

Hereditary hemochromatosis and alcohol: pathogenic synergism – a clinical case

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Abstract

A 35-year-old man with strong ethanol habits was referred to the Internal Medicine consultation due to a right hypochondrium grinding pain for several months and increase on serum aminotransferases. Skin hyperpigmentation was observed and very high ferritin values detected. Due to a suspicion of hemochromatosis, genotyping was performed and revealed a homozygosis H63D mutation. Hepatic biopsy showed signs of hemochromatosis. With

hemapheresis therapy, on a regular basis, there was a favourable clinic and laboratory response. Homozygosis H63D mutation is not usually associated with clinical hemochromatosis, but several cases have been detected recently, sometimes associated with other contributing factors to iron overload.

Key words: hereditary hemochromatosis, homozygosis H63D.

Introduction

Hereditary hemochromatosis (HH) is a hereditary disorder in which occurs an abnormal iron intestinal uptake with its subsequent excessive accumulation in the body, leading to tissue injury and dysfunction in several organs, quite often to liver cirrhosis diabetes mellitus, arthropathy, hypogonadotropic hypogonadism, skin hyperpigmentation and cardiac disorder.^{1,2,3}

HH is the most frequent autosomal recessive genetic disease in European origin population, namely of Celt origin. Similar incidence seems to occur in Portugal, where it can be seen a higher prevalence in the northern region.^{1,2,3,4}

It was described for the first time in 1865, by Trousseau, who followed-up a patient with diabetes mellitus, liver cirrhosis and skin hyperpigmentation, the so called “bronze diabetes”. In 1889, von-Recklinghausen describes the disease with the main characteristics of the advanced stages identifying a pigment containing iron in the cirrhotic liver of these

patients, having named the disease as “Hemochromatosis” because he assumed the pigment had origin in the blood. Sheldon, in 1935, has described for the first time the pathophysiology mechanism linked to the iron metabolism in this disease and its hereditary nature. In 1977, Stevens refers the existence of an HH gene, located in the chromosome 6, near the HLA-A locus, as well as the heredity autosomal recessive disease. Finally, in 1996, Felder identified an iron uptake regulator gene, HFE gene, located in the chromosome 6 short arm and its main mutations C282Y and H63D. Nowadays it is known that C282Y mutation accounts for most HH cases, in homozygosis and in a lower percentage for compound heterozygosis C282Y/H63D.

The best course of action regarding HH has to do with an early diagnosis, based mainly in the iron metabolism study, on the genotype and on the liver biopsy as well as in the timely implementation of the appropriate therapy. This is made of regular hemapheresis, and in some cases, with deferoxamine. The prognosis is reserved in cases where HH is detected in an advanced stage. On the other hand, life expectancy is normal when there is an early diagnosis, reason why, next to the family screening already recommended, it is already debated the need for a large scale population screening.

Clinical case

Male patient, 35 years old, white race, with a complaint of a grinding type pain, progressing for the last

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six months, located on the right hypochondrium, without irradiation or other symptoms, without any relief or aggravating factors. He went to his GP who detected increased aspartate aminotransferase (AST) 107 UI/L and alanine aminotransferase (ALT) 119 UI/L and diffuse hepatic steatosis documented by abdominal ultrasound. For all these reasons he was referred to an Internal Medicine appointment.

From his personal history it was highlighted uncontrolled hypertension, smoking 16 pack year and drinking 60 grams of ethanol per day. He denied taking any toxics, contact with toxic drugs or pharmacotherapy as an outpatient. The family history was irrelevant.

At the initial observation it was verified a good general status (body mass index 28), axillary temperature 36.2°C [97.16F], blood pressure 137-71 mmHg, rhythmic pulse rate 98/mn, normal color hydrated mucosa and apparent skin hyperpigmentation in the forearms, hands, feet, being less evident in the face. No adenomegaly was found, no changes in the cardiopulmonary auscultation, the abdomen was loose, painless to palpation, without organomegaly, and palpable and symmetric distal pulse. The neurology exam was normal.

