Diagnosis and Management of Hereditary Hemochromatosis

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INSTRUCTIONS

The following case study, “Diagnosis and Management of Hereditary Hemochromatosis,” is accompanied by a continuing medical education (CME) evaluation that consists of 5 multiple-choice questions. After reading the case study, carefully consider each of the questions in the CME evaluation on page 51. Then, circle your selected answer to each question on the CME evaluation form on page 52. In order to receive one CME credit, at least 3 of the 5 questions must be answered correctly. The estimated time for this CME activity is 1 hour.

OBJECTIVES

After participating in the CME activity, primary care physicians should be able to:
1. Appreciate the importance of early diagnosis and treatment of hereditary hemochromatosis (HHC) in preventing morbidity
2. Recognize the typical clinical presentation of expressed HHC
3. Interpret results of biochemical screening for HHC
4. Describe the role of liver biopsy in the evaluation of patients with iron overload
5. Describe the role of genetic testing for mutations associated with the HHC candidate gene
6. Describe approaches to treatment

INTRODUCTION

Hemochromatosis is the pathologic deposition of iron in the parenchymal cells of organs (primarily the liver, pancreas, pituitary, and heart), leading to tissue damage and loss of function. The term hemochromatosis is used most commonly to refer to hereditary hemochromatosis (HHC), the human leukocyte antigen (HLA)-linked inherited disorder [1]. HHC is a primary iron overload disease that occurs as a result of an inherent defect in iron regulation, causing excessive absorption of iron from the gastrointestinal tract. HHC should be distinguished from secondary iron overload syndromes, which occur under conditions that promote increased absorption of iron such as disorders of ineffective erythropoiesis (e.g., thalassemia and sideroblastic anemia); secondary iron overload also can occur through excessive transfusions or ingestion of iron supplements. These scenarios may lead to the syndrome of hemochromatosis once iron accumulates in the extrahepatic tissues. Secondary hepatic iron overload also can be seen in patients with chronic liver diseases such as alcoholic cirrhosis and hepatitis C infection but is usually not associated with iron loading of other organs.

HHC is the most common genetic disorder among white persons; it is particularly common among those of northern European ancestry. Long recognized as an inherited autosomal recessive trait, the disorder has an estimated frequency of 7% and a prevalence of 1 in 300 in western countries [2,3]. HHC remains underdiagnosed, however, because of its nonspecific symptoms and a lack of awareness of its prevalence. Yet it is one of the few genetic disorders for which simple, effective therapy exists. If phlebotomy is begun prior to the development of cirrhosis, a normal life expectancy is predicted [4].

A candidate gene for HHC, called HFE, was recently identified. Two mutations, designated C282Y and H63D, have been described in patients with HHC [5]. Presently, only homozygosity for C282Y and compound heterozygosity for C282Y and H63D are clearly associated with phenotypic expression. DNA-based genetic testing is now widely available for these mutations. The discovery of the HHC gene raises the possibility that morbidity could be significantly decreased in patients affected by HHC through earlier and more precise identification of the disorder. It will become increasingly important for physicians to learn how best to integrate genetic testing into their diagnostic approach for patients with suspected HHC. The following case study focuses on the current diagnostic and management issues...
faced by clinicians, with specific emphasis on the roles of liver biopsy and genetic testing.

CASE STUDY

Initial Presentation

A 61-year-old man is referred to a gastroenterologist because of ascites. He presents with fatigue and increasing abdominal girth that was first noted after an umbilical hernia repair several months earlier.

History

The patient reports a several-month history of abdominal bloating, occasional diarrhea, and, more recently, early satiety associated with nausea and vomiting. He reports an 8-lb weight loss over the past 6 months without polydipsia or polyuria. He describes arthralgias and impotence, with loss of erection upon awakening. Past medical history is significant for umbilical hernia and rhinoplasty, but otherwise he has been in good health. He denies alcohol use.

The patient lives at home with his wife and 2 children, who are well. He is of Irish and German descent.

