The myths and realities of hemochromatosis

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Hemochromatosis is a common genetic condition and yet there are still a number of misperceptions surrounding the diagnosis and management of this condition. Hemochromatosis affects both men and women. Typical patients do not have alcoholism or viral hepatitis, and often have normal liver enzymes. Clinical expression is highly variable. Genetic testing is widely available and particularly useful in family studies. Hemochromatosis can be readily diagnosed and treated. The purpose of the present review is to address the medical myths and misconceptions of hemochromatosis.

Key Words: *Genetic testing; Hemochromatosis; Iron*

Les mythes et les réalités de l'hémochromatose

L'hémochromatose est un trouble génétique courant, mais il existe encore un certain nombre de conceptions erronées au sujet de son diagnostic et de sa prise en charge. L'hémochromatose touche à la fois les hommes et les femmes. D'ordinaire, les patients ne sont pas alcooliques et ne souffrent pas d'hépatite virale, et leurs enzymes hépatiques sont souvent normaux. L'expression clinique de la maladie est hautement variable. Les tests génétiques sont facilement accessibles et particulièrement utiles dans le cadre d'études familiales. L'hémochromatose peut être diagnostiquée et traitée rapidement. La présente analyse vise à examiner les mythes et les conceptions erronées à son sujet.

The medical landscape is vast with an expanding array of information about old and new diseases. Thus, it becomes an insurmountable task for any physician to be up-to-date on all of the recent developments in modern medicine. For most physicians, it is acceptable to inform patients that they may not have all of the current information about their medical condition. This may lead to further study in textbooks or increasingly on the Internet, or they may seek a referral to a specialist with expertise in this area. In the present review, some of the common myths and misconceptions of hemochromatosis are explored.

HEMOCHROMATOSIS MYTHS

Hemochromatosis is rare

A large population study (1) has demonstrated that one in 227 Caucasians in North America is homozygous for the C282Y mutation of the hemochromatosis gene. This is the typical genetic pattern seen in over 90% of typical patients; however, there are many C282Y homozygotes who are asymptomatic. Approximately, 20% of male homozygotes and 50% of female homozygotes will have normal serum ferritin levels. If the disease is defined based on symptoms, the prevalence would be much lower, and because the symptoms may be nonspecific, it is more difficult to assess the prevalence of symptomatic hemochromatosis. This differs significantly between referred patients and participants in population screening studies. There has also been considerable debate about whether the genotype should be used to define hemochromatosis or whether it should be based on the presence of iron overload, independent of genotype (2). The bottom line is that this condition is extremely common within the Caucasian population and physicians should have a low index of suspicion when ordering screening tests, such as the transferrin saturation test and the serum ferritin test, for iron overload.

Women are not affected by hemochromatosis

As an autosomal recessive condition, hemochromatosis affects men and women equally in regard to the inheritance of the hemochromatosis gene. It has been considered that the effects of menses and pregnancy will significantly offset the lifelong accumulation of iron with tissue injury. A study (3) of 176 female hemochromatosis patients, matched to 176 male patients with respect to birth year, demonstrated similar hepatic iron concentrations in both sexes. However, male patients had a higher prevalence of cirrhosis compared with female patients (26% versus 14%). Cirrhosis in a female hemochromatosis patient has rarely been discovered in a population screening study. It is also important to assess women so that genetic counselling can be provided to their children and siblings.

Most hemochromatosis patients are alcoholics

The misconception that most hemochromatosis patients are alcoholics stems from the fact that most alcoholics have elevations in serum ferritin levels and some patients with alcoholic liver disease have increased iron deposition in the liver (alcoholic siderosis). This latter condition was widely reported from the Boston area in the 1960s (4) and likely 'contaminated' the hemochromatosis literature with patients who did not actually have genetic hemochromatosis. Studies (5,6) on the prevalence of alcoholism based on hemochromatosis pedigrees have shown no increased evidence of alcoholism. The genetic test for hemochromatosis remains a powerful diagnostic tool to help separate alcoholic liver disease from hemochromatosis.