The initial analytical evaluation has shown: hemoglobin 17.2 gr/dl, hematocrit 48%, red blood cells 4900000/mm³, mean corpuscular volume 98.5 fL, leukocytes 8.600/mm³ (neutrophils 61.9 - eosinophils 1.9 - basophils 0.1 - lymphocytes 29.2 - monocytes 6.9%), platelet count 202.000/mm³, C-reactive protein <0.1 mg/dL, prothrombin time 78%, Activated Partial Thromboplastin Time (APTT) 1.25, glycemia 182 mg/dl, urea 33.2 mg/dL, creatinine 0.9 mg/dL, serum ionogram without changes, AST 107.1 UI/L, ALT 119.67 UI/L, alkaline phosphatase 50.4 mg/dL, gamma-glutamyl transpeptidase 467.3 mg/dL, total cholesterol 259 mg/dL, triglycerides 188 mg/dL, and normal values for protein electrophoresis and type II urinalysis. Both the electrocardiogram as the film-screen chest radiography showed no alterations. The abdominal ultrasound kept on showing a homogenous hepatomegaly, with aspects of diffuse fat infiltration, without any lithiasis sign, and without biliary ducts ectasia.

In spite of drinking, the clinic and laboratory setting did not suggest an alcoholic causality, and other causes of chronic liver disease needed to be sought-after. In this sense, A, B and C hepatitis serological

tests were negative, Alpha-1 Antitrypsin and ceruloplasmin dosage levels were normal, serum iron 267 µg/dL, transferrin 199 mg/dL and ferritin 2151.3 ng/mL. The auto-immune hepatitis study has shown negative AMA [Antimitochondrial antibody] and ASMA [Anti Smooth Muscle antibody], as well as serum protein immunoelectrophoresis within normal ranges; angiotensin converter enzyme was also normal. Before such results the diagnostic hypotheses were hemochromatosis, alcoholic liver chronic disease, apart of dyslipidemia. It must be highlighted that hemoglobin immunoelectrophoresis was normal, not taking into account some congenital hemolytic anemia which could imply some iron overload.

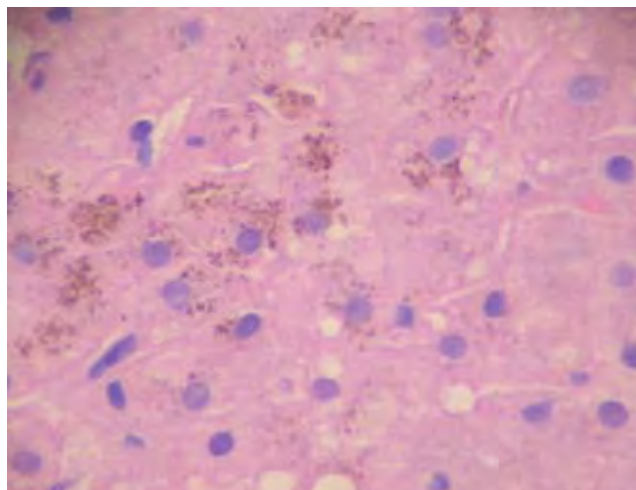
In order to confirm the diagnosis, the patient was admitted for a short period of time, while it was made a genetic study to detect HFE gene mutations, showing H63D homozygosis, a risk factor for hereditary hemochromatosis. There was no mutation on C282Y. Liver biopsy was also performed, detecting aspects compatible with hemochromatosis, with a significant fibrosis and liver steatosis (*Fig. 1, 2 and 3*). On the other hand, the nuclear magnetic resonance has just shown some liver steatosis changes, already known (*Fig. 4*). Hormonal dosage (FSH, LH, prolactin, testosterone and thyroid function) were normal. Both the thorax echocardiogram as the 24 electrocardiogram (Holter) have shown no changes.

Therapy started with regular hemapheresis, resulting in a progressive clinical improvement and laboratory normalization, and he was then followed-up as an outpatient of Immuno-Hemotherapy and Gastroenterology.

In parallel, it was started a family screening being detected in his two children simple heterozygosis H63D.