Physical Examination

Physical examination reveals a somewhat cachectic, tanned man in no acute distress. Vital signs include a blood pressure of 136/78 mm Hg, heart rate of 80 bpm, and respiratory rate of 18 breaths/min. The patient is afebrile. Skin has a slight gray discoloration, with few spider angiomata. HEENT examination reveals mild temporal wasting and anicteric sclera; there is no lymphadenopathy of the neck. Lungs are clear and heart rhythm is regular, with no murmurs, rub, or gallops. Abdomen is protuberant but soft, with a detectable fluid wave. Liver span is 9 cm, and spleen tip is not palpable. Testicular atrophy, muscle wasting, 1+ pedal edema, and palmar erythema are noted. Neurologic examination is normal, with no asterixis. Completion of number connection test takes 46 seconds.

Laboratory Evaluation

Laboratory studies reveal the following:

- Hematocrit: 42%
- White blood cell count: 5.4 × 10^3/mm³
- Mean corpuscular volume: 84 µm³
- Platelet count: 141 × 10^3/mm³
- Prothrombin time: 13.5 sec
- Total bilirubin: 3.5 mg/dL
- Serum glucose: 104 mg/dL
- Alkaline phosphatase: 99 U/L
- Aspartate aminotransferase (AST): 66 U/L
- Alanine aminotransferase: 87 U/L
- γ-Glutamyl transferase: 90 U/L
- Albumin: 3.3 g/dL
- Urine: no glucose

Radiologic Evaluation

An abdominal computed tomography (CT) scan shows findings suggestive of cirrhosis and portal hypertension including small esophageal varices, ascites, a small nodular, heterogeneous liver, and mild splenomegaly. Upper endoscopy confirms the presence of 1+ esophageal varices.

- What diagnoses should be considered in this patient?

Differential Diagnosis

This patient presents with a subacute illness characterized by fatigue, muscle wasting, ascites, edema, and jaundice. Physical examination findings suggest cirrhosis. New-onset ascites in association with multiple systemic complaints may occur with other, noncirrhotic conditions such as gastrointestinal or ovarian malignancy metastatic to the liver or widespread tuberculosis; these conditions should be ruled out with appropriate tests. This patient's history and laboratory and radiographic findings, however, are most consistent with cirrhosis secondary to a primary liver disease.

The evaluation of a patient with abnormal liver function test results and/or clinical evidence of liver disease should include serum studies for hepatitis B and C viruses, antinuclear antibody (ANA) and antimitochondrial antibody tests for autoimmune liver disease, alpha-1-antitrypsin levels, serum ceruloplasmin measurement for Wilson's disease, and serum iron studies for hemochromatosis. Abdominal ultrasound with Doppler studies should be done in a patient presenting with new-onset ascites and/or evidence of portal hypertension to rule out hepatic or portal vein obstruction. It also can be used to assess for biliary disease or hepatic masses.

Results of Additional Testing

Results of further testing are normal except for serum iron levels, which are as follows:

- Ferritin: 1602 ng/mL
- Serum iron: 163 µg/dL
- Total iron-binding capacity: 170 µg/dL
- Transferrin saturation: 97%

- What are the clinical features of HHC?
- How important is early diagnosis in preventing morbidity?
Clinical Features

HHC is characterized by a congenital predisposition to hyperabsorb iron. During the earlier stages of HHC the characteristic symptoms are fatigue, abdominal pain, impotence, hepatomegaly, and arthralgias. Hepatomegaly and arthritis appear to be related to iron deposition in liver and joints; impotence is due to hypogonadotropic hypogonadism caused by iron deposition in the pituitary. As iron continues to accumulate in tissues, increased skin pigmentation, diabetes, cardiomyopathy, arthropathy, and cirrhosis are seen (Table 1). These later symptoms and signs typically do not develop until significant iron accumulation in tissues (approximately > 5 g) has occurred, usually at age 40 to 60 years [1,6,7]. Phenotypic expression, however, is variable and depends upon many other factors, such as alcohol intake, diet, and physiologic or pathologic blood loss (menstruation, childbirth, voluntary blood donation). Patients who are heterozygous for the HFE gene mutation (ie, patients with only 1 copy of the C282Y mutation) do not appear to develop the complications associated with iron overload, although they may express some of the phenotypic features such as elevated transferrin saturation or ferritin levels. In contrast, compound heterozygosity (heterozygosity for both C282Y and H63D) may be associated with significant hepatic iron loading or fibrosis in the presence of other liver diseases such as alcoholic cirrhosis or hepatitis C infection [8].

