International Journal of Applied Sciences: Current and Future Research Trends
(IJASCFRT)
ISSN (Print) , ISSN (Online)

https://ijascfrtjournal.isrra.org/index.php/Applied_Sciences_Journal

A Distinctive Case of Hereditary Haemochromatosis with Multiorgan Involvement in a Pakistani Male Harbouring H63D Mutation in the HFE Gene: A Case Report

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Abstract

Hereditary haemochromatosis (HH) is an inherited disorder of iron metabolism characterized by excessive iron overload and end organ damage. It is a genetically heterogenous hereditary disease caused by mutations that are broadly categorized into HFE and non HFE hereditary haemochromatosis (including Hemojuvelin, hepcidin (HAMP), Transferrin receptor 2 gene (TFR2) and Ferroportin (SLC11A3) gene mutation). We are reporting a case of a 55-year-old man resident of Baluchistan who was investigated for non-viral causes of cirrhosis and thrombocytopenia. His transferrin saturation was 63.7% and was found to have a Metavir score of F3 (moderate to severe fibrosis) on Ultrasonography Shear Wave Elastography of liver. His molecular analysis revealed Homozygous HFE: H63D mutation. Transferrin saturation, serum ferritin and liver transaminases were normalized following Iron chelation.

Keywords: Haemochromatosis; HFE gene; Transferrin saturation; Iron chelation.

1. Introduction

The HFE gene plays a pivotal role in iron homeostasis [1]. It is an atypical MHC class I- like gene located at 6p21 [2]. The association of HH with HLA- A suggested a founder mutation in a chromosome carrying the A3 haplotype [3]. Homozygosity for a G→A substitution at nucleotide 845 of the HFE gene results in a cysteine to tyrosine substitution at amino acid 282 resulting in the C282Y variant [4].

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A second variant (187C→G) results in histidine to aspartic acid substitution at amino acid 63 (His63Asp or H63D) [5]. H63D mutation was introduced in 1998 into Southern Asia with European chromosomes [6]. H63D gene mutation, which was first considered as polymorphism of HFE gene, is now widely recognized as haemochromatosis associated allele but few H63D homozygotes with clinical manifestations of haemochromatosis have been reported [7]. H63D homozygotes do not show significant iron accumulation and only have mildly increased serum ferritin levels [8].

2. Case Presentation

A 55-year-old man, presented to the Department of Haematology, Armed Forces Institute of Pathology, with complaints of easy fatiguability, hematuria, epistaxis, abdominal discomfort, and transient memory loss for the past two weeks. He was a newly diagnosed case of Diabetes Mellitus type 2 for 01 year. He had no history of joint pains. He also denied any history of hypertension, coronary artery disease, viral hepatitis, tuberculosis and any history of surgery, trauma, food, or drug allergy. He was a non-smoker and a non-alcoholic. He had history of 26 x units of platelets transfused in the past 02 weeks.

On general physical examination, he had normal vital signs. Clubbing and bronze discoloration of skin were noted. Spleen was palpable 5cm below left costal margin. Haematologic findings included haemoglobin of 12.4 g/dl with a haematocrit of 42% and a red cell count of $4.06x10^{12}$/L. The white blood cell count was $4.71x10^{9}$/L. The patient had thrombocytopenia with a platelet count of $41x10^{9}$/L. His ESR was 80mm after the 1st hour. Bone marrow biopsy performed to rule out causes of thrombocytopenia showed cellular fragments and trails with normoblastic erythropoiesis and adequate megakaryopoiesis. The cause of thrombocytopenia was likely peripheral destruction due to hypersplenism. Iron staining revealed markedly increased iron in the fragments.

On iron studies, serum ferritin was 370 ng/ml (20-250 ng/ml), serum iron 144 µg/dl (75175µg/dl), TIBC 226 µg/dl (250-410µg/dl) and fasting transferrin saturation 63.7% (19.7-36%). Fasting blood sugar levels were 160 mg/dl (<100mg/dL). Liver function test revealed Bilirubin 1.1 mg/dl (0.0-2.0 mg/dl), ALP 208 U/L (53-128 U/L), ALT 51 U/L (<45 U/L) and GGT 56 U/L (<55 U/L). Urea and creatinine were within normal limits. His viral screening for Hepatitis A, B, C and HIV were also negative. Autoimmune profile including ANA, autoimmune liver disease related antibodies and immunoglobulins were normal. ECG and 2D Echocardiography were normal. His upper Gastrointestinal endoscopy revealed small esophageal varices and a lax lower esophageal sphincter.