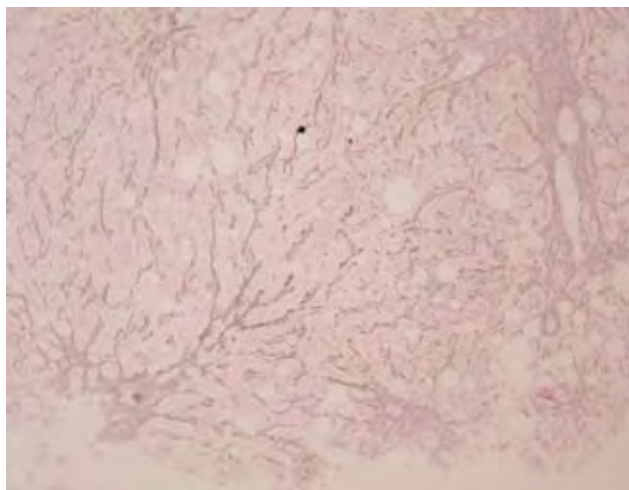
Discussion

HH is the most common cause of serious iron overload in the body. The disease genetic substrate, since the gene HFE was discovered in 1996, has been the subject of profuse research, having been identified new genes, their mutations and different forms of HH. HH, in the past considered a monogenic disorder has, at present, its genetic heterogenicity well documented.⁵ The HFE gene interacts with the transferrin receptor linked to iron, thus reducing its absorption. This mechanism is altered when there are HFE gene mutations. Among these, as it was referred, the most



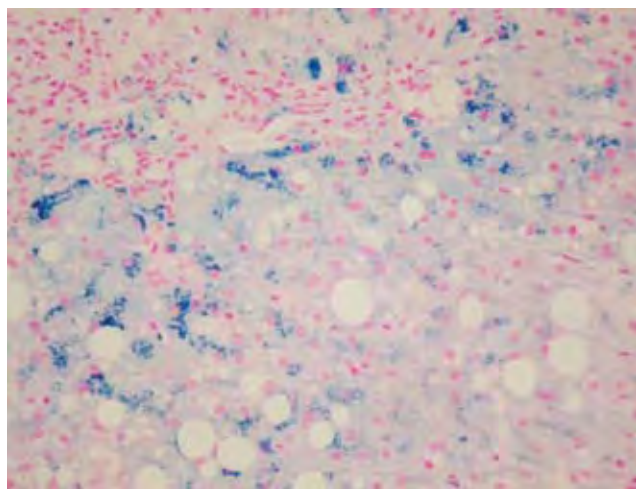
Liver biopsy fragment with hematoxylin eosin stain where the iron pigment stains unspecifically brown.

FIG. 1



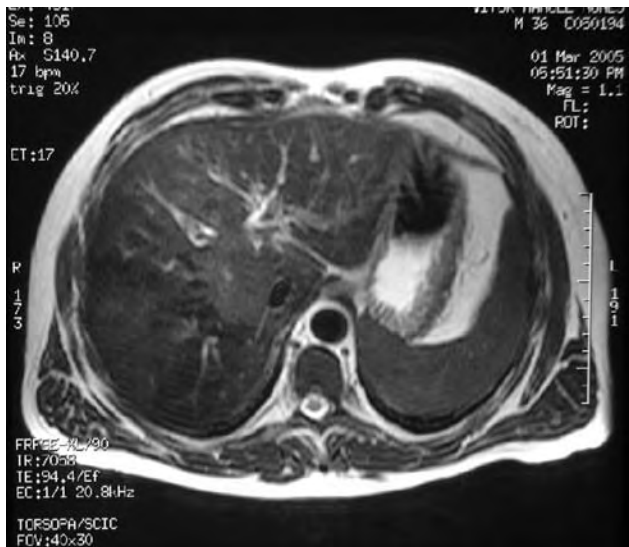
Liver biopsy fragment with a Sweet stain, where all collagen fibrosis bands get a brown color.

FIG. 3



Liver biopsy fragment with Pearls stain fragment where the blue pigment gets a blue color.