Importance of Early Diagnosis

The case patient shows evidence of advanced liver disease, presumably due to cirrhosis from HHC. HHC can lead to cirrhosis and end-stage liver disease if not diagnosed and treated early. Once cirrhosis has developed, attempts at iron reduction therapy likely have little impact on mortality. In contrast, long-term studies of patients with HHC who do not have cirrhosis or diabetes reveal that survival is excellent if patients are treated with iron reduction therapy [4,9]. In addition, once cirrhosis is present, liver neoplasm risk is increased 100- to 200-fold and accounts for 27% to 45% of deaths among affected patients [9]. Clinicians therefore need to have a low threshold for consideration of a diagnosis of HHC. HHC should be considered in any patient with an elevated transferrin saturation or ferritin level or hepatomegaly, loss of libido, and abnormal aminotransferases. Although hemochromatosis is the obvious consideration in this patient, evaluation for other illnesses such as chronic liver disease from hepatitis C infection or alcohol should be performed, as these conditions often lead to abnormal serum iron studies.

- What is the role of serum iron studies in evaluating asymptomatic patients?
Laboratory Screening

Management objectives in HHC emphasize early diagnosis in asymptomatic patients with the hope of preventing the degree of organ damage seen in the case patient. As a result, the diagnostic focus has shifted from clinical symptoms to biochemical markers.

Because persons with HHC have a propensity to overabsorb iron from the gastrointestinal tract, the first phenotypic expression of HHC is an elevation in serum transferrin saturation (serum iron divided by total iron-binding capacity) [10]. This elevation occurs before significant tissue iron overloading develops. Ferritin, a measure of the body’s iron stores, increases when iron accumulates in the tissues. There is a direct linear relation between the level of ferritin and the total body iron stores [11,12]. For these reasons, biochemical measures of iron status are used to screen for hemochromatosis (Figure). Specifically, ferritin and serum transferrin saturation are recommended.

Serum transferrin saturation is the most specific and sensitive of the iron studies in screening for HHC among asymptomatic persons. Persistently elevated transferrin saturation, in the absence of other causes, correctly identifies 98% of affected individuals [13]. Generally, if the transferrin saturation is greater than 45% in women or greater than 55% in men, evaluation of iron stores through a measure of the ferritin level is warranted. In the setting of an elevated transferrin saturation due to HHC, a normal ferritin level likely represents nonexpressed HHC (no iron loading); an elevated ferritin level (greater than 200 ng/mL in women or greater than 300 ng/mL in men) represents primary iron overload.

Figure. Screening and diagnostic algorithm for hemochromatosis. *At the time of the second transferrin saturation test, tests for serum ferritin level and liver function, physical examination, and complete blood count should also be done; †A genetic test to show whether a patient is a homozygote or a mixed heterozygote for HFE gene mutations may be useful for risk assessment, but the positive and negative predictive values of this test have not been established. If a patient is heterozygous, the physician may want to evaluate for such conditions as hepatitis C virus infection, nonalcoholic steatohepatitis, and porphyria cutanea tarda. Homozygotes with normal iron measures might have follow-up with annual serum ferritin tests. HC = hemochromatosis; HIC = hepatic iron concentration; HII = hepatic iron index; LFT = liver function test; SF = serum ferritin; TS = transferrin saturation. (Adapted with permission from Powell LW, George DK, McDonnell SM, Kowdley KV. Diagnosis of hemochromatosis. Ann Intern Med 1998;129:929.)
Serum iron studies can be influenced by many variables leading to several caveats in their interpretation. Because these studies can be affected by diurnal variation and food intake [11], levels should be measured during a fasting state. Normal values and those expected in HHC are shown in Table 2. As discussed, both ferritin and transferrin saturation will be elevated in the majority of patients who are symptomatic from iron overload. There are, however, reports of a syndrome of mild iron overload with an elevated ferritin level but normal transferrin saturation in patients without classic HHC [14].

