Hemochromatosis – Screening for a Common Condition

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Hemochromatosis is a common genetic disorder in the Caucasian population. It can go unrecognized in many patients for years before manifesting itself as multisystem end-organ damage. There is debate as to whether this condition should be screened for on a routine basis; as such this article serves to explore the basics of the disease and to review current guidelines for screening at the primary care level.

Case

A 26 year old female fashion student getting lab work for allergy testing was incidentally found to have significantly increased serum transferrin and ferritin levels. Subsequent genetic testing revealed homozygous mutation for the gene encoding the HFE protein. Retrospectively, the mother reports a history of improvement in chronic fatigue and joint pains following elective phlebotomies at the local blood bank. Her testing revealed a compound (double) heterozygous mutation in the HFE gene, but no abnormality in her liver function tests or iron levels. The father and 24 year old brother have normal ferritin and liver enzymes; the 28 year old brother, however, has markedly increased iron stores.

Introduction

Hereditary hemachromatosis (HH) is an autosomal recessive inherited disorder in which mutations in specific genes related to iron transport proteins lead to increased iron absorption from the diet. This eventually leads to deposition of iron in the parenchyma of the liver, heart, pancreas and pituitary glands if left untreated, and can cause significant long term morbidity.1

This disorder was originally described as “bronze diabetes” by Armand Trouseau in 1865, when he observed an association of skin pigmentation with diabetic patients.2 The first report of deposition of iron in tissue leading to dysfunction was by Von Reckinghausen in 1890. The sequencing of the human genome has allowed identification of the specific mutations associated with the HFE protein, the commonly affected protein in HH. Mutations in this protein are the focus of this article. Note that there are other, less common hereditable defects in iron metabolism.

Genetics

The most common genetic defect is in the HFE protein, which interacts with the transferrin receptor and other iron regulating proteins to regulate absorption of iron from the GI tract.

There are two common mutations in HFE, C282Y and H63D. The mutation is most prevalent in Caucasians of European decent, with a homozygote prevalence (C282Y) of about 1 in 200. The prevalence is about 1 in 250 in the general population.

In this same population, 12% are carriers of the C282Y and 25% the H63D mutation. Most HH patients are homozygous for the C282Y mutation. The penetrance of the H63D mutation is considerably lower, thus compound heterozygotes (C282Y/H63D) and H63D homozygotes constitute 10% of HH patients.3-5
Pathogenesis

The HFE protein as mentioned is important in regulating the uptake of iron from the diet in the GI tract. Iron can only be lost through sweat, skin and the GI tract, menses in females, and during times of growth such as pregnancy and adolescence. Males lose approximately 1mg/day and females proportionally more (1.5-2mg/day). In HH, the ability of the body to sense overall iron stores is lost, leading to an extra absorption of 1-4mg of iron daily, which averages over a year approximately 1 gram. The slow accumulation of iron is generally asymptomatic until the total body iron stores are greater than 20 grams.

Excessive iron is toxic to tissues by free radical reactions, stimulation of collagen formation, and interaction with DNA. Most of these changes are reversible if the iron is removed. Deposition of hemosiderin, an intracellular iron storage complex, in the cells of the liver, pancreas, myocardium, pituitary, adrenal, thyroid and parathyroid glands, joints and skin lead to discoloration, fibrosis, and dysfunction. Interaction with DNA has lead to increased risk for hepatocellular carcinoma (HCC) in advanced cases. HCC and cirrhosis are the leading causes of mortality due to HH.

Presentation and Differential

Most cases of HH are discovered through screening, as either an incidental finding when bloodwork is done for another reason or because of a relative with a diagnosis. The manifestations of HH usually occur after age 40 in males (50 in females), after iron stores are greater than 20 grams. The most frequent symptoms include hepatomegaly, abdominal pain, skin pigmentation (especially on sun exposed areas), altered glucose metabolism or diabetes, cardiac arrhythmias, and an atypical arthritis. Hypogonadism resulting in amenorrhea in females and a drop in libido in males is also a common initial presentation.

