Hereditary hemochromatosis: Presentation of 2 cases and literature review

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Abstract
Hemochromatosis includes a variety of chronic syndromes of genetic origin with iron overload, which can be classified according to genetic mutations in four groups, from type 1 to type 4. Of these, the most frequent type is type 1 hereditary hemochromatosis, which corresponds to over 90% of cases. Hereditary hemochromatosis is a recessive disorder in which a dominant mutation of the hemochromatosis gene (HFE) generates an increased absorption and severe iron overload. The American study showed that a multi-ethnic population of every 227 white people is homozygous for the C282Y HFE gene mutation, implicated in hemochromatosis type 1. The HFE is located on chromosome 6, and may have three types of mutations of this gene, however the most common mutation is C282Y.

Key words
Iron, hemochromatosis, iron homeostasis, iron overload, HFE, genetic disease.

INTRODUCTION

Hemochromatosis includes a variety of chronic iron overload syndromes of genetic origin. They can be classified into 4 groups from type 1 to type 4 according to genetic mutations. The most frequent is type 1, hereditary hemochromatosis, which accounts for more than 90% of all cases (1). Hereditary hemochromatosis is a dominant recessive disorder in which mutation of the HFE hemochromatosis gene generates increases in iron absorption and severe iron overload. A North American study of a multiethnic population showed that 1 out of every 227 white people is homozygous for the mutation of the HFE C282Y gene involved in hemochromatosis type 1 (2, 3).

HFE has been located in chromosome 6. Possibly there are 3 types of mutations of this gene. However, the most frequent mutation is C282Y (4).

CLINICAL CASE REVIEW

A 45 year old male patient came to the emergency service after three days of melenas and massive hematemesis. Concomitantly he had asthenia, adynamia, dizziness and orthostatism. He had a record of diabetes mellitus treated with insulin for 6 years with periodic check-ups. The patient regularly drank aguardiente until intoxication, with significant ingestion of aguardiente 5 days before hospital admission.

- Patient was admitted in generally bad condition with generalized mucocutaneous paleness, but patient was conscious and alert.
- Blood Pressure 90/60; Heart Rate 96/min; Respiratory Rate 20/min
- Cardiopulmonary assessment: Satisfactory
- Abdomen: No collateral circulation, ascites or hepatosplenomegaly.
The patient was initially medicated with crystalloid and given a transfusion of 3 units of packed red blood cells (PRBCs). Omeprazole infusions achieved hemodynamic stability.

**REINTERROGATION**

**Personal Medical Record:** Patient was hospitalized for alcoholic pancreatitis two years prior to admission.

**Family Medical Record:** Father and paternal uncle died of cirrhosis before they were 50 years old. Brother and sisters are reported to be healthy.

**Epidemiologic Records:** Occupation stockbreeder. No contact with toxins, no transfusions, no hepatitis, occasional smoker. Ingestion of aguardiente until intoxicated 3-5 times a week for 15 years. Based on family and personal records, one diagnostic hypothesis is hepatopathy of a family type. A high digestive endoscopy was performed with a finding of esophageal varices. Band ligation (using #6 bands) was then performed starting from the cardia. A sonogram showed normal sized and shaped liver with slightly increased echogenicity. The gall bladder, intrahepatic and extrahepatic bile ducts, aorta and cava were all normal.

The patient’s evolution was adequate, showing no signs of rebleeding. Clotting times were corrected. Patient was given an appointment for an endoscopic check-up at the gastroenterology service with an order for lab tests to rule out hepatitis and for iron overload hepatopathy.

Two weeks later a new endoscopy was performed showing the scars of the previous ligatures. New ligatures of the esophageal varices (3 packages) and cardial varices (2 packages) were performed.

Negative markers for hepatitis A, B, C.

Abnormally high levels of ferritin were found, while the transferrin level was found to be at the point of saturation. A preliminary diagnosis of hemochromatosis was established. With clotting time corrected, a percutaneous hepatic biopsy guided by echography (PHBE) was requested.

Anatomic pathology confirmed cirrhosis. Abundant ocher pigment in the cytoplasm of the hepatocytes was found. The Prussian blue coloring confirmed the presence of iron. A family study of siblings, nephews and children was initiated. Levels of ferritin and the percentage of saturation of transferrin were tested. A 43 years old brother was found to be asymptomatic, with abnormally high levels of ferritin and transferrin saturation percentage.

A hepatic biopsy was carried out. It confirmed hepatic siderosis.

The patients were managed with biweekly phlebotomies until levels of hemoglobin between 10 and 12 gr/dl and normal levels of ferritin were obtained. Appropriate patient evolution was achieved without the need for additional therapy. Patients have an adequate quality of life. They have been monitored for the past year.

