Juvenile Hemochromatosis in Iran: A Case Report with 5-Year Follow-up after Treatment

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INTRODUCTION

Hereditary hemochromatosis (HH) refers to a group of hereditary disorders of iron metabolism characterized by iron overload, which leads to excessive accumulation of iron in tissues. It is classified into five major categories based on the age of onset and other factors, such as genetic cause and mode of inheritance. Type 1, or classic hemochromatosis, which is associated with the Human hemochromatosis gene (also known as the HFE gene), is the most common type and is often seen in Caucasians. The other four rare types include type 2 (A and B) or juvenile hemochromatosis (JH), type 3 hemochromatosis (transferrin receptor 2 hemochromatosis), type 4 (A and B) hemochromatosis (Ferritoprotein disease), and a hypoceruloplasminemia.1,2

JH is a rare autosomal recessive disorder, which typically occurs in the first to third decades of life. Its symptoms are more acute and severe than those of classic hemochromatosis and its incidence is equal in men and women.3,4

The first case of JH was reported by Bezain and colleagues in 1932. Their report was about a 20-year-old woman with pigmentary cirrhosis, hepatomegaly, and multiple endocrine insufficiencies who died of cardiac failure.3 In 1978, the disease was recognized as a distinct clinical entity with the description of a 26-year-old woman with heart failure, insulin-dependent diabetes, amenorrhea, and hepatomegaly and a review of previously reported cases of symptomatic idiopathic hemochromatosis.3,6

Case reports of HH have usually been published from western countries. However, in Iran, a few cases of HH type 1 have been reported.⁷⁸ Recently, JH has been reported in three family members in Iran.⁹

CASE REPORT

A 27-year-old, married, male student, a known case of secondary hypogonadism and diabetes mellitus from 2 years prior who was receiving tes-
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Table 1: Laboratory data

| Test                             | Result     | Normal Range             |
|----------------------------------|------------|--------------------------|
| White Blood Cells                | 5000 per cubic millimeter | (4000-11000) per cubic millimeter |
| Hemoglobin                       | 14.7 g/dl  | (11.5-15) g/dl           |
| MCV                              | 95 fL      | (80-100) fL              |
| Platelet                         | 128000 mcL | (150000-450000) mcL      |
| FBS                              | 153 mg/dl  | <126 mg/dl               |
| Triglyceride                     | 132 mg/dl  | (40-200) mg/dl           |
| Cholesterol                      | 155 mg/dl  | (40-200) mg/dl           |
| Aspartate transaminase (AST)     | 70 IU/L    | (6-40) IU/L              |
| Alkaline phosphatase             | 156 IU/L   | (20 to 140) IU/L         |
| Thyroid-stimulating hormone (TSH)| 1.3 μIU/mL | (0.6-6.2) μIU/mL          |
| Luteinizing hormone (LH)         | 2 mIU/ml   | (1-6) mIU/ml             |
| Follicle-stimulating hormone (FSH)| 0.3 mIU/ml | (1-14) mIU/ml            |
| Testosterone                     | 0.2 ng/ml  | (0.2-1.30) ng/ml         |
| Total protein                    | 7.2 g/dL   | (6-8) g/dL               |
| Albumin                          | 4.6 g/dL   | (3.5 to 5) g/dL          |
| HBs antigen                      | Negative   | -                        |
| Anti HCV                         | Negative   | -                        |
| ANA                              | Negative   | -                        |
| Serum Iron                       | 259 μg/dL  | (35-180) μg/dL           |
| Total iron binding capacity (TIBC)| 360 μg/dL | (230-450) μg/dL          |
| Transferrin saturation           | 72%        | 20%-50%                  |
| Serum Ferritin                   | 2200 ng/mL | (20-300) ng/mL           |
| Serum protein electrophoresis    | Normal     | -                        |

tosterone and oral medication for diabetes control, was referred to gastrointestinal clinic with the probable diagnosis of fatty liver, due to impaired liver function tests. He did not complain of arthralgia or dyspnea. There was no family history of diabetes mellitus or thyroid dysfunction. He did not smoke or use alcohol. A pigmented tan skin and hepatosplenomegaly were the positive findings in his physical examination. Various tests were performed to investigate the possibility of iron overload and chronic liver diseases (Table 1).

