Non HFE Related Hereditary Haemochromatosis


Abstract
Hereditary hemochromatosis (HH) is manifested as iron overload in different organs due to homozygosity of a single autosomal mutation. Two different mutations C282Y and H63D in the HFE gene have been associated with hereditary hemochromatosis cases. This disease is seen in northern european populations, but in India it is a rare disease. We report a young male with severe abnormality of liver functions due to Non HFE related Hereditary Hemochromatosis.

Introduction
Hereditary Hemochromatosis (also called Genetic Hemochromatosis) is the term used for the inherited disease of iron overload, due to inappropriately elevated rate of intestinal iron absorption. The iron overload affects multiple organs like liver, pancreas, heart, gonads etc resulting in organ failure if not treated early. Human body has limited capacity of eliminating the excessively absorbed iron. Trousseau was the first to describe a case of Hemochromatosis in the French literature in 1865. Several population surveys have shown that the frequency of the homozygous disease ranges from 1 in 100 to 1 in 400 in white populations in Europe.2

Hereditary hemochromatosis is inherited as an autosomal recessive trait and is very common among Caucasians (1 in 400 individuals are homozygote and 1 in 10 – 20 are heterozygote).2,3 The frequency varies widely between populations. The defective gene, identified as...

Table 1: Types of Hereditary Hemochromatosis (HH)

<table>
<thead>
<tr>
<th>Features</th>
<th>HFE related HH</th>
<th>Juvenile HH</th>
<th>TfR-2 related HH</th>
<th>Ferroportin related iron overload</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMIM class</td>
<td>Type 1</td>
<td>Type 2 (A and B)</td>
<td>Type 3</td>
<td>Type 4</td>
</tr>
<tr>
<td>Implicated Gene</td>
<td>HFE</td>
<td>Hemojuvelin</td>
<td>Transferin receptor 2 and Hepcidin</td>
<td>SLC 40A1 (Ferroportin)</td>
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</table>

Fig. 1: Deep icterus
the HFE gene, is on the short arm of chromosome 6 and the two major HFE mutations are H63D and C282Y.\textsuperscript{2,3} The Online Mendelian Inheritance in Man (OMIM) database\textsuperscript{4} currently lists four types of hereditary hemochromatosis (Table 1), each caused by mutations involving different gene.

**Case Report**

A 20-year-old unemployed male presents for 1 week fever, pain abdomen and fatigue. Progressively developed yellow coloration of eyes (Figure 1), generalised itching, clay colour stools and generalised darkening of skin, with no distension of abdomen, haematemesis, malena or abnormal behaviour. There was no history of jaundice, blood transfusion, alcohol intake in the past. Patient’s father was type 2 diabetic, while other family members were normal.

Physical examination in our hospital reveals afebrile patient with Pulse 110/min and Blood Pressure 100/70, deep icterus, generalized pigmentation of body, scratch marks on skin. Patients anthropometric examination showed, Weight 56 Kgs, Height 180 cms, BMI 16 Kg/m\textsuperscript{2}, Waist to Hip ratio 0.8, chest circumference 76 cm and triceps skin fold thickness 8mm. On systemic examination, Liver was palpable 5 cms, soft, tender, with smooth surface and liver span was 17 cms. There was no ascites or splenomegaly. Cardiovascular, Respiratory and Nervous Systems were Normal on examination. No joint tenderness or swelling noted. The axillary and pubic hair were sparse (Figure 2). Testicular size was normal and...
there were no other signs of liver cell failure or encephalopathy.

Ultra sonography was suggestive of, Hepatomegaly (16.6 cm) normal in shape and echotexture, CBD and portal vein normal. Acalculous cholecystitis, both kidneys normal in size and shape, but shows mildly altered echotexture. ECG (Figure 6) and Chest X ray (Figure 7) were normal. 2D Echocardiography was normal with Left ventricular ejection fraction of 60%.

Laboratory findings are listed in Table 2 and 3.

Bone marrow aspiration showed grade 5+ iron deposition on prussian blue staining (Figure 3). Abdominal CT Scan (Figure 4) showed diffuse hepatomegaly with smooth outlines and homogeneous parenchymal density. No IHBR dilatation seen. Mild ascites in pelvis, both kidneys appear bulky with delayed function and shows multiple ill defined hypo dense areas.

MRI hepatic iron index (Figure 5) showed moderate iron deposition in the hepatic parenchyma (software maps suggest approximate values equivalent to a range of 40-75 micromols/gm). The above findings were compatible with the diagnosis of Hereditary Hemochromatosis. Genetic study for C282Y and H63D by genomic DNA extraction and then RFLP method were negative.

Phlebotomy was initiated with 500 ml weekly. After 8 weeks there wasn’t significant decrease in ferritin levels (11,313 ng/ml), the MCV (85.0 fL) remained same as the baseline, but the Hemoglobin improved to 9.6 gm/dl. During further course of phlebotomy the MCV level remained same with each bleed. But symptomatically the patient was better. After 6 months, the Hb improved (11.9gm/dl), the ferritin level decreased to 6,545 ng/ml and liver function tests improved (comparison of baseline and post 6 month therapy Tables 2 and 3). After the initial treatment we lost the patient for follow up and lastly in October 2011, he succumbed with septicemia.

Discussion

The diagnosis of iron overload can be made using a variety of methods.5 The most sensitive method of diagnosis is to measure the iron content of a liver biopsy sample. Identifying mutations in the C282Y and H63D genes is also helpful.8 Another method frequently used for screening purposes is transferrin saturation. Values above 50% are reported to be 98% specific for C282Y homozygosity in Caucasians. Radiologic techniques, especially MRI, are very helpful in diagnosing hemochromatosis. The dark hypointense appearance of the liver in T1-weighted MRI is quite characteristic. Clinical response to iron...
depletion is also occasionally used to confirm the diagnosis.

Due to the risks associated with liver biopsy in hyperbilirubinemia and prolonged prothrombin time, liver biopsy was not performed and the hepatic iron content is not available in our patient. Nevertheless, considering the clinical and laboratory findings available, the diagnosis of hemochromatosis appears to be secure.

Although conditions such as hemolytic anemia, multiple transfusions, alcoholic liver disease, nonalcoholic steatohepatitis, porphyria cutanea tarda, and chronic HCV infection can also lead to iron overload, none of these applies to the patient in this case report. Normal hemoglobin electrophoresis, and the T1-weighted MRI finding of normal splenic texture along with a classic hypointense liver image, are adequate evidence to exclude secondary hemochromatosis. Therefore, we can safely assume that our patient has Hereditary Hemochromatosis.

Hereditary Hemochromatosis occurs worldwide, in Europe it is endemic and occurs with a prevalence close to 1 per 200 population. In this patient, we did not find the classic H63D or C282Y mutation. Thus, it’s quite possible that other mutations may be involved. Mutations other than H63D or C282Y have been described in the literature. These include mutations in transferring receptors, ferroportin, hepcidin, and others. None have been extensively studied and all are only rarely reported. Therefore, maintaining a high index of suspicion for Hereditary Hemochromatosis in clinical practice is recommended in order not to miss this treatable chronic debilitating disease.

References