**LABORATORY TEST RESULTS**

Blood type: B negative, hemoglobin 6.6 gr/dl, hemoglobin 19%, leukocytes 9100/mL, platelets 145 K/µL, partial thromboplastin time (PTT) 26.6"/31", prothrombin time (PT) 28.2"/14.1", international normalized ratio (INR) 2.36, glycemia 264 mg/dl, creatinine 1.1 mg/dl, total proteins 4.6 gr/dl, (6.6-8.3), albumin 2.9 gr/dl (3.5-5), globulins 1.7 gr/dl (2.5-3.5), total bilirubin 0.5 mg/dl, direct bilirubin 0.1 mg/dl, ALT 26 U/L, AST 24 U/L, alkaline phosphatase 200 U/L (50-250), Gamma GT 25 U/L, ANA negative, anti-mitochondrial antibodies negative, HBSAg negative, anti HBs negative, anti-HAIgM negative, anti HVC non reactive.

Serum iron: 187 ug/dl (59 – 158); Ferritin: 1144 ng/dl (9 – 120); Saturation percentage of transferrin 96.3% (12 – 36); Total iron fixing capacity: 194 ug/dl (259 – 388)

**BROTHER LABORATORIES**

Hb 15.4 gr/dl; Hto 48%; ALT 72 (40); AST 42 (40); Total bilirubin 0.8; direct bilirubin 0.5; Alkaline phosphatase 186 UI/L.

Serum iron 207 ug/dl (60 – 160); Ferritin 1810 ng/ml (18 – 370); Total iron fixing capacity 281 ug/dl; Transferrin saturation percentage: 74% (10 – 39).

**LITERATURE REVIEW**

Hemochromatosis includes a variety of chronic iron overload syndromes of genetic origin. They can be classified into 4 groups, from type 1 to type 4 according to genetic mutations (1, 4).

Hemochromatosis type 1, or hereditary hemochromatosis1, which results from mutation of the HFE gene, is the most frequent form of the disease. 90% of all cases are type 1. Hemochromatosis type 2 is the juvenile form. Mutation of Hemojuvelin (HJV) results in type 2a, while mutation of the Hepcidin HAMP gene results in type 2b. Hemochromatosis type 3 is caused by mutation of the type 2 transferrin receptor gene. Hemochromatosis type 4 is caused by the mutation of the ferroportin gene (4).

There are other hereditary types associated with iron overload. These result from mutations of other types of
genes, for example hemochromatosis type 4 may result from mutation of the ceruloplasmin transferrin, gene type 1 divalent metal transporter 1 (DMT1).

Recessive autosomal type transmission accounts for almost all of these types and possible mutations, except for hemochromatosis type 4 which has a dominant method of transmission (4). Hereditary hemochromatosis (HH) is recognized as one of the most common recessive autosomal diseases. It occurs in one of every 64 to 400 people with North European or Caucasian ancestors (1, 5, 6).

The hemochromatosis gene has been located in an area of chromosome 6 bound to the HLA complex. There are approximately 3 mutations of this gene: c.A193T (S65C) in exon 2, and c.G845A (C282Y) in exon 4 (7-10).

Mutation C282Y has a substitution of amino acids at position 282 where a residue of tyrosine substitutes for a cysteine (C282Y). This alteration is responsible for most cases of hereditary hemochromatosis. The simple heterozygous state of this mutation does not seem to produce iron overload. Another mutation has been found at position 65 where a substitution of histidine for aspartic acid takes place (H63D) (11, 12). Another mutation found at position 65 has a substitution of serine for a cysteine (S65C). It seems to explain the hemochromatosis phenotype in some patients who do not have mutation C282Y (9).

The prevalence of these mutations varies in different parts of the world. The prevalence of the C286Y form is highest among the populations of northeastern Europe and among Caucasians in general. It is almost absent in the non-Caucasian population and in regions of southwestern Europe (3, 12-15). Studies in Colombia show a frequency of the H63D mutation similar to those in other Latin American countries (7).

The HFE hemochromatosis gene codes a glucoprotein of 343 amino acids. Together with the transferrin type I receptor it can inhibit absorption of iron.

HFE is a protein which is a homologue of the proteins of the major histocompatibility complex class I (11, 12). This unique protein has 3 extracellular domains which can be analogous to the domains a 1,2 and domain type Ig a3 of CMH class I. The last two are produced in the endoplasmic reticulum. At this site they interact with a B2 microglobulin binding with a non covalent form of the homologous region a3 (8). This complex is indispensable for HFE transport to the cell membrane.