The interpretation of serum iron studies becomes problematic in both young women and in those who have other underlying illnesses such as chronic liver disease and malignancy. The sensitivity and specificity of transferrin saturation and ferritin measures in these situations are less than ideal. For example, serum ferritin can be elevated in up to 40% of patients with chronic viral hepatitis [15], 50% of patients with nonalcoholic steatohepatitis [16], and in patients with alcoholic liver disease [17]. In addition, because of the monthly blood loss that occurs with menstruation, 30% of premenopausal women with HHC may have normal transferrin saturation [18]. Because the level of ferritin does not distinguish between parenchymal (hepatocyte iron seen in primary iron overload) and reticuloendothelial system iron (Kupffer’s cell iron seen in conditions of secondary iron overload), it is not diagnostic for HHC. In these clinical scenarios, histologic evaluation of liver tissue is the only means by which one can determine whether elevated iron studies represent HHC or are secondary to another condition. Ferritin is an acute phase reactant and can therefore be elevated in malignant, inflammatory, or chronic liver disease. The ferritin level, however, does appear to correlate with the degree of iron stores and liver iron concentration in the setting of a patient with HHC as long as other potential causes of elevation are excluded.

In summary, transferrin saturation and ferritin levels are excellent screening tests for HHC in asymptomatic persons but are much less reliable in patients with acute inflammation and chronic illness. More specific tests, such as liver biopsy or genetic testing, are required to confirm the diagnosis of HHC in these populations.

- Are there other noninvasive tests that can confirm HHC?

There are other indirect methods for confirming the diagnosis of HHC. Quantitative phlebotomy is a valuable retrospective indicator of the severity of iron overload. Each unit of blood phlebotomized removes 250 mg of iron. By calculating the number of units required to reach a state of iron depletion, the total body iron burden can be determined. As patients with HHC typically have more than 5 g [6], patients who are iron depleted after removal of less than 4 g are unlikely to have phenotypically expressing HHC. Lastly, radiologic imaging techniques such as magnetic resonance imaging (MRI) and CT are too insensitive for the evaluation of HHC [11,12]. MRI, however, may be more sensitive in individuals with iron overload [19]. Liver-to-muscle proton density ratio on MRI was highly correlated with HHC in one study [20]. With refinements of this technique, MRI may provide a noninvasive adjunct to diagnosis of HHC.

Liver Biopsy

The patient undergoes a percutaneous liver biopsy. Biopsy findings are consistent with cirrhosis: hepatic iron index, 7.1; hepatic iron concentration, 24,469 µg/g, dry weight.

- When is liver biopsy indicated in HHC? Was liver biopsy warranted in this patient?

- What are pitfalls in interpreting hepatic iron?

### Table 2. Laboratory Values in Hemochromatosis

<table>
<thead>
<tr>
<th>Determination</th>
<th>Normal Range</th>
<th>Hemochromatosis</th>
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<tbody>
<tr>
<td>Serum Iron (µg/dL)</td>
<td>60–180</td>
<td>180–200</td>
</tr>
<tr>
<td>Total iron-binding capacity (µg/dL)</td>
<td>250–410</td>
<td>200–300</td>
</tr>
<tr>
<td>Transferrin (mg/dL)</td>
<td>220–410</td>
<td>200–300</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>15–50</td>
<td>55–100</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>20–200</td>
<td>300–6000</td>
</tr>
<tr>
<td>Women</td>
<td>15–150</td>
<td>250–6000</td>
</tr>
<tr>
<td>Hepatic Iron concentration (µg/g, dry weight)</td>
<td>300–1500</td>
<td>5000–30,000*</td>
</tr>
<tr>
<td>Iron index† (µmol/g, dry weight ÷ age in years)</td>
<td>&lt; 1.5</td>
<td>&gt; 1.9</td>
</tr>
</tbody>
</table>

*Some young homozygotes may have hepatic iron concentration less than 5000 µg/g.
†Some homozygotes (~ 10%) will have hepatic iron index less than 1.9.
Liver Biopsy