Each of the symptoms is due to hemosiderin deposition in organ parenchyma and the ensuing fibrotic reaction from chronic damage. Cirrhosis, pancreatic insufficiency secondary to islet cell destruction and skin pigmentation are all fairly late findings, but are considered the classic “triad”. Hypogonadism is related to alteration of the hypothalamic-pituitary axis.

The differential for HH includes other causes for elevated iron stores. Most alternative diagnoses are secondary causes of iron overload, most commonly chronic transfusions, either alone or in association with ineffective erythropoiesis. The latter condition results from RBC being destroyed before they can leave the bone marrow.

Screening

The understanding of the underlying pathophysiology of this disorder has come a long way. At a population level, it has been debated whether routine screening (via a fasting serum transferrin saturation) should be implemented, due to the high prevalance of the mutation, ability for early diagnosis and treatment, and ease of genetic testing. However, at this time widespread screening has not been recommended, due to lack of predictability about the expression of the mutations and lack of information on risk-stratifying patients. Labelling of individuals who test positive through genetic testing but are asymptomatic is also another concern and could lead to difficulties with obtaining insurance, for example.

The variable expression in this condition has been a focus of some relatively large screening studies, including a study by Beutler et al. (2002) which involved 41,000 US individuals tested for the C282Y and H63D mutations. They found no difference in the age distribution or frequency of signs and symptoms of HH between the cases and controls. However, a more recent study of 31,000 Australian patients of northern European decent (followed for 12 years), showed iron-overload related disease in 28% of male and 1.2% of female homozygotes. Other observational studies have identified a substantial percentage of first degree relatives of
homozygotes with subclinical conditions related to HH.\textsuperscript{10}

Following from this, a reasonable strategy for screening would include targeting high risk individuals, such as adult men > 25 years old of northern European decent and first degree relatives of patients with known hereditary hemochromatosis. The screening test of choice would be a fasting serum transferrin saturation (men >52% and women >50%) or a fasting serum unsaturated iron binding capacity. Follow-up to this would be genetic testing.\textsuperscript{3,4,8,10}

Diagnosis

The diagnosis of HH rests on a combination of the clinical features mentioned above, and an elevated serum ferritin and fasting transferrin saturation. In the past, a liver biopsy was used in confirmation of the disease; however, genetic testing has largely replaced this invasive test except in the case of documented liver impairment and need to determine extent of cirrhosis. The serum ferritin value needs to be analyzed with caution as it is an acute phase reactant. Excluding the secondary causes of iron overload is important (Table 1).

Treatment

The definitive treatment of HH and the associated iron-overload is phlebotomy, 500ccs weekly. This is continued until iron-deficiency erythropoiesis is induced as evidenced by a reduced MCV and decreased Hb value, and/or serum ferritin levels and transferrin saturation markers are within the target range, which are below 50% and 50ng/mL, respectively. Patients will usually require a phlebotomy every 2-3 months as maintenance therapy, which in many cases can be accomplished by regular donations to the local blood bank. Patients testing positive for HFE mutation but without laboratory evidence of iron overload can be followed annually for evidence of disease, but do not require active treatment.

There is no need for patients to avoid red meats and other dietary sources rich in iron; a well balanced diet is acceptable. Patients can be at higher risk for certain infections such as \textit{Vibrio vulnificus}, and as such eating raw seafood is discouraged.

Case Discussion

The case represents a common scenario, in this case a Caucasian family with a compound heterozygote mother (C282Y/H63D) and the daughter homozygous for the C282Y mutation. This case illustrates the need for awareness on the part of family doctors of at-risk populations to determine the need for genetic testing. Had the fashion student (homozygote) not had her blood tested she may have gone years without any knowledge of her condition, until presentation with signs of end organ damage. While a number of incidental cases of iron-overload are inevitable until better evidence is available for specifically identifying those at risk, targeting the at-risk subgroups should minimize this occurrence.

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<tr>
<th>Table 1: Causes of iron overload\textsuperscript{6} (*focus of article)</th>
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<td><strong>Heredity hemochromatosis</strong></td>
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<td>Related to \textit{HFE} gene*</td>
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<td>African (Bantu) hemochromatosis</td>
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References