



Hemochromatosis: How many cases are we missing?

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Case 1

PG, a 42-year-old, married, security guard, presents to your office with symptoms of fatigue and multiple arthralgias over several months. He immigrated to Canada from England three years ago. He has no other specific complaints.

Review of physical systems reveals that he consumes 24 bottles of beer per week but has never smoked cigarettes nor used illicit drugs. He describes his sleep as being nonrestorative, but partially attributes this to his shift work. His only medications are lansoprazole, which he takes for gastroesophageal reflux, and a multivitamin. Examination of his family history reveals that both parents have heart disease, and his father has Type 2 diabetes. He has a healthy brother, and no children.

The physical examination and the following blood tests were found to be normal: hemoglobin, fasting glucose, thyroid-stimulating hormone, erythrocyte sedimentation rate and rheumatoid factor. However, the alanine aminotransferase was 56 U/L (0 - 40 U/L) and aspartate transaminase was 78 U/L (0 - 37 U/L). Subsequent testing for hepatitis B surface antigen and anti-hepatitis C virus antibody were negative. Repeat testing of transaminases, one month after decreasing alcohol intake, showed continued elevations.

While you are waiting for him to see the specialist, the patient tells you that he has participated in a screening study, and was found to have the genes for hemochromatosis (C282Y homozygote). His transferrin saturation was 96% and his ferritin was 2,499.

See case discussion on page 104.



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What are the implications of his positive tests for hemochromatosis?

Hereditary hemochromatosis (HH) is a genetic condition in which more iron is absorbed than is required by the body. As iron is absorbed over several years, it is deposited in organs such as the liver, pancreas and heart with the potential to develop life-threatening complications such as hepatic cirrhosis, diabetes and heart failure.¹ Other sequelae of the disease include decreased fertility, arthritis (especially of the hands) and a bronzed appearance of the skin. Unfortunately, diagnosis of this disease is often delayed. During the initial phases of increased iron absorption, there are no symptoms. Early symptoms include fatigue and arthralgias, which are common in a myriad of other disorders. The diagnosis is often made after a family physician orders a serum ferritin to test for iron deficiency in a patient with weakness or fatigue. Instead of the expected low level, the ferritin is actually elevated (Table 1).

Late symptoms can be correlated with significant iron overload, and include symptoms associated with diabetes (*i.e.*, thirst, polyuria, *etc.*) and heart failure (*i.e.*, shortness of breath, edema, *etc.*)² Other signs and symptoms include impotence, decreased libido, elevated aspartate transaminase (AST), hepatomegaly, cirrhosis and increased skin pigmentation, often of a grey or bronze hue.

Table 1

Ranges of Serum Ferritin and Transferrin Saturation

Measure	Normal Range	Possible Iron Overload
Serum Ferritin	22-322 (mcg/L) (men)	>300 (mcg/L) (men)
	10-291 (mcg/L) (women)	>200 (mcg/L) (women)
Transferrin Saturation	20%-50%	>50% (men)
		>45% (women)



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A large screening study in San Diego reported that the prevalence of the nonspecific symptoms of hemochromatosis is similar in C282Y homozygotes and control patients.³ This may be due to the fact that they screened healthy, relatively asymptomatic subjects. The method of assessing liver disease was also unconventional, as liver biopsies were not performed.

Does your patient have a rare condition?

HH is perceived to be a rare condition, reflected in the estimate that only about one in 10,000 people are diagnosed with the condition.²

In reality, HH is the most common genetic condition known in people of European descent.⁴ It is estimated that nearly one in 200 people with Northern European ancestry have the typical genetic pattern associated with this condition.⁸ HH follows an autosomal recessive pattern of inheritance. The gene for hemochromatosis, the HFE gene, was discovered in 1996, and was found to be located on the short arm of chromosome 6.⁵ A mutation in this gene, in which tyrosine is substituted for cysteine at amino acid number 282 of the HFE protein (the C282Y mutation) was found to be present in over 90% of people who had been clinically diagnosed with hemochromatosis.⁶ Another mutation was found at amino acid 63 (H63D), and has a lesser understood effect. People who are homozygous for this H63D mutation have about a 1% risk of developing elevated iron tests, but are not likely to develop a clinically significant iron overload.⁷

The discrepancy in the rates of diagnosis versus prevalence of positive gene tests for HH can be explained by two causes. First, not all people who are C282Y homozygotes go on to develop evidence of iron overload. It is estimated that 50% of these women and between 50% to 90% of these men



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will “express” the genes as evidenced by high serum iron tests.⁸ Second, as the symptoms are nonspecific, many cases of hemochromatosis may go undiagnosed.

Will your patient need a liver biopsy?