Instead of binding to the receptor of the lymphocyte T, as proteins of the HLA class 1 complex do through their domains a 1 and 2, the HFE protein binds to the transferrin type I receptor resulting in inhibition of iron absorption. Nevertheless when the C282Y mutation is present, binding of domain a3 to the B2 microglobulin is avoided, preventing intracellular transport to the membrane. The lack of a bound to the transferrin I receptor means that iron absorption is not inhibited. The increased absorption of iron in the intestine and other organs results, and iron is not exported from these tissues (8, 16).

The other more current mechanism which has a primary explanatory role for iron overload is that generated by hepcidin. Transcriptional regulation of hepcidin production is mediated by a MAP Kinase Transduction pathway in which HFE has an important role. When a mutation appears, there is a significant reduction in the production of hepcidin. This protein is produced primarily by the liver. Macrophages and adipocytes bind hepcidin to the ferroportin of the cell membrane. This generates internalization with a resulting decrease in expression of ferroportin within the membrane. Consequently, iron is not released to the plasma but accumulates within the cell. When this diminution of hepcidin occurs, protoporphyrin stimulates the liberation of iron to the plasma resulting in the depletion of intracellular iron deposits. This stimulates intestinal iron absorption. The plasmatic concentration of non-transferrin-bound iron also increases. This is avidly and precociously absorbed by the liver and other tissues. A component of this form of iron, labile plasma iron, is released when transferrin saturation exceeds 75%. This becomes a big donor of free radicals, and therefore is believed to be is one of the main causes of tissue damage (13, 17).

Tissue Damage and Iron Induced Fibrosis

In HH a 3–4 mg/dl excess of iron absorption has been observed. This causes a net annual excess of 500 mg to 1000 mg during a normal lifetime.

Cirrhosis and hepatic fibrosis are the main alterations in anatomical pathology of HH.

In the early stages of hemochromatosis iron is located inside the hepatocytes in the biliary pole of the cell. This is distributed along a descending gradient from the periporal area to the centrolobular area resulting in a parenchymatous ferric overload. Over time the iron overload increases leading to peroxidation of iron dependent lipids causing damage and periportal hepatocellular death (siderotic necrosis).

Siderotic necrosis is responsible for the activation of macrophages which causes the development of fibrosis and redistribution of iron towards the non-parenchymal cells. Cirrhosis develops when the hepatic concentration surpasses 400 µmol/g (18, 19).

Accumulations of iron in parenchymatous cells have also been found in late stages of the disease, especially in the pancreas, gonads, endocrine glands and myocardium.
CLINICAL MANIFESTATIONS

Most patients with symptomatic HH are between 40 and 50 years old at the moment of diagnosis. In most series more men that woman have been identified with HH. Proportions range from 2:1 to 8:1.

The most commons symptoms are weakness, lethargy, loss of libido and arthralgias. Physical findings include hepatomegaly, splenomegaly ascites, edema, jaundice and other manifestations of hepatic disease (20).

Cardiac manifestations include cardiomyopathy, cardiac arrhythmias and congestive cardiac insufficiency. The heterozygous mutation C282Y is most frequently found (21). The classic finding of “bronze diabetes” is actually seen in less than 10% of these patients and is usually found late (22). Many asymptomatic patients with HH are indentified in chemical analyses of serum for iron in routine scree- ning because of homozygous relatives in index cases.

DIAGNOSIS

In different series 25% to 50% of those diagnosed with hereditary hemochromatosis are diagnosed when they are already cirrhotic (19). This demonstrates the absence of specific symptoms and signals that would cause suspicion of the disease and a diagnosis of the disease.

The identification of HFE mutations in different racial populations could have a significant impact in reducing the sequelae of this disease.

NON-INVASIVE TESTS

The methods used to establish the presence of iron overload include the study of serum iron, several radiologic techniques, hepatic biopsies, and evaluations of response to phlebotomy and chelation therapy.

Genetic testing for hereditary hemochromatosis should be done for all patients suspected of having iron overload, although different methods’ sensitivity and specificity for diagnosis, and utility for screening, may vary.

Saturation of transferrin >45% has a sensitivity of 58% and a specificity of 98% for detection of the C282Y homozygote. High concentration of plasmatic ferritin greater than 200 for women and greater than 300 for men has a sensitivity of 66% and a specificity of 85% (23-25). Despite the above, guides from the U.S. Preventive Services Task Force do not recommend genetic screening for hereditary hemochromatosis because they do not have a balanced cost-benefit (26). Nevertheless, some recent publications have postulated that genetic screening should be carried out when patients show levels of ferritin of over 1000 micro/lit. Studies with greater statistical power are still necessary (24, 25).

