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HEMOCHROMATOSIS - THE MASKED CULPRIT

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ABSTRACT

HH is one of the few genetic disorders in which phenotypic manifestations (organ damage) is delayed to adult life. However, sensitive and specific phenotypic and genotypic testing now allows diagnosis of HH while it is still a disorder of iron metabolism and before it results in end-organ damage. Our case study deals with a similar situation in which the disease exhibits itself in the individual as an unexplained liver and endocrine dysfunction. We have discussed the practical clinical approach, preemptive diagnostic approach whereby early identification of individuals at risk and initiation of life-saving phlebotomy therapy in the pre-symptomatic stage of the disorder are facilitated.

INTRODUCTION

Hemochromatosis is a preventable disease that is rarely diagnosed. Hereditary hemochromatosis (HH) was first described as a triad of glycosuria (diabetes), bronze skin pigmentation, and cirrhosis of liver. At present HH is defined as an inherited disorder resulting from an inborn error of iron metabolism, characterized by increased iron absorption which leads to progressive iron loading of parenchymal cells in liver, pancreas, joints, pituitary gland and heart [1]. HH is an autosomal recessive disorder, where the mutation of the HFE gene is found in the short arm of chromosome 6. Its geographic distribution is worldwide, but it is most commonly seen in populations of northern Europe and America.Symptoms of HH usually appear between 40 and 60 years, with later onset in women,due to the loss of iron with menstruation, pregnancy, and lactation and lower iron intake [2]. Causes of secondary or acquired haemochromatosis are thalassemias, chronic hepatitis C infection, alcoholic liver disease, nonalcoholic steatohepatitis, blood transfusions and long-term kidney dialysis. We present a case of an adult male diagnosed to have alcoholic cirrhosis for the last one year, developed diabetes and was found to have HH.

Case report

36 year old male, diagnosed to have alcoholic cirrhosis one year ago was admitted with massive hematemesis, ascites and hepatic encephalopathy. Investigations showed hemoglobin of 7.2gm%, deranged LFTs and renal function tests, blood sugar random 84mg% and 76mg% on two separate occasions. Gastroscopy revealed bleeding esophageal varices for which banding was done. He was transfused three units of packed cells. There was no prior history of blood transfusion. Patient slowly recovered and was discharged on diuretics, iron + vitamin supplements, propranolol and advised to abstain from alcohol. He abstained from alcohol but omitted all the medications after 2 months.

Six months later he presented with taenia corporis. The blood sugar done by the family physician was 284mg%. A fasting, post prandial blood sugar was done which was 250 and 310mg/dl respectively. HbA1c was 10.2%. He had no family history of diabetes mellitus. He was put on insulin therapy. The insulin requirement was around 90units per day. At this point of time, he complained of darkening of skin all over of the body.

Surprisingly simultaneous hemogram done revealed Hb of 15gm%, hematocrit of 58%. With previous history of hematemesis and underlying alcoholic cirrhosis and portal hypertension, this seemed out of place, so we investigated further and found - serum ferritin 706ng/ml (N:30-300), serum iron 223mcg/dl(N:60-150), serum TIBC 285mcg/dl(N:250-400), transferrin saturation 70.73% (N:20-50) done after overnight fasting and withholding and vitamin or mineral supplements for more than 24 hours. He was not on any iron supplements since 4 months. Serum sodium 118mmol/l. LFTs: SGOT/SGPT/AlkP at 50/62/161 IU/L and Serum Total Bilirubinand direct at 5.80/2.07 mg/dl. Prothrombin time was 28sec (control: 14sec). HBsag and Anti-HCV were negative. In view of cirrhosis, diabetes and the above laboratory features a diagnosis of HH was made. Liver biopsy was deferred because of deranged prothrombin time. MRIof the abdomen showed shrunken liver with nodular surface suggestive of cirrhosis along with marked T2 darkening. Pancreas and adrenals appearedhypo-intense onT2 WI. Gross ascites is seen the gall bladder is partially distended. Splenomegaly is seen without any focal lesion. Both kidneys appeared normal. (Figure 1).

Figure 1. T2 weighted coronal image of the abdomen showing a shrunken uniformly hypo intense liver showing a nodular surface. Splenomegaly is also noted along with diffuse hypo intense signal of the adrenal glands and a small amount of ascites

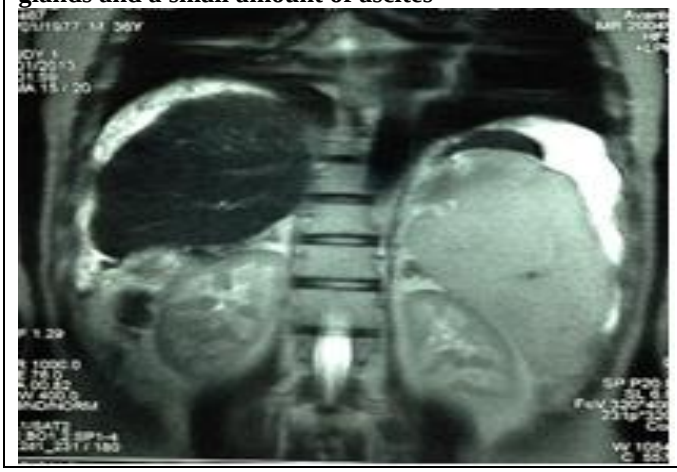
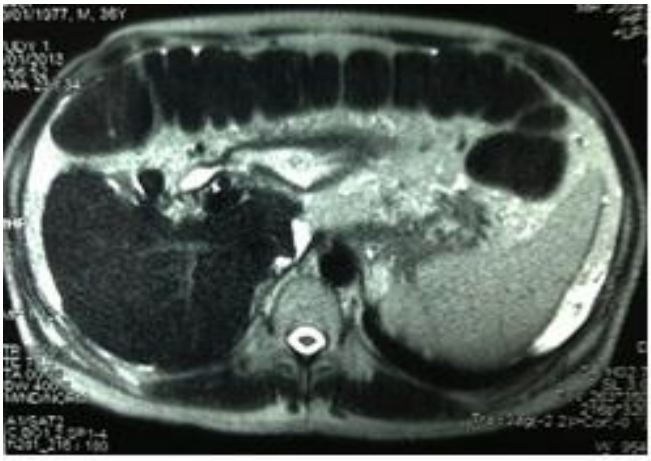