One of the current controversies in the management of HHC is the role of the liver biopsy. Until the discovery of the HFE gene, liver biopsy with histologic evaluation and quantification of iron concentration was the gold standard for the diagnosis of HHC [6,11,21]. Now the diagnosis can be confirmed by the presence of either the C282Y/C282Y (homozygote) or C282Y/H63D (compound heterozygote) mutation on genetic testing, especially in the setting of elevated transferrin saturation and ferritin. Histologic assessment in HHC, however, provides important additional information. The quantitation of iron and the presence or absence of cirrhosis (the major determinant of prognosis) can only be determined accurately with a biopsy. Identification of patients with cirrhosis is important because their risk of developing hepatocellular carcinoma is increased, and effective treatment is available for hepatocellular carcinoma if it is discovered early.

In patients who present with cirrhosis and abnormal iron studies and whose history suggests a high likelihood of another liver disease, a liver biopsy is indicated to determine whether other factors may be contributing to the clinical picture. Also, because 20% to 25% of heterozygous persons will have an elevated transferrin saturation, a liver biopsy is helpful in differentiating the few heterozygous patients who have iron stores in the range of those expected for C282Y homozygous patients from those with the more typical scenario of normal iron stores.

Liver biopsy is not needed when cirrhosis is clinically apparent (eg, splenomegaly, evidence of portal hypertension, decreased synthetic function). In the case patient, for example, genetic testing might have confirmed the diagnosis of HHC, thus abrogating the need for liver biopsy, which in cirrhotic patients carries a higher risk due to the presence of coagulopathy and ascites.

There are other clinical scenarios in which liver biopsy may not be necessary. A recent study has shown that in a cohort of C282Y patients, none had severe fibrosis in the absence of hepatomegaly, normal AST, and a ferritin level below 1000 ng/mL, suggesting that noninvasive markers could replace liver biopsy in predicting the absence of cirrhosis [22]. However, these guidelines cannot be applied to patients with suspected iron overload who are not C282Y homozygous because the relationship between serum ferritin level and fibrosis is unknown. Other studies suggest that young, asymptomatic individuals with normal iron and liver function studies identified during family screening as being C282Y homozygous have an extremely low likelihood of having fibrosis at the time of diagnosis and therefore do not need a liver biopsy if followed and phlebotomized when ferritin becomes elevated above normal. In all other situations, other causes of iron overload and concomitant liver disease should be ruled out and evaluated further by histologic assessment.

Hepatic Iron Measurement

Quantitative testing for iron concentration in the liver should be performed whenever liver biopsy is performed in the context of suspected iron overload or HHC. The hepatic iron index can then be calculated (hepatic iron concentration [µmol/g] divided by patient’s age in years) [21]. This index provides important diagnostic information and is based on the concept that iron accumulates in a linear fashion over time in patients with HHC. A hepatic iron index greater than 1.9 has been used to reliably differentiate HHC homozygotes from heterozygotes, alcoholics, and those with other causes of iron overload [21,23,24]. In addition, a multicenter U.S. study suggested that a hepatic iron concentration of more than 71 µmol/g (400 µg/g) might provide a sensitive adjunct [6]. When the hepatic iron index is greater than 1.5 but less than 1.9, the diagnosis remains equivocal, and some homozygotes have been found to have an index less than 1.9. The advent of genetic testing for the C282Y mutation may be particularly helpful in this setting. Alternatively, quantitative phlebotomy, as discussed in the previous section, may be employed as a diagnostic tool. The biopsy specimen is also evaluated for the pattern of iron staining. Perl’s stain typically reveals grade 3 to 4 iron stores in perportal hepatocytes [11]. This is in contrast to specimens from patients with alcoholic liver disease, for example, in which the iron is found in the Kupffer’s cells.

Airing of Children’s Concerns

The patient’s family history is remarkable for a father and sister who reportedly died from alcoholic liver disease; workups for HHC were never performed. The patient has 4 daughters who are concerned about having inherited the gene for hemochromatosis and who ask about genetic testing.

- What are the clinical implications of genetic testing in HHC?
- Who should undergo genetic testing?