This patient does not need a liver biopsy for diagnostic purposes, as the gene test has already revealed that he has HH. Liver biopsy is currently most important for the diagnosis of non-HFE related iron overload in patients with concomitant risk factors.

This man should still be considered for liver biopsy as he has evidence of liver dysfunction (elevated transaminases) and because the chance of organ damage is increased in homozygotes with ferritin greater than 1,000 mcg/L.⁹ Patients with a ferritin > 1,000 mcg/L, elevated AST, and platelet count < 200 have approximately an 80% chance of having cirrhosis.¹⁰ Prognosis is best in hemochromatosis patients when there is no evidence of cirrhosis before the commencement of treatment. Presence of cirrhosis decreases life expectancy, and increases risk of hepatocellular carcinoma by about 200-fold as compared to normal subjects.¹¹ Patients who are found to have cirrhosis can be monitored for hepatocellular carcinoma with ultrasound of the liver at six month intervals.

PG agrees to liver biopsy, and his results show 3+ iron deposition in hepatocytes, but not in the Kupffer’s cells, with no cirrhosis nor fibrosis.

How should your patient’s hemochromatosis be managed?

PG should consider undergoing phlebotomy treatments until his ferritin is in the low normal range (50 mcg/L). During treatment, about 500 ml of blood is removed weekly. Hemoglobin is determined each week, and the frequency of phlebotomy is decreased to biweekly if the hemoglobin falls below 100 g/L. With PG’s ferritin at 2,499 mcg/L, it may take six to 12 months until he reaches iron depletion. Once the ferritin is below 50 mcg/L, the patient begins maintenance therapy, which involves around three to four phlebotomies per year. As long as other criteria are met, Canadian Blood Services will accept blood donations from hemochromatosis patients during this maintenance phase of treatment.

Phlebotomy has been found to be highly effective therapy for HH, preventing morbidity while promoting normal longevity.¹ Symptoms may improve differentially during treatment. Positive effects are more often noted with fatigue, symptoms of cardiomyopathy and skin pigmentation, rather than with arthritis or problems with libido.

As his family physician, you can also suggest that he make some lifestyle

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changes to minimize the effect of HH on his health. He should consider limiting alcohol to two drinks or less per day. Abstinence would be recommended in cirrhotic patients. If he wishes to continue using the multivitamin, he should use one that does not contain iron. As there is some evidence that high doses of vitamin C can enhance iron absorption from the gut, he should take no more than 500 mg daily. PG will not require a “low iron” diet, as the iron is removed by phlebotomy faster than it is absorbed from the diet.

Which other patients should you screen for hemochromatosis?

Case 2

KH, 32-years-old, informs you that her brother has been found to have the genes for hemochromatosis (C282Y homozygote). She is requesting to be tested for this condition, as her brother told her it was hereditary.

The patient is a healthy, married nurse, with a five-year-old son. You have treated her for iron deficiency anemia related to menorrhagia in the past. Her ferritin of a year ago was 22 g/L after three months of taking ferrous gluconate during menstruation. She is currently taking oral contraceptive pills, but plans to stop these soon to attempt another pregnancy. She feels well.

Case discussion follows.

Because the early symptoms are nonspecific, hemochromatosis should be added to the list of possible causes of fatigue, arthropathies, and signs and symptoms which may result from organ damage due to iron deposition. The report of the European Association for the Study of the Liver Consensus Conference on Hemochromatosis included recommendations that physicians be encouraged to order serum iron tests (such as transferrin saturation and serum ferritin) on patients who have chronic parenchymal liver diseases, cardiomyopathy and arrhythmias, diabetes Types 1 and 2, impotence and loss of libido, infertility and arthritis or arthralgia, among others.² Family members of confirmed cases of HH should also be assessed for evidence of iron overload, whether or not they

are symptomatic.

The American Association for the Study of Liver Diseases practice guidelines recommend genetic testing to detect HFE mutations in all individuals who have abnormal iron studies (Test solution [TS] > 45 % with a serum ferritin for > 200 g/L for females and > 300 g/L for males) and for all first degree relatives (parents, siblings and offspring) of identified C282Y homozygotes.¹²

Assessment of patients with high iron indices should include questions about symptoms of liver disease, arthritis, impotence/infertility, heart failure, bronzed skin, blood transfusions or donations, ethnic background, inflammatory or autoimmune conditions, anemia, alcohol use, and any history of malignancy.

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How should you go about screening this patient for hemochromatosis?

You do not feel that this patient is at risk for iron overload, as she has experienced iron deficiency in the recent past. However, all siblings of homozygotes should have the gene test done, as they have a one in four chance of also being homozygotes for the C282Y mutation of the HFE gene.¹³ It is not uncommon for young female homozygotes to have a lower ferritin during child bearing years. Several studies have suggested that women may be less likely than men to express the gene by going on to develop biochemical or clinical evidence of iron overload.¹³ Alternatively, they may express the gene, but may be protected from accumulating iron during their menstruating years. These people may have TS above normal, and their risk for developing iron overload may increase after menopause.