On radiological evaluation, ultrasonography abdomen and KUB revealed splenomegaly and left renal calculi with mild hydronephrosis. CT Scan KUB confirmed left renal calculi. His Ultrasonography Shear Wave Elastography for the assessment of hepatic fibrosis was suggestive of moderate to severe liver fibrosis with a Metavir score of F3. MRI Brain showed iron deposition in the region of basal ganglia. This most probably explained the neurological symptomatology. We evaluated the patient for the presence of hereditary haemochromatosis genetic mutations.

Molecular studies for H63D and C282Y mutations in the HFE gene were performed by Polymerase Chain

Reaction- Restriction fragment length polymorphism. After DNA extraction and amplification, the amplified fragments were digested with RsaI for the C282Y and BclI for H63D mutations. PCR digests were analyzed on 2.5% agarose gels. The relative position of the mutation analyzed showed the patient was homozygous for H63D mutation.

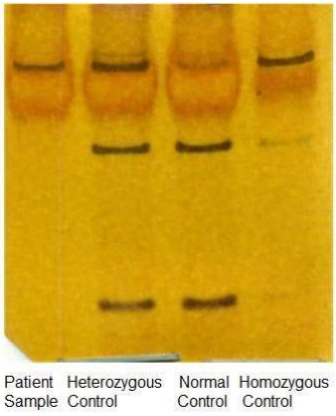

Figure 1: Patient positive for H63D mutation

One of his brothers had died at an early age due to non-hepatitis liver cirrhosis. On family screening, his mother and one sister were found to be heterozygous for the mutation. Of his four offspring, only two were screened, both of which were heterozygous for the mutation. He was started on oral iron chelation with tab Deferasirox 800 mg/day and tab Eltrombopag 500 mg/day. He was followed up after 02 months and his platelet count was 152 x 10^9/L and serum ferritin levels were below 100mg/dl.

3. Case Discussion

Hereditary Hemochromatosis is caused by an excessive tissue accumulation of iron as a result of increase rate of iron absorption which starts in early years and slowly progresses and usually presents between the age of 40 to 60 years [9]. The C282Y mutation prevents the appearance of HFE on cell membrane whereas H63D mutation prevents formation of a salt bridge that is normally present within the alpha 1 domain and impairs the binding of transferrin receptor by HFE protein so that the iron uptake from plasma is restricted [10,11].

In hemochromatosis, ferritin and hemosiderin accumulate in many tissues specially in hepatocytes, in Beta cells of islets of Langerhans in the pancreas, in myocardium, in pituitary and in joints [12]. The gradual iron overload leads to tissue damage which may present as liver cirrhosis, diabetes, hypogonadism, cardiomyopathy and skin pigmentation (slate grey or brownish bronze) [13].

Our case presented with epistaxis secondary to thrombocytopenia which led to multiple platelet transfusions. The likely etiology of low peripheral platelet count was hypersplenism as evident by adequate number of normal megakaryocytes in bone marrow examination. Hypersplenism and esophageal varices were a sequelae to the portal hypertension secondary to liver cirrhosis caused by hereditary hemochromatosis. Iron chelation with adjuvant thrombomimetic therapy improved the thrombocytopenia and resulted in decreased serum ferritin and

liver transaminases. Serum ferritin levels in our patient were mildly raised, indicating that serum ferritin is not a reliable indicator of iron overload in patients having H63D HH. Inspite of mildly raised serum ferritin levels, our patient had significant iron deposition in both the liver and the basal ganglia accounting for his symptomatology.

Identification of a genetic predisposition to iron overload early in the course of disease is pivotal for preventing organ failure by periodic phlebotomies and/or timely initiation of iron chelation.[1][4] While a presumptive diagnosis of haemochromatosis can be made on raised serum transferrin levels, molecular testing remains the final decisive diagnostic modality. Family screening is also pertinent to timely identify other family members and prevent long term complications in those individuals [13].

4. Conclusion

Our data reveals that serum ferritin levels are not an accurate measure of iron stores in patients of hereditary haemochromatosis harbouring the H63D gene mutation. Serum transferrin levels are a better indicator and guide diagnosis. Evaluation of iron stores in the organs including liver and brain can prove valuable in ascertaining the diagnosis. Molecular testing for a definitive diagnosis and timely management according to clinical presentation is a key to successful outcome. Informed consent of the patient was taken for the publication of this case report.

5. Limitations

This case study has following limitations: (1) The study documents one patient with HH having thrombocytopenia; other individuals with HH can present without having thrombocytopenia. (2) Only HFE mutations were analyzed, since testing of other genes was not available in our laboratory.

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