Genetic Testing in HHC

The gene associated with HHC was identified in 1996 by positional cloning in a defined cohort of patients with the disorder [5]. The gene encodes a class I major histocompatibility complex-like protein, initially coined HLA-H and recently renamed HFE. Two missense mutations have been identified in the HFE gene; these have been designated C282Y (G-to-A mutation resulting in a cysteine-to-tyrosine substitution at amino acid position 282) and H63D (histidine-to-aspartic acid substitution at amino acid position 63). The homozygous C282Y mutation is present in more than 80% of
the HHC patients of northern European descent but is much less common (50% to 60%) among patients from other ethnic groups [25–27]. In addition, approximately 8% to 10% of patients with phenotypic evidence of HHC lack the HFE mutation [8,28–30]. Compound heterozygosity also appears to be associated with iron overload, although to a lesser degree. Individuals who are heterozygous for the C282Y mutation appear to have excess total body iron but do not seem to develop significant iron overload except in the presence of another disorder such as hepatitis C virus infection or alcoholic liver disease [31]. For this reason, only C282Y homozygosity or C282Y/H63D compound heterozygosity should be considered indicative of HHC (Table 3) [32].

Genetic testing from deoxyribonucleic acid (DNA) for the HFE mutations is now available clinically. The cost of the blood test varies from $150 to $200. The availability of a non-invasive test to confirm homozygosity for HHC has dramatically changed the approach to management. Patients found to be homozygous for the C282Y mutations do not need a liver biopsy for confirmation of the diagnosis of HHC. Liver biopsy is only needed in such cases to evaluate for the presence of cirrhosis. In contrast, liver biopsy will be of diagnostic and prognostic value in patients who are not C282Y homozygous; such patients may have non-C282Y HHC or iron overload secondary to chronic liver disease (eg, nonalcoholic steatohepatitis) that has yet to be diagnosed.

The precise role of genetic testing for HFE mutations in the diagnosis of HHC has yet to be fully delineated. Studies examining whether such screening is cost-effective, warranted, and practical have not yet been done. Testing for the HFE mutations is indicated, however, in persons with evidence of iron overload on screening serum iron studies or excess iron concentration on liver biopsy.

Family Screening
Controversy exists regarding the roles of genetic testing versus transferrin saturation in family screening. Disadvantages of genetic testing include concerns about insurability and genetic discrimination; furthermore, the genetic test is helpful in family screening only if the proband is C282Y homozygous. Family screening among relatives of HHC probands is appropriate because siblings of HHC probands have a 25% chance of being homozygous. In addition, since the carrier frequency is 8% to 10% in the white population, children of HHC parents should also be screened.

Population-Based Screening
The crucial issues for population-based screening remain which tests to use and in which population to use them. The relationship between iron overload and the HHC genotype is complex. There remains considerable uncertainty about the penetrance of the C282Y and H63D mutations, the prevalence of these mutations among patients with phenotypic expression of HHC, and the possible existence of other mutations. Given these limitations, DNA testing for population screening for HHC cannot be recommended without further studies.

The patient’s children are informed about the caveats of the different screening methods and offered transferrin saturation measurement or genetic testing. All 4 choose genetic testing. All 4 are found to be heterozygous, and no further intervention is necessary. The patient is begun on weekly phlebotomy.

• What are therapeutic options in patients with early, mid- and late HHC?

Once the diagnosis of HHC is established by either genotyping and/or elevated hepatic iron on liver biopsy, attention should be directed toward providing adequate treatment. Therapy is safe, easy, and inexpensive and should not be delayed until the development of symptoms. Patients who do not have significant fibrosis or cirrhosis at the time of diagnosis will have a normal life expectancy if they are compliant with iron reduction therapy. Conversely, patients with cirrhosis have increased mortality despite therapy [4].