Figure 2. T2 weighted axial image shows the pancreas appearing diffusely hypo intense in addition to the hepatic findings described



DISCUSSION

Phenotypic expression of HH is variable and depend on the severity of the genetic defect, age, sex, and such environmental influences as dietary iron, the extent of iron losses from other processes, and the presence of other diseases or toxins (e.g., alcohol). Early complaints may include fatigue, weakness, joint pain, palpitations, and abdominal pain. As these symptoms are relatively nonspecific, HH is not diagnosed at an early stage. The disease can further lead to hyperpigmentation of the skin, arthritis, cirrhosis, diabetes mellitus, chronic abdominal pain, severe fatigue, hypopituitarism, hypogonadism, cardiomyopathy, primary liver cancer, or an increased risk of certain bacterial infections. Most of these advanced complications are also common primary disorders, and iron overload can be missed[2]. In our patient alcohol and blood transfusions and hematinics given in view of haematemesis were the additional influenes. But he had abstained from alcohol for 6 months and was not on any iron supplements for 4 months.

The liver is usually the first organ to be affected, and hepatomegaly is one of the most frequent findings followed by cirrhosis. The number of patients with cirrhosis at clinical presentation has varied from 22 to 60 percent. Primary hepatocellular carcinoma is 200 times more common in HH patients. Diabetes mellitus is the major endocrine disorder associated with HH. Iron deposition causing damage to the pancreatic beta cells and insulin resistance is the main cause. Other endocrine disorders involved are an effect of HH on the thyroid, parathyroid, or adrenal glands, but is rarely seen. Cardiac manifestations include cardiomyopathy and arrhythmias. Congestive heart failure has been observed in 2–35 percent and arrhythmias are present in 7–36 percent of HH patients. Increases in melanin leads to hyperpigmentation in 27–85 percent of patients. Loss of body hair, atrophy of the skin, and koilonychia (dystrophy of the fingernails) may also occur. Arthropathies are found in 40–75 percent of patients. Symptoms and disease complications increase with age[2].The most reliable test for HH is, saturation of TIBC. In this diagnosis is made by "transferrin saturation" testing. This test indicates whether excess iron is being absorbed from the body. For both sexes, excess iron absorption is suggested by >50% saturation in randomly drawn specimens. In our patient it was 70.73%. To assure a reliable conclusion, free of confounding influences, any

initial test showing elevated iron levels should be repeated after the patient has fasted overnight and not consumed any vitamin or mineral supplements for at least 24 hours; vitamin C (ascorbic acid) supplementation is particularly responsible for raising serum iron levels (especially in heterozygotes) because it increases intestinal absorption and releases iron from ferritin. Measurement of serum ferritin level gives useful--though imperfect--estimates of total body load. In our patient both serum iron and ferritin were elevated. Serum ferritin levels remain normal in all patients at the early stages of hemochromatosis. False results are seen in alcoholism and in unrecognized chronic hepatitis. Liver biopsy is an important diagnostic tool in HH, it can detect iron overload and organ damage but only to the extent that an affected patient has had sufficient time to absorb excess iron; liver biopsy can thus diagnose only advanced cases. This limitation of liver biopsy is a limitation that makes negative results non-diagnostic, it is the same with computed tomography (CT) and MRI. For the same reason, biopsy (or autopsy) of organs other than liver, skin, atrophic testis, gastric mucosa, and even myocardium may be non-diagnostic for hemochromatosis that has not yet progressed to phenotypic expression in that organ. The diagnosis of HH can be confirmed by, quantitative demonstration of body iron overload by phlebotomy or chelation, biopsy or autopsy demonstration of tissue iron overload, HLA typing identical to a proven case in a close relative and genetic analysis demonstrating homozygous presence of the HFE gene [3].

The mainstay of treatment for HH remains phlebotomy. One phlebotomy (removal of 500 mL of blood-equal to about 250 mg of iron) weekly or biweekly as per the requirement. Hematocrit has to be checked prior to each phlebotomy; it should not fall by any more than 20% of prior level. Serum ferritin levels should be checked every 10-12 phlebotomies. Frequent phlebotomy should be stopped when serum ferritin falls below 50ng/mL. Continue phlebotomy should be done to keep serum ferritin to between 25 and 50 ng/Ml. Vitamin C supplements are to be avoided, as pharmacologic doses of vitamin C accelerate mobilization of iron to a level that may saturate circulating transferrin, which results potentially in an increase in pro-oxidant and free-radical activity [4].

Secondary iron overload due to dyserythropoiesis (Iron-loading anemias like transfusion, Thalassemia major, Sideroblastic anemia, Chronic hemolytic anemias), dietary iron overload, chronic liver diseases, Hepatitis C and B, alcohol-induced liver disease, porphyria cutanea tarda, fatty liver disease - is treated with Deferoxamine (Desferal) in a dose of 20-40 mg/kg body weight per day. Follow-up liver biopsy to be done to ascertain adequacy of iron removal [5].

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