arrhythmias are the leading cause of death in the absence of treatment (10). In some cases, HH might be asymptomatic which makes diagnosis difficult. Symptoms are observed more frequently in men than in women, as certain amounts of iron are discharged from the body during menstruation (9). In the present case, the symptoms of JH presented in both the patient and his brother at a young age. A satisfactory recovery is achievable; however, the affected individuals should be monitored for the rest of their lives. Screening of family members is a critical step in the management of JH. Hence, awareness of the diagnosis is crucial for early detection and treatment (11).

Conclusion

c.950G>A (p.Cys317Tyr) in exon 4 of the HJV gene is a novel pathogenic variant, leading to hemochromatosis type 2A.

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Conflict of interests

The authors declare that there are no known competing financial interests of personal relationships that could have influenced the case reported in this paper.

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