By sonography, his liver was reported larger than normal (165 cm) with heterogeneous echo. In his esophagogastroduodenoscopy, there was no evidence of esophageal varices. His echocardiography was normal. In non-contrast abdominal computed tomography, increased density of liver compared with spleen was reported (figure 1). A T2-weighted, gradient echo axial image of the patient demonstrated diffuse abnormal low signal intensity of the liver. The pancreas and spleen appeared normal (figure 2). Finally, a liver biopsy was performed, which showed extensive liver fibrosis and nodule formation. Iron staining (pearl’s stain) showed diffuse extensive iron deposition in all hepatocytes and Kupffer cells. The diagnosis based on the biopsy was extensive cirrhosis (6/6) with severe iron overload (4/4).

According to the clinical presentations, age less than 40 years, high ferritin levels (2200 ng/mL), transferrin saturation (72%), and MRI findings, iron overload was considered in this patient, and JH was diagnosed.

Follow-up: The patient was treated with phlebotomy every two weeks for 18 months, but there was no significant drop in iron saturation despite a drop in hemoglobin to 12 gr/dL. An iron chilor, deferasirox (500 mg twice daily), was added to the treatment. After 18 months of treatment with deferasirox, his iron saturation decreased to 20%, ferritin level decreased to 20 ng/mL, and liver function test normalized. Deferasirox was discontinued, and the phlebotomy interval was increased based on his
After 5 years of treatment, his insulin requirement decreased by 50%, but sexual dysfunction persists. A non-contrast computed tomography of liver showed significant decrease in liver density (figure 3).

**DISCUSSION**

HH is rarely reported in Iran. The first report of HH in Iran was published by Nobakht and colleagues in 2006, and few cases of this disease have been reported after that. Review of the scientific literature reveals only one recent (2014) report of JH in Iran by Malekzadeh and co-workers.

JH is a rare autosomal recessive disease. Its physiopathology is associated with impaired regulation of hepcidin hormone, which is produced by hepatocytes. Hepcidin plays an important role in iron homeostasis by regulating its absorption and release in enterocytes and macrophages.

Prevalence of HH varies in different ethnic groups. It is more prevalent in northern Europe, where almost 10% of its population are heterozygous carriers and approximately 0.5% are homozygous. More than 80% of cases have HH type 1 (associated with the gene HFE), and 20% have other rare types of this disease.

JH should be suspected in any child, adolescent, or young adult with findings of iron overload. The suspicious findings are hypogonadotropic hypogonadism, hepatomegaly, cirrhosis, liver cancer, diabetes mellitus, cardiomyopathy, arrhythmia, arthritis, and progressive skin pigmentation.

Initial manifestation in our case was secondary hypogonadism and diabetes mellitus. The first presentation of the disease has not been considered conclusive, but the signs and symptoms of hypogonadism, cardiac involvement, and an impaired liver function test are the most common findings reported in this disease.

Although diabetes mellitus is common in patients with classic HH, its prevalence is not well defined in patients with JH. However, in our case, the chief complaints that led the patient to refer to a physician were the symptoms of polyuria and polydipsia. De Gobbi and colleagues have also pointed to the presence of diabetes mellitus symptoms in their report of several patients with JH.

Presenting symptoms in the first or second decade may be less specific. They include lack of appetite, fatigue, amenorrhea, or arthralgia. If it is not diagnosed in early stages or remains untreated, it can lead to death, mainly due to heart failure.

Laboratory data for JH is limited because documented cases of JH are rare. However, tests for serum ferritin
concentration and transferrin-iron saturation should be performed. MRI is useful as a non-invasive method to determine the iron overload in the liver. Also in a liver biopsy, a hepatic iron index greater than 1.9 is suggestive of iron overload. Two gene mutations associated with JH are HJV and Hepcidin antimicrobial peptide (HAMP) genes, which encode hemojuvelin and hepcidin, respectively. HJV mutation is seen in more than 90% of patients, and HAMP is based on the clinical presentations, abnormal laboratory data, and proper response to treatment. Genetic tests were not performed due to their lack of availability.

Despite the more severe iron overload seen in JH (as compared with classic HH), hepatocellular cancer has not been reported in JH. A possible explanation is that untreated individuals with JH die prematurely as a result of cardiac complications. Effective treatment can significantly restrict the progression of the symptoms, complications, and mortality if the disease is diagnosed in early stages.

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CONFLICT OF INTEREST
The authors declare no conflict of interest related to this work.

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