Some publications posit that testing unsaturated iron-binding capacity could be a less expensive and easier-to-evaluate screening test than the test for saturation of transferrin (13).

A combination of high serum ferritin values and elevated saturation levels of serum transferrin in an otherwise healthy individual has a sensitivity of 93% for diagnosing HH. Slight elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have been described in 65% of HH patients. The AST average is typically less than 100 U/L in cirrhotic and non cirrhotic patients.

The images used come from CAT scans MRI images which are sensitive non invasive methods for evaluation of iron deposits (1, 11).

GENETIC TESTS

Because penetrance of mutations which cause hemochromatosis is low, in the study of hemochromatosis type 1 the search for genetic alterations has become important for relative pathological risk. At least three mutations which cause hereditary hemochromatosis have been detected: c.C187G (H63D) and c.A193T (S65C) in exon 2; and c.G845A (C282Y) in exon 4. There are also different combinations of these mutations (7, 10).

C282Y homozygote. This is the classic genetic pattern seen in more than the 90% of typical cases. The expression the disease goes from no evidence of iron overload to massive overload with organ dysfunction.

C282Y/H63D heterozygote component. The patient carries a copy of the main mutation and one of the minor mutations. Most of these patients have normal levels of iron.

C282Y heterozygote. This pattern is seen in 10% of the white population. It is usually associated with normal levels of iron.

H63D homozygote. Most of those patients have normal levels of iron. A small percentage show moderately increased levels or iron.

H63D heterozygote. This pattern is seen in 20% of the white population. Usually normal levels of iron are seen. The C282Y and H63D homozygote mutations are mutually excluding (27-29).

HEPATIC BIOPSIES

Prior to diagnostic imaging and genetic studies biopsies are taken and dyed. Special tints such as Prussian blue confirm deposits of iron inside hepatocytes (30, 31) and are diagnostic tests of iron overload.
Recent progress in imaging and in genetic testing has decreased the role of hepatic biopsies in diagnosis of iron overload (1, 19). For this reason biopsies are no longer considered to be the gold standard of diagnostic testing for this disease.

After diagnosis of iron overload by imaging, an evaluation of the degree of hepatic damage is mandatory. Currently this has become the primary objective of hepatic biopsies in these cases.

Hepatic biopsy indication depends on the phenotypic presentation of the excess iron. In typical cases of chromatic phenotypes with high concentrations of transferrin and increased parenchymatous concentrations of iron the genotype becomes very important for the evaluation.

In the presence of the C282Y2 homozygote a hepatic biopsy is useful for prognosis. It is especially useful for evaluation of hepatic fibrosis when there is an enlarged liver and the ferritin level is over 1000 ng/ml and when there are high levels of AST.

The presence of the C282Y-H63D heterozygote is not a clear indication for biopsy, especially if levels of transferrin saturation are normal or medium and ferritin levels are lower than 500 ng/ml. Without an altered hepatic profile these patients appear to be free of the risk of hepatic fibrosis.

In atypical cases of chromatosis the use of biopsies is independent of the genotype presented (19, 32).

TREATMENT

The objective of therapy is depletion of iron deposits iron to prevent tissue damage since there is no specific treatment for each of the visceral alterations that may exist.

Phlebotomy is still the treatment of choice for iron depletion. The use of iron chelators is suitable in cases in which there are contraindications for phlebotomy (13, 33). The phlebotomy should be started in patients with high concentrations of ferritin. The volume to be extracted should be determined in accordance with body weight. 7ml/kg should be extracted in each session, but without exceeding 550 ml per phlebotomy (6).

Weekly phlebotomies of 550 ml of blood (250 mg of iron) are carried out until concentrations of hemoglobin reach 11mg/dl (6). Once this level can be maintained for three consecutive weeks, the levels of ferritin and percentage of transferrin saturation should be measured. The depletion is confirmed if the concentration of ferritin is less of 50 microgram/ml and the percentage of transferrin saturation falls below normal values. Generally 4 to 8 phlebotomies per year are required as maintenance therapy (1, 6, 13, 26, 34-36).

Other measures to be taken into account, although their efficacy has yet to be proven, are decreased consumption of iron rich foods, iron supplements, and ascorbic acid. (Ascorbic acid is included because of its effect on absorption and the cardiovascular implications) (13, 37, 38).

PROGNOSIS

Cirrhosis is the clinical factor that most influences survival over the long term. A patient with cirrhosis at the moment of diagnosis has 5.5 times greater probability of mortality than a non-cirrhotic patient. Diagnosis and phlebotomies before the onset of cirrhosis can give patients with HH a much higher probability of survival, no different than that of the general population (16, 39).

REFERENCES