DIAGNOSIS AND MANAGEMENT

OF

HEMOCHROMATOSIS

By

JILL B. COTOIA

A research manuscript submitted in partial fulfillment of
the requirements for the degree of

MASTER OF NURSING

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College of Nursing

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To the Faculty of Washington State University:

The members of the committee appointed to examine the ICNE Research requirements and manuscript of Jill B. Cotoia find it satisfactory and recommend that it be accepted.

[Signatures]

Lorna Schumann
Chair

[Additional signatures]
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Hereditary hemochromatosis is an autosomal recessive genetic disease which results from intestinal absorption of iron in excess of bodily requirements. The excessive iron is deposited and stored in organs such as the liver, heart, endocrine glands, pancreas, joints, and skin. This results in damage and possible failure of these organs leading to premature death. Unfortunately, this disease is often misdiagnosed and may go untreated for years. Screening tests for this disease are serum transferrin saturation and serum ferritin. Liver biopsy will diagnose the disease, though often not needed due to the high reliability of the laboratory tests. Treatment depends upon disease progression. In mild cases, phlebotomy programs with laboratory monitoring are initiated. In more severe cases, phlebotomy programs with close laboratory and abdominal ultrasound monitoring are completed. Secondary diseases from organ damage may also need to be treated. It is important that all of the possible problems associated with the disease be explained and the importance of the treatment be stressed.
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ABSTRACT

Hereditary hemochromatosis is an autosomal recessive genetic disease which results from intestinal absorption of iron in excess of bodily requirements. The excessive iron is deposited and stored in organs such as the liver, heart, endocrine glands, pancreas, joints, and skin. This results in damage and possible failure of these organs leading to premature death. Unfortunately, this disease is often misdiagnosed and may go untreated for years. Screening tests for this disease are serum transferrin saturation and serum ferritin. Liver biopsy will diagnose the disease, though often not needed due to the high reliability of the laboratory tests. Treatment depends upon disease progression. In mild cases, phlebotomy programs with laboratory monitoring are initiated. In more severe cases, phlebotomy programs with close laboratory and abdominal ultrasound monitoring are completed. Secondary diseases from organ damage may also need to be treated. It is important that all of the possible problems associated with the disease be explained and the importance of the treatment be stressed.
**Introduction**

Hereditary hemochromatosis (HHC) is the most common autosomal recessive genetic disease found in the Caucasian population. It is estimated that one in ten to twenty Caucasians carry this gene and one in four hundred are homozygotes at risk for developing clinical problems seen with this disease. (Rouault, 1993; Bacon & Peterson, 1998) This is a serious disease, that if untreated, will cause premature death. Fortunately, with early diagnosis, HHC is easily treated and has a mortality rate equal to those who do not have the disease. Early diagnosis and treatment is therefore, essential.

With the current concern over health care costs, insurance companies will not reimburse health care providers for routine screening tests without presenting symptoms and a differential diagnosis. This means that many patients who have this disease will not be diagnosed until symptoms are present and organ failure may have begun. Another problem in diagnosing these patients early is that varying symptoms may lead primary care providers to the wrong diagnosis (Bacon, 1997). It is estimated that usually more than five physicians have been consulted before diagnosis is established and approximately five years has elapsed between initial presentation and treatment (Rouault, 1993). The purpose of this article is to familiarize health care providers with HHC so that diagnosis and treatment can be initiated as early as possible in order to save lives and costly disabling complications.

**What is hemochromatosis?**

As stated earlier, HHC is an autosomal recessive disease. This disease results from intestinal absorption of iron in excess of bodily requirements. Iron is carried throughout the body and then deposited and stored in organs such as the liver, heart,
endocrine glands, pancreas, joints, and skin (Marlow, 1998; Himmelmann & Fehr, 1999).

It was first recognized by Europeans as “bronze diabetics” and described by von Recklinghausen in 1889. In 1935, Shelden discovered its genetic relationship and in 1975, HHC was linked to a human leukocyte antigen on chromosome 6 (Edwards & Kushner, 1993; Peterson & Bacon, 1998).