FIG. 2



Hepatic nuclear magnetic resonance imaging which shows only liver steatosis aspects.

FIG. 4

frequent HH cause is the C282Y mutation (where cystine replaces tirosoine on the 282nd position). Another frequent mutation is H63D (where histidine replaces aspartic acid on the 63rd position), being S65C (where cystine replaces serine on the 65th position) the rarest mutation of HFE gene and also of most controversial importance. On the other hand, it is known at present that hepcidine, a 25 amino-acids peptide of liver origin, seems to be the main

hormone involved in the iron metabolism, leading to its retention by the reticuloendothelial system reducing iron uptake. Rare cases of HH linked to the HAMP gene mutation which codifies hepcidine, leading to a form of juvenile HH, are already known. Another rare forme of juvenile HH is linked to HJV gene mutation on 1q chromosome, responsible for

TABLE I

Etiology Classification of Hereditary Hemochromatosis (OMIM)

- Hemochromatosis type 1 (OMIM 235200): HH linked to HFE gene(6p21.3)
- Hemochromatosis type 2 (OMIM 602390): HH juvenile:
 - Type 2 A – HFE 2 A (1q21)
 - Type 2 B - (OMIM 606464): hepcidine antimicrobial peptide mutation (HAMP) or HFE 2B (19q13)
- Hemochromatosis type 3 (OMIM 604720): transferrin receptor- 2 (TFR2 or HFE3, 7q22)
- Hemochromatosis type 4 (OMIM 604653): HH autosomal dominant mutation (SLC 11 A 3) of ferroportin gene (2q32)

producing hemojuvelin (modulating hepcidine expression). Some HH cases were also described due to gene mutations codifying receptor 2 of transferrin (TfR 2). Due to this new discoveries HH classification has been changing, being the most recent, the Online Mendelian Inheritance in Man (*Table I*) classification including chromosome locations.^{5,6}

In the current clinical case, it is highlighted that the patient was virtually asymptomatic, mentioning only frequent episodes of a grinding pain in the right hypochondrium. As a matter of fact, most HH patients did not have more exuberating complaints or present in the most advanced stage of hemochromatosis, related with liver cirrhosis, diabetes mellitus, cardiac failure and impotence or libido changes. On observation it could be verified hyperpigmentation on exposed areas of the skin, observed in around 90% of HH cases, and considered as one of the earliest signs of the disorder. Aminotransferases increase is also a manifestation, that often even without symptoms leads to a diagnosis suspicion.^{1,2,3}

High levels in the serum iron, ferritin and transferrin saturation led to the diagnosis. Saturation, when above 62%, identifies 92% HH patients. Ferritin levels, as a rule, overtake 500 mcg/L and when above 1000 mcg/L, suggest a serious liver lesion with fibrosis. At present there is a consensus that formal recommendations for hepatic biopsy are precisely the ferritin levels deriding from such values.^{3,4,7}

In the studied patient, the ferritin levels were above 2000 mcg/L, liver biopsy was very suggestive of hemochromatosis with marked fibrosis. Before

the suspicion, it was made the study of all organs usually involved in this pathology. The hormonal study, namely hypogonadotrophic hypogonadism, which is frequent in this disorder, has shown normal values. In most cases of HH congestive cardiac failure is secondary to a dilated cardiomyopathy and less frequent than restrictive cardiomyopathy. In spite of not existing complaints of cardiac failure, it was performed an ultrasound which was within normal ranges. Other cardiac changes occurring in HH are arrhythmias and conduction changes, reason why it was made a 24 hours electrocardiogram (Holter) also normal. The glycemic profile while in admission, and under diet without carbohydrate has excluded a possible diabetes mellitus. The absence of arthralgia and joint inflammatory signs dispensed the study of possible arthropathy.

