Japanese Journal of Gastroenterology and Hepatology

Case Report

ISSN: 2435-1210 | Volume 10

Severe Hereditary Hemochromatosis Due to Heterozygous H63D Mutation: Unusual Presentation

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Received: 01 Aug 2023
Accepted: 06 Sep 2023
Published: 14 Sep 2023
J Short Name: JJGH

Keywords:

Hereditary hemochromatosis; H63D mutation; Diagnosis; Treatment

Citation:

Sarraj R. Severe Hereditary Hemochromatosis Due to Heterozygous H63D Mutation: Unusual Presentation. J Gastro Hepato. 2023; V10(1): 1-3

1. Abstract

1.1. Introduction

Diagnosis of hereditary hemochromatosis is based on molecular sequencing of the HFE gene in search for one of the three most frequent mutations: p.Cys282Tyr (C282Y); p.His63Asp (H63D) and pSer65Cys (S65C). Iron overload linked to the H63D mutation especially in the heterozygous state is not conventionally considered significant enough to cause the disease. We report two observations of advanced hereditary hemochromatosis that are linked to the H63D mutation in heterozygous state.

1.2. Observations

A 41-year-old patient admitted for exploration of mechanical polyarthralgia. Hereditary hemochromatosis was suspected due to the discovery of moderate hepatic cytolysis and type 1 diabetes. Iron blood level assessments showed elevated serum iron, transferrin saturation capacity and ferritinemia levels. The diagnosis was confirmed through liver biopsy, which revealed hepatic hemosiderosis and cirrhosis.

Family investigation suspected hereditary hemochromatosis in the first case's 46-year-old brother due to similar clinical manifestations which were more severe in the latter case. The two patients had osteoporosis with a T-score of -3 SD for the first and a T-score of -6 SD for the second. In both cases, liver magnetic resonance imaging showed hyposignal intensity in both T1 and T2 weighted scans, indicating iron overload. The diagnosis of HH was confirmed by genetic study, the mutation responsible was H63D of the HFE gene in heterozygous state.

1.3. Conclusion

The clinical presentation in our two patients underlines the importance of considering potential disease expression in subjects carrying the H63D mutation in heterozygous state.

2. Introduction

Hereditary hemochromatosis (HH) is a recessive single gene disorder, which is secondary to an excess of non-transferrin-bound iron that is readily absorbed by cardiomyocytes, hepatocytes, pancreatic beta cells and gonadotropic cells. Iron overload causes tissue damage through necrosis and fibrosis which in turn lead to organ damage that progressively causes dysfunction of the various organs affected. Although diagnosis is easy to make at an advanced stage, it is important to consider hemochromatosis at an earlier stage, mainly when asthenia, arthralgias, moderate hypertransaminasemia and osteoporosis are present. These findings should lead to screening examination for the disease if transferrin saturation capacity (TSC) surpasses 45% [1]. Genetic abnormalities are mainly the C282Y mutation in the homozygous or composite C282Y/H63D state. Individual heterozygosity of the C282Y and H63D mutations or homozygosity of the H63D mutation do not cause hemochromatosis [2]. We report two cases with severe disease presentation, caused by the H63D mutation in the heterozygous state and discuss the specifics of this mutation.

3. Case Report

The index subject was a 41-year-old man, non-alcoholic, admitted for exploration of low back pain and mechanical polyarthralgia affecting the wrists, metacarpophalangeal joints, knees and ankles evolving for one year. The patient had a BMI of 22.4 kg/m2. Clinical examination noted skin hyperpigmentation associated with a tanned appearance and spinal stiffness. There was no hepatosplenomegaly. X-rays of the hands showed signs of osteoarthritis especially in the radiocarpal and metacarpal-phalangeal joints as well as in the left ankle. The diagnosis of hemochromatosis was suspected due to skin hyperpigmentation, the location of osteoarthritis, the discovery of hepatic cytolysis at twice the normal level and type 1 diabetes. Blood iron tests showed increased serum iron levels of 40μmol/L (UL <27μmol/L), increased transferrin saturation capacity of 68.2% (UL <45%), and very high ferritinemia at 2547μg/L (UL: 10-250μg/L). Urinary iron was elevated at 444μg/24h (UL: 201-402μg/L). Ultrasound showed normal liver size and echostructure. Oeso-gastro-duodenal fibroscopy did not show any signs of portal hypertension. Magnetic resonance imaging (MRI) of the liver showed hyposignal in T1 and T2 weighted images indicating iron overload. Liver biopsy showed hepatic fibrosis at the stage of cirrhosis with significant hepatic hemosiderosis and signs of hepatocyte damage. Cardiac function was normal on heart-ultrasound.

This patient had osteoporosis with a T-score of -3 SD at the spine and -2.2 SD at the femoral neck using the DEXA technique. Testosteronemia was normal as well as FSH and LH. Thyroid and parathyroid functions were normal. 25 Hydroxy-vitamin D levels were low at 44.8nmol /L (UL >75 nmol/L). Blood and urine phosphocalcic tests were normal. Family investigation suspected hemochromatosis in the case's brother. Both brothers were from a first-degree consanguineous marriage. The latter is 46 years old, developed type 1 diabetes two years prior requiring high doses of insulin. Interrogation did not find any history of ethylism, but noted the presence of physical and mental chronic asthenia as well as a decreased libido. He had mechanical polyarthralgias affecting the hands, knees and ankles. Clinical examination revealed a BMI of 22 kg/m2, skin hyperpigmentation with hypotrichosis and homogeneous hard hepatomegaly without signs of cytolysis. Iron blood levels were increased with serum iron at 44.6μmol/L, urinary iron at 351.9 μg/L, transferrin saturation capacity at 98.5% and ferritinemia at 2870 μg/L.