Abnormal absorption occurs in the epithelial cells of the duodenal mucosa in the proximal small intestine. Due to a high absorption rate, circulating cells are overloaded with iron and transferrin (an iron transporting protein) may become completely saturated. Normally, once this occurs the transferrin receptor expression is down-regulated, leading to a decrease in iron absorption. In persons with HHC this regulatory mechanism is not in place (Kowdley & Tavill, 1998). After transport in the bloodstream and deposition in the liver, heart, pancreas, skin and joints, iron is sequestered in ferritin (an iron protein complex) in individual cells of the tissue. At this point there is no mechanism for excretion other than blood loss, exfoliation of skin and mucosal epithelial cells, and small losses in sweat and urine (Rouault, 1993; Bacon et al., 1999).

**Clinical Presentation**

HHC is more prevalent in males than females (ratio of 8:1), and usually presents in the fourth through sixth decade of life (Moirand et al., 1997). Signs and symptoms are included in Table 1. In the diagnostic work-up, diseases such as diabetes mellitus, thyroid diseases, arthritis, and cardiac and liver disease may be confirmed. It is important to remember, however, that these may be present due to iron deposits in these organs from HHC (Bacon & Sadiq, 1997).
Diagnostic Tests

The best screening test for HHC is serum transferrin saturation. It is calculated by dividing serum iron concentration by total iron-binding capacity (TIBC) x 100. The normal transferrin saturation is less than 50%, and generally 30%. If the transferrin saturation is 40% to 60%, a fasting transferrin is recommended, which will give a more accurate reading. A fasting serum transferrin saturation > 60% in men or >50% in women is a sensitive indicator in asymptomatic individuals older than 30 years of age with HHC (Kowdley & Travill, 1998). When the test is greater than 62%, it is 96% sensitive for HHC in individuals older than 30. This means that in individuals older than 30, 96% of the time HHC is present (true positive test) with a transferrin saturation of more than 62%. Ninety-nine percent of the time individuals older than 30 who test negative, or have normal tests, do not have HHC (99% specific or true-negatives) (Edwards & Kushner, 1993). Sensitivity and specificity for transferrin saturation have been found to be much lower in younger individuals and when patients have abnormal iron studies in the context of other illnesses such as viral hepatitis, nonalcoholic steatohepatits and alcoholic liver disease (Bacon, 1997).

If the transferrin saturation is greater than 50%, a serum ferritin level should be obtained (Edwards & Kushner, 1993). Serum ferritin generally reflects cellular iron stores and may be high in HHC. Serum ferritin levels will also be high in liver disease, such as that caused by HHC, due to ferritin escaping from necrotic hepatocytes. Normal serum ferritin concentrations vary with age and gender. A value of more than two standard deviations above the appropriate value is considered abnormal. The reference
range for a typical male is 20 to 250 ng/mL; for females older than forty years it is 12 to 263 ng/mL. Serum ferritin levels in HHC may by greater than 1000 ng/mL (Jacobs et al., 1996). This test is about 85% sensitive for HHC and less than 75% specific. Inflammatory disorders such as rheumatoid arthritis and various neoplasms can cause elevated serum ferritin levels (Bacon, 1997). It is important to note that a normal serum ferritin cannot rule out HHC (Adams, Bradley & Henderson, 1997). An individual may have this disease without much or any hepatic damage, making this test normal.

A new, widely available genetic screening test for HHC will contribute to diagnoses confirmation, though a liver biopsy is considered “the gold standard” by many (Adams, Bradley, & Henderson, 1997; Bacon, 1997; Bacon et al., 1999). Presence of substantial stainable iron in parenchymal liver cells is characteristic of iron overload. Figure 1 shows liver cells containing iron. From biopsy, the hepatic iron index may be calculated; this distinguishes patients with homozygous HHC from patients with other diseases, such as alcoholic liver disease and hepatitis (Bacon et al., 1999).