Phlebotomy
Therapeutic phlebotomy remains the treatment of choice for iron overload. Weekly phlebotomy of 500 mL whole blood (250 mg iron) is performed until a mild iron deficiency anemia develops (hematocrit 33%, ferritin level < 40 ng/mL), provided the patient is able to tolerate it. Induction phlebotomy

Table 3. Genetic Testing in Hemochromatosis

<table>
<thead>
<tr>
<th>Genetic Test Result</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>C282Y homozygous mutation</td>
<td>Associated with iron overload</td>
</tr>
<tr>
<td>C282Y heterozygous mutation</td>
<td>Usually not associated with iron overload; transferrin saturation may be elevated</td>
</tr>
<tr>
<td>H63D/C282Y compound</td>
<td>May be associated with iron overload</td>
</tr>
<tr>
<td>heterozygous mutation</td>
<td></td>
</tr>
<tr>
<td>H63D homozygous mutation</td>
<td>Unknown due to inadequate data</td>
</tr>
<tr>
<td>H63D heterozygous mutation</td>
<td>Not associated with iron overload</td>
</tr>
</tbody>
</table>

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should be performed so that iron depletion occurs within the first 2 years after diagnosis of HHC. Thereafter, maintenance phlebotomy is continued throughout the life of the patient. Typically, this amounts to removal of 1 unit of blood 3 to 4 times each year. The goal of therapy is to achieve a serum ferritin level below 50 ng/mL, indicating the removal of excess iron deposits. The decision to offer phlebotomy for those who are C282Y homozygous and have not had a liver biopsy is based on elevated transferrin saturation or ferritin level. For those patients who have had a liver biopsy (the majority), the decision to phlebotomize is based on the liver tissue quantitative iron studies rather than the presence or absence of the C282Y genotype [33]. In addition, therapy should be offered to patients even if they have cirrhosis (provided they can tolerate it), since it likely improves quality of life and may improve portal hypertension [4,9,34]. Serum ferritin has been shown to be the most reliable means by which to monitor therapy [11,12]. Iron chelation therapy with deferroxamine should be considered only in patients who have elevated iron levels and anemia because it requires parenteral administration, has side effects, is expensive, and mobilizes only approximately 50 mg of iron per day.

Patients undergoing phlebotomy can expect a decrease in their fatigue, liver enzymes, and hepatomegaly and occasionally an improvement in their diabetes mellitus [35,36]. Iron reduction may improve some of the cardiac abnormalities, especially if undertaken before the development of dilated cardiomyopathy [37]. On the other hand, phlebotomy rarely improves cirrhosis and does not decrease the risk for development of hepatocellular cancer in these patients [9,12,38]. Joint symptoms also tend not to respond to phlebotomy.

Dietary factors may influence the expression of HHC. Because vitamin C increases the absorption of iron, ingestion of it should be limited to fruits and vegetables, with avoidance of vitamin C supplements [33]. Iron supplements should also be avoided. Restriction of red meat is probably not necessary provided the patient can tolerate therapeutic phlebotomy.

Liver Transplantation

In patients who progress to end-stage liver disease despite iron reduction therapy, orthotopic liver transplantation remains the only therapeutic option. So far, results of liver transplantation for HHC have been disappointing. One- and 5-year survival rates are 58% and 42%, respectively [39,40]. This is compared with a 1-year survival rate for all liver transplants of 80% [41]. The increase in posttransplant mortality appears to be due mostly to infections (typically within the first year after transplant) and cardiac complications such as congestive heart failure and arrhythmias rather than hepatocellular carcinoma [39,40,42]. Preliminary observation suggests that routine pretransplant cardiac evaluation with 2-dimensional echocardiography and stress test are not sensitive in predicting posttransplant cardiac dysfunction [Kowdley, unpublished data]. Failure to correctly identify HHC before transplant could contribute to an increase in mortality [39,43]. Iron reduction therapy before and after transplantation in patients who progress to liver transplant may reduce mortality. A preliminary study reports 1-year survival rates ranging from 75% to 80% if phlebotomy was performed prior to transplant [44].

Clinical Course

The patient discontinues therapy because of fatigue. He experiences a 25-lb weight loss and worsened fatigue over the ensuing 7 months. Subsequent evaluation reveals deterioration in liver function, and he is placed on a waiting list for orthotopic liver transplantation. Preoperative echocardiogram does not reveal cardiac abnormalities, and MRI does not suggest lesions suspicious for hepatoma. The patient undergoes orthotopic liver transplant, which is complicated by sudden portal vein thrombosis with resultant fulminating hepatic failure requiring a second transplant. The patient survives the second transplant but unfortunately succumbs to heart failure and sepsis 6 weeks later.