Gastrointestinal endoscopy showed grade I esophageal varices with moderate antral gastropathy. MRI of the liver confirmed hepatomegaly with the presence of an hyposignal in T1 and T2 weighted sequences that increased after fat saturation. Liver biopsy showed micronodular cirrhosis with significant hepatic hemosiderosis. Bone mineral density was very low with a T-score of -6 SD at the spine and -3.7 SD at the femoral neck. This patient had central hypogonadism with a very significant decrease in testosteronemia to 0.32μg/L (UL: 2.5-10μg/L). Parathyroid hormone, blood calcium, blood phosphorus, calciuria, and phosphaturia levels were normal. Hydroxy-vitamin D was low at 34.8 nmol/L.

For these two patients, the diagnosis of HH was retained after eliminating other etiologies of acquired iron overload. Genetic study concluded that the C282Y mutation was absent and that the H63D mutation of the HFE gene was present in the heterozygous state. Screening for the disease in other family members could not be performed. For these two patients, treatment consisted of weekly bloodletting to reduce iron overload, calcium and vitamin D supplements and bisphosphonates for osteoporosis, combined with testosterone replacement therapy for the second patient for hypogonadism. After 6 months of follow-up, iron tests showed a normalization of iron parameters. The second case reported an improvement in sexual asthenia, but no improvement in arthralgia and diabetes for both cases.

4. Discussion

HH is a recessive disease secondary to mutation of the HFE gene, which codes for a transmembrane protein involved in the positive feedback loop of hepcidin, the major regulator of iron metabolism. This dysregulation is thought to be the cause of severe iron overload that can lead to cardiomyopathy, cirrhosis, primary liver cancer, diabetes and other endocrinopathies [3].

The clinical polymorphism of HH is explained by its genetic diversity. There are three mutations, the main one is C282Y and then there are H63D and S65C which are much less common. In Europe, 64 to 92% of HH cases are related to C282Y homozygosity with a decreasing gradient from north to south [4]. Composite heterozygous C282Y/H63D and C282Y/S65C genotypes may develop variable iron overload if other genetic and/or iatrogenic factors are associated [5]. The association between the H63D and the C282Y mutations (composite heterozygous state) is only present in 5 to 10% of patients with HH [2]. Single heterozygosity of the C282Y and H63D mutations or homozygosity of the H63D mutation does not result in clinically significant iron overload and does not therefore lead to hemochromatosis [5]. The H63D mutation exists in 17- 70% of non-C282Y chromosomes observed in patients [2]. However, the penetrance of the composite heterozygous phenotype is very low (about 1%) and homozygous patients are very rare [6].

We report two cases of severe hemochromatosis with liver cirrhosis, diabetes, osteoporosis and in one of the patients hypogonadism, for which the genetic study showed the presence of the H63D mutation in the heterozygous state, and absence of the C282Y and S65C mutations. The etiological investigation in our two patients did not find any iatrogenic factors that could contribute to the development of hemochromatosis. This underlines the interest in searching for mutations in other genes involved in iron metabolism. Analysis of the association between the HFE genotype and clinical manifestations has led to the conclusion that the penetrance of hemochromatosis is incomplete and that the severity of the disease is variable from

one subject to another. Several factors influence the severity of iron overload such as age, gender, diet and the presence of other comorbidities (alcoholism, viral hepatitis, multiple transfusions) [1, 5].

The disease is 5 to 10 times more common in men than in women and about 70% of patients develop the first symptoms between the ages of 40 and 60 years, as was the case in our two patients. During the first years of disease onset, the diagnosis of hemochromatosis is difficult because of the lack of specificity of the clinical presentation. The disease is most often discovered fortuitously from abnormalities of iron parameters that appear early in the second to fifth decade of life [1]. Patients often begin to complain of weakness, fatigue, weight loss, abdominal pain, joint pain and loss of libido, followed by liver involvement with hepatomegaly mainly in the left lobe in 95% of symptomatic patients. Hepatomegaly is rarely associated with symptoms of dysfunction indicative of cirrhosis at the initial stages of the disease. Liver function tests are usually normal [5], with the exception of a modest increase in serum aminotransferase activity, which was the case for our first patient. The major complication of hepatopathy is the development of liver cancer [7].

Joint manifestations are frequent and diverse, but the most characteristic is a chronic arthropathy affecting the second, third metacarpophalangeal and radiocarpal joints. Secondary chondrocalcinosis may be observed especially in knees. An association of metacarpophalangeal joints and ankle arthropathy with the H63D mutation has been reported as was the case in our two patients [8, 9].

Osteoporosis is usually due to hypogonadism in this context as was the case in our second patient. Hepatopathy found in our two cases, iron overload and increased Parathyroid hormone (fraction 44-68) are also incriminated in this osteoporosis [10].

5. Conclusion

Early diagnosis of Hemochromatosis is highly challenging due to its non-specific early clinical presentation. The diagnosis is supported by paraclinical indicators of iron overload in particular transferrin saturation capacity. MRI of the liver is currently an interesting alternative to liver biopsy for the diagnosis of iron overload but especially for quantification of hepatic iron concentration. The hereditary origin of hemochromatosis has been confirmed by genetic study, screening of family members is essential. Treatment of HH is currently well codified and relies essentially on bloodletting. Isolated presence of the H63D mutation in our two patients with the absence of promoting factors of iron overload underlines the interest to search for mutations in other genes involved in iron metabolism.

6. Acknowledgment: Declared none.

7. Conflict of Interest: The authors declare no conflict of interest, financial or otherwise.

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