Completing a liver biopsy in all patients suspected of HHC remains a controversial issue. Some argue that an elevated transferrin saturation and ferritin provide sufficient information for a diagnosis of iron overload and the harmless treatment can be initiated on this information (McDonnell et al., 1998). Others are concerned that without a definitive liver biopsy, many patients would not be diagnosed appropriately and follow-up and family screening would not be initiated (Bacon, 1997).

Once the diagnosis of HHC has been established, a blood glucose level should be obtained due to the effects of the disease on the pancreas. Also, if impotence has been noted on the history, a testosterone level should be ordered. If symptoms of liver disease
appear, a prothrombin time should be ordered to determine liver damage. Table 2 shows other tests that may be abnormal in HHC. Figure 2 contains the pathways to diagnosing and treating HHC.

An echocardiogram may be considered to rule out cardiomegaly. Computed tomography (CT) scan, magnetic resonance imaging (MRI), and magnetic susceptibility measurement (MSM) are being studied for measuring body iron, but have not yet reached validation and general availability is low due to costs (Marlow, 1997).

Treatment

Upon presumptive diagnosis of HHC, two groups will appear. The first group will have elevations in both transferrin saturation and serum ferritin. The second group will have only elevations in transferrin saturation. In the group with elevations in both tests, the Center for Disease Control is now recommending a liver biopsy (Rouault, 1993; Bacon, 1997; Witte, 1997).

Once the diagnosis is made from biopsy, an initial phlebotomy program or “de-ironing” is initiated. Weekly phlebotomies of 500 mL of blood (about 250 mg of iron) are recommended to establish and maintain mild anemia (hematocrit of 37% to 39%), or until transferrin saturation falls below 50% and the serum ferritin level is reduced to below 20-50 ng/ml. This may need to be conducted biweekly or weekly, taking from 1 month up to 3 years. After initial therapy is completed, maintenance phlebotomy is initiated. This involves removal of one unit of blood every 2-3 months to keep the transferrin saturation below 50%. (Bacon, 1997; Friedman, 1997; Hughes, 1998; McDonnell et al., 1998).
If diagnosis is made after cirrhosis has developed, the chances of the patient’s developing hepatocellular carcinoma are greatly increased. In this case, alpha-fetoprotein levels may be drawn, as they are frequently elevated in hepatocellular carcinoma. Yearly abdominal ultrasounds are also indicated, because early resection is the only therapy, if cancer is found (Rouault, 1993).

In the seconded group, when only transferrin saturation levels are elevated, the clinician is faced with a few choices. These individuals may or may not have presenting symptoms. As mentioned earlier, liver biopsy is controversial in asymptomatic individuals. The choice of obtaining a liver biopsy is left up to the primary care provider and the patient (Witte, 1997). Other choices concern phlebotomy treatment options. One approach is to initiate phlebotomy therapy, three to four times a year. Serum ferritin can be monitored annually or biannually, and the frequency of phlebotomy adjusted to maintain a normal serum ferritin level. Another approach is to monitor transferrin saturation and serum ferritin at 2-year intervals and to institute phlebotomy therapy when the ferritin concentration is above the normal range. This approach should detect the development of iron overload before end-organ damage occurs (Edwards & Kushner, 1993).

**Patient Teaching**

Because HHC is a hereditary disease, family members including children and siblings of the patient need to be tested. It is important that all the possible problems associated with the disease be explained and the importance of treatment is stressed. Patients diagnosed with this disease can contact the following associations and support groups with questions: Hemochromatosis Research Foundation, Iron Overload Diseases
Association, and the American Liver foundation. An Internet website about this condition is located at <http://sadieo.ucsf.edu/ALF/ALFfinal/proghemocrom.html>.