You order the iron tests and gene test for KH. She is found to be a C282Y homozygote, with TS 65% and ferritin 25 mcg/L.

What other family members should be tested?

Any other siblings should be tested, and KH's parents may also consider having the gene test done. At our centre, we have discovered several cases where both parent and child were C282Y homozygotes. Based on population genetics of those with Northern European ancestry, there is a 6% chance that one or both parents are C282Y homozygotes.¹³

Children of homozygotes have about a one in 20 chance of being homozygous for C282Y themselves, assuming their other parent is also of Northern European descent. If the other parent's ancestry is from other areas of the world, the likelihood decreases. It is not recommended that young children have the gene test done. There is very low risk of organ damage occurring before age 20. If the child was tested, and found to be a C282Y homozygote, there is the risk that the child would be "labeled" as having an illness. Any symptom the child may happen to have could be inappropriately attributed to having these genes.

KH is very interested in knowing her son's chances of having hemochromatosis. She agrees to wait until he is older to have the testing done, but she requests that his father undergo a gene test to give them a better estimate of the child's risk. The father agrees, and is found to be a carrier of the minor mutation of the HFE gene, or to be an H63D heterozygote. This is very common in the general population, with about one in five people having this genotype. The large majority of people with this gene test result have normal serum iron measures, and those who do have higher TS and ferritin usually have a concomitant risk factor such as daily alcohol use or hepatitis.

What is the son's risk of iron overload?

As his father does not carry the C282Y mutation, the boy has no chance of inheriting the gene from his father. However, the boy is an obligate carrier of this variation as he can inherit only a C282Y mutation from his mother. From his father, he has a 50% chance of inheriting a normal HFE gene, and a 50% chance of inheriting an H63D mutation (Figure 1). The boy, then, has a one in two chance of being a C282Y heterozygote, with minimal risk of iron overload. His other one in two chance is of being heterozygous for both the C282Y and the H63D variations, or of being a compound heterozygote. This would give him about a 2% risk of developing iron overload during his lifetime.¹⁴

Should the entire population be screened?

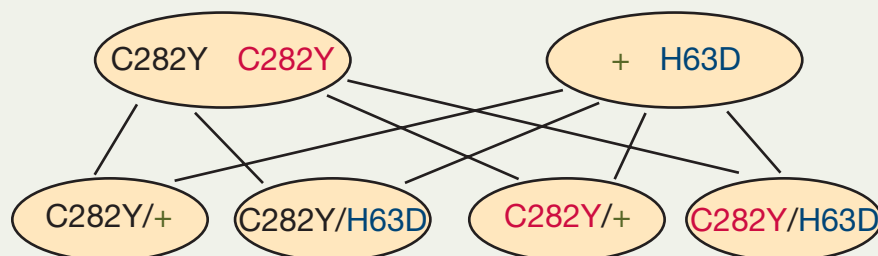
Hemochromatosis meets many of the World Health Organization criteria for conditions which are appropriate for population screening. However, there are still gaps in our knowledge such as the disease burden and the natural history of untreated hemochromatosis. Genetic screening has been cautioned against by some because detection of C282Y homozygous patients who may never express the disease raises psychosocial issues such as discrimination by employers and insurance agencies, difficult family dynamics and stigmatization.¹⁵ In a study of over 5,000 volunteer blood donors, no adverse psychosocial effects of genetic testing were demonstrated.¹⁶



Figure 1

Expected HFE Genotypes of Offspring of C282Y Homozygote and H63D Heterozygote

50% of offspring will be C282Y heterozygotes and 50% will be compound heterozygotes (C282Y/H63D).



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Despite these barriers, there is mounting evidence that population screening for hemochromatosis should be implemented. With the decreasing cost of the gene test, and the low cost of biochemical tests, screening for hemochromatosis could become a cost effective strategy. The Hemochromatosis and Iron Overload Screening (HEIRS) study plans to screen 100,000 people in Canada and the United States for hemochromatosis and iron overload using both biochemical and gene tests. Important components of the study are the ethical, legal and social implications of genetic testing.⁸

What does all this mean for the family physician?

Recently, there have been increasing numbers of patients with hemochromatosis who have been identified through family studies and population screening studies.¹⁷ Several of your patients may present to you with gene test results, or may request that you order gene tests for them.

In the absence of population screening in your area, you may enhance early diagnosis of hemochromatosis in your own practice by maintaining a high index of suspicion in patients who present with the early signs and symptoms, or who have conditions associated with hemochromatosis. [CME](#)

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