SUMMARY

HHC is a common inherited disorder that leads to iron accumulation in the liver, pancreas, heart, and other organs. Physicians will likely diagnose and treat more cases of HHC in the future because of the increased awareness of its prevalence along with more readily available diagnostic tests, such as genetic testing for HHC mutations. Early diagnosis followed by phlebotomy to maintain normal body iron stores can prevent most complications of HHC. The transferrin saturation is the recommended test for population screening, since it is the earliest phenotypic marker of HHC and becomes elevated prior to significant iron loading. Further tests, such as genetic testing and liver biopsy, are used to confirm the diagnosis of HHC, rule out concomitant disease, and provide vital prognostic information.

Wayne State University acknowledges Y. Ravindranath, MD, Professor of Pediatrics, Division of Hematology/Oncology, Children’s Hospital of Michigan, Wayne State University School of Medicine, for reviewing this CME case study.

REFERENCES


35. Hayashi H, Takikawa T, Nishimura N, Yano M, Isomura T, Sakamoto N. Improvement of serum aminotransferase levels after phlebotomy in patients with chronic hepatitis C and...


1. The prevalence of hereditary hemochromatosis (HHC) in western countries is approximately
   (A) 1 in 1000
   (B) 1 in 500
   (C) 1 in 300
   (D) 1 in 100

2. Extrahepatic manifestations of HHC include all of the following EXCEPT
   (A) Diabetes mellitus
   (B) Heart failure
   (C) Impotence
   (D) Dementia

3. All of the following can result in a false-positive elevation in transferrin saturation EXCEPT
   (A) Alcoholic liver disease
   (B) Menstruation in women
   (C) Steatohepatitis (fatty liver)
   (D) Chronic hepatitis C virus infection

4. All of the following statements about HHC are true EXCEPT
   (A) HHC is an autosomal recessive disorder
   (B) Two mutations, C282Y and H63D, are associated with the candidate gene (HFE) for HHC
   (C) Patients who are heterozygous for the C282Y chromosome typically develop complications of iron overload
   (D) The probability of siblings of HHC probands having HHC is about 25%

5. Therapeutic phlebotomy will accomplish all of the following EXCEPT
   (A) decrease the risk for hepatocellular carcinoma in HHC patients with cirrhosis
   (B) Normalize the life expectancy in HHC patients who have not yet developed cirrhosis
   (C) Improve fatigue and possibly diabetes mellitus associated with HHC
   (D) Improve liver enzymes and hepatomegaly
EVALUATION FORM: Diagnosis and Management of Hereditary Hemochromatosis

To receive CME credit for this case study, read the case study and then answer the multiple-choice questions on page 51. Circle your answers below. Also, please respond to the four questions that follow. Then, detach the evaluation form and mail or FAX, along with your payment of $15.00 (check, MasterCard, or VISA accepted) to:

JCOM® CME Evaluation
Wayne State University
University Health Center, 5E
4201 St. Antoine
Detroit, MI 48201
Phone: (313) 577-1453  FAX: (313) 577-7560

Circle your answer to the CME questions below:
1. A  B  C  D
2. A  B  C  D
3. A  B  C  D
4. A  B  C  D
5. A  B  C  D

Please answer the following questions:
1. In general, how do you rate the information presented in the case study?
   - excellent
   - good
   - fair
   - poor

2. Do you find the information presented in this case study to be fair, objective, and balanced?
   - yes
   - no

3. Name three clinical conditions that, in your experience, lead to less than optimal patient outcomes:
   Condition 1: ________________________________________
   Condition 2: ________________________________________
   Condition 3: ________________________________________

4. Name three clinical topics you would like explored in future JCOM® case studies:
   Topic 1: ____________________________________________
   Topic 2: ____________________________________________
   Topic 3: ____________________________________________

Please print clearly:
Name: ______________________________________________
Address: ____________________________________________
City: ________________________________________________
State: ______________________ Zip: __________________
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Note: CME credit letter and correct responses will be sent to the above-named person.

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