Patients with HHC need to avoid alcohol, iron-fortified foods, and iron-containing supplements. Vitamin C must be restricted to small doses between meals (Herbert, Shaw & Jayatilleke, 1996). Drinking tea with meals is encouraged. Tea chelates iron and helps to decrease iron availability for absorption (Marlow, 1998). Information about phlebotomy sites and costs, needs to be provided. If imaging tests are being performed, the patient needs to know what to expect.

**Conclusion**

Screening for HHC has been advocated by many (Baer et al., 1995; Adams, Bradley & Henderson, 1997; Bacon, 1997; Witte, 1997). With the current concern over health care costs, screening may, unfortunately, be limited. This makes primary care providers even more dependent upon their assessment and history taking skills, and knowledge of the disease process. Providers with knowledge of HHC and its presenting clues can prevent the development of serious and deadly organ failure in their patients and can potentially save Medicare and insurance companies millions of dollars each year.
References


http://sadieo.ucsf.edu/ALF/ALFfinal/prohemocroma.html


Table 1

**Signs and symptoms of hemochromatosis**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>(83%)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>(13%)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>(83%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>(12%)</td>
</tr>
<tr>
<td>Bronze colored skin</td>
<td>(75%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>(10%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>(58%)</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>(8%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>(43%)</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>(6%)</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>(38%)</td>
</tr>
<tr>
<td>Testicular atrophy</td>
<td></td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>(22%)</td>
</tr>
<tr>
<td>Hepatic tenderness</td>
<td></td>
</tr>
<tr>
<td>Loss of body hair</td>
<td>(20%)</td>
</tr>
<tr>
<td>Diabetes mellitus symptoms</td>
<td></td>
</tr>
<tr>
<td>Dypsnea on exertion</td>
<td>(15%)</td>
</tr>
</tbody>
</table>

Note. These percentages are based on individuals diagnosed as having the disease. If general screening tests were obtained, many people would present with none of few of symptoms (Marlow, 1998; Rouault, 1993).
Table 2

Laboratory tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Normals</th>
<th>Value</th>
<th>Cost</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary iron</td>
<td>none</td>
<td>present</td>
<td>$27.25</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>60-110 mg/dl</td>
<td>high</td>
<td>$13.50</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>FSH</td>
<td>&lt; 22 IU/L</td>
<td>low</td>
<td>$8.75</td>
<td>0%</td>
<td>99%</td>
</tr>
<tr>
<td>LH</td>
<td>7-24 mIU/ml</td>
<td>low</td>
<td>$8.75</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Testosterone</td>
<td>9-30 mg/dL</td>
<td>low</td>
<td>$15.00</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>SGOT (AST)</td>
<td>20-48 u/L</td>
<td>high</td>
<td>$8.75</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Albumin</td>
<td>0-6 ng/mL</td>
<td>low</td>
<td>$15.55</td>
<td>99%</td>
<td>99%</td>
</tr>
</tbody>
</table>

Note. The values listed are for adult men (Jacobs et al, 1996). The sensitivity and specificity are related to the accuracy of each individual test not to HHC.
Figure 1

Liver cell showing iron deposits.

Note. The brownish areas are iron deposits.
Figure 2.

**Hemochromatosis Algorithm**

Patient presents with arthralgias, abdominal pain, hepatomegaly, weakness, and loss of libido.

Measure transferrin saturation
If >60% in m or >50% in f

If normal, rethink your diagnosis

Draw Serum ferritin

Above normal for age and sex

Refer for liver biopsy

Measure ferritin and transferrin saturation biannually. Initiate phlebotomy if high.

Initiate phlebotomy immediately. One to two units weekly until serum ferritin levels are normal. Adjust frequency to maintain normal ferritin levels. Continue throughout lifespan.

Below normal for age and sex

Initiate phlebotomy (3-4 u/yr), measure ferritin every 2 years and adjust frequency to ferritin level.

If cirrhosis present draw alphafetoprotein to check for carcinoma. Obtain yearly abdominal ultrasound to check for carcinoma. Obtain Serum glucose to rule out diabetes and an echocardiogram to rule out cardiomegaly.