It should be highlighted that in spite of the liver nuclear magnetic resonance may present HH typical imaging, this exam has a low diagnosis sensitivity, what justifies the unspecified aspects present in this clinical case. It was not performed the hepatic iron score (HIS) as the genetic study was available revealing H63D homozygosis. In fact, around 15% of HH cases have a lower HIS than the values considered as diagnosis, as well as some hemolytic anemia or dyserythropoiesis can show similar HIS similar to the expected in HH. For all these reasons, HIS is not at present considered essential for the diagnosis.^{2,8,9,10}

It is known that this gene HFE mutation is frequent, probably older than the C282Y mutation.¹¹ However, C282Y homozygosis is the most prevalent HH cause and until a while ago, there was the notion that H63D homozygosis would not lead to an open clinically HH. However when in compound heterozygosis, C282Y/H63D accounts for HH cases usually milder. At present, several cases of H63D homozygosis linked to HH have already been detected, being that in some there were a number of other predisposing factors to iron organic overload. For this reason, some authors even consider this mutation as a hemochromatosis co-factor.^{7,12}

The disorders which may trigger an iron overload and be associated to this mutation are the causes of the so called secondary hemochromatosis, as some congenital hemolytic anemias, as thalassemia, sideroblastic anemia, C virus chronic hepatitis (but also the B virus disease), the alcoholic chronic liver disorder, the non-alcoholic fatty liver disease, the porphyria

cutanea tarda and the portocaval shunt.^{1,2,3,11,13} In this patient case it was apparent the co-existence of H63D homozygosis and alcoholic liver disease, association which is surely responsible for the hemochromatosis setting.

HH therapy is based on the regular performance of hemapheresis, with the objective of reaching transferrin saturation values lower than 50% and serum ferritin levels lower than 50 ng/ml, if possible 20 ng/ml. Chelation therapy with deferoxamine is less effective, more expensive and must be reserved for odd cases where hemapheresis is not recommended or badly tolerated.^{1,2,3,5}

The main causes of death by HH are cardiac failure (30%), hepatic cirrhosis (25%) and hepatocellular carcinoma (30%).¹ The most important prognosis factor is the absence of liver fibrosis as in this case, survival under treatment is normal. For such reason it is of the utmost importance to have the earliest possible diagnosis and a family screening. As this patient showed marked fibrosis in the liver biopsy, it was crucial clinical and laboratorial monitoring to an early detection of hepatocellular carcinoma. ■

References

1. Powell LW. Hemochromatosis in Harrison's Principles of Internal Medicine, 16 th Ed, Mc Graw-Hill 2005: 2298-2303.
2. Drobnik J, Schwartz RA. Hemochromatosis. Emedicine July 21, 2005.
3. Sfeir HE, Klachko DM. Hemochromatosis. Emedicine June 8, 2005.
4. Fraga J, Pinho R. Hemocromatose in Diagnóstico em Hepatologia. 2004 Permanyer Portugal: 65-72.
5. Pietrangelo A. Hereditary hemochromatosis – A New look at an Old Disease. N Engl J Med 2004; 350: 2383-2397.
6. Fleming RE, Bacon BR. Orchestration of Iron Homeostasis. N Engl J Med 2005; 352: 1741-1744.
7. Tavill AS. Diagnosis and Management of Hemochromatosis. Hepatology 2001; 33 (5): 1321-1328.
8. O'neil J, Powell L. Clinical Aspects of Hemochromatosis. Semin Liver Dis 2005; 25(4): 381-391.
9. Mc Carthy GM et al. Hereditary hemochromatosis: a common, often unrecognized genetic disease. Cleveland clinical Journal Med 2002; 69 (3): 224-237.
10. Ayoub W, Martin P, Tran T. Hereditary Hemochromatosis. Medscape General Medicine 2003; 5 (2).
11. Adams PC, Reboussin DM, Barton JC., e tal. Hemochromatosis and Iron-overload screening in a racially diverse population. N Engl J Med 2005; 352: 1769-1778.
12. Brissot P. Hemochromatosis. Orphanet Encyclopaedia, Oct 2003.
13. Martins R, Picanco I, Fonseca A et al. The role of HFE mutations on iron metabolism in beta-thalassemia carriers. J Hum Genet 2004; 49 (12): 651-655. (abstract)