Many hemochromatosis patients have chronic viral hepatitis

The prevalence of both hepatitis B virus (HBV) and hepatitis C virus (HCV) is not consistently higher in hemochromatosis

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patients. A screening study (7) that identified 302 C282Y homozygotes found one case of concomitant HCV and none with HBV. Much like alcoholic liver disease, both chronic HBV and HCV have been associated with elevations in serum ferritin levels and less commonly associated with increases in hepatic iron concentrations with advanced liver disease (8). Genetic testing is useful in this setting to differentiate hemochromatosis from iron abnormalities secondary to chronic viral hepatitis.

Diabetes is a cardinal feature of hemochromatosis

Although hemochromatosis was once called 'bronze diabetes', recent population screening studies (1,9) have not demonstrated an increased prevalence of diabetes in C282Y homozygotes compared with a control population. The pathogenesis of diabetes in hemochromatosis is likely multifactorial and can include defects in insulin secretion and insulin resistance (10,11).

Most hemochromatosis patients have elevated liver enzymes

Although liver disease is the most consistent feature of the disease, hemochromatosis is not an inflammatory liver disease and, therefore, many patients will have normal liver enzymes (12). In a review (13) of 351 C282Y homozygotes from our hemochromatosis clinic at the London Health Sciences Centre in London, Ontario, 277 of 351 (79%) patients had an aspartate aminotransferase level of less than 40 U/L and 238 of 351 (68%) patients had an alanine aminotransferase level of less than 40 U/L. It remains prudent to screen patients with unexplained enzyme elevations with transferrin saturation and serum ferritin tests.

Most patients with an elevated serum ferritin level have hemochromatosis

A population screening study (1) has demonstrated that elevation in serum ferritin levels is seen in approximately 10% of primary care patients. When these patients are investigated in a referral clinic, only 33% to 42% have genetic hemochromatosis. More common causes of increased serum ferritin levels include obesity, fatty liver and daily alcohol consumption (14).

An elevated hemoglobin is common in hemochromatosis

Some physicians have told patients that they do not have hemochromatosis because their hemoglobin levels are normal. Perhaps this is based on the concept that if iron deficiency reduces hemoglobin, iron excess could increase hemoglobin. A review of 634 C282Y homozygotes at our clinic at the London Health Sciences Centre (London, Ontario) showed a mean hemoglobin level of 145±13 g/L, which suggests that polycythemia is not a reliable marker for iron overload.

Hemochromatosis is not a cause of significant liver disease

It has been well established that with timely diagnosis and institution of iron depletion therapy, patients with hemochromatosis can be expected to have a prognosis equal to that of controls. However, among patients with severe iron accumulation, the risk of progression to cirrhosis is significant. As in other causes of cirrhosis, morbidity and mortality rates are increased due to the many associated complications of end-stage liver disease including the development of hepatocellular carcinoma. However, in the case of cirrhosis due to hemochromatosis, the incidence of hepatocellular carcinoma is significantly higher than that of many other causes of liver disease. Iron overload in hemochromatosis has also been shown to potentiate alcoholic liver disease and may have a similar effect on the course of HCV and nonalcoholic fatty liver disease (15-17). Given that 1.8% of the population in the United States are HCV-positive and that up to 24% have nonalcoholic fatty liver disease, the coexistence of these disorders with hemochromatosis is likely to affect a reasonable proportion of our population.

Carriers of the hemochromatosis gene often have iron overload

It has been common for physicians to tell patients with mild elevations in serum ferritin levels that they may be carriers of the hemochromatosis gene. Mild elevations in serum ferritin levels in the general population are very common and occur in all ethnic groups, so they are unlikely to be explained on the basis of heterozygosity for the hemochromatosis gene. A large population study (1) has now demonstrated that C282Y heterozygotes have iron studies similar to those of the general population. There is an increased prevalence of mild iron overload in compound heterozygotes (C282Y/H63D), and some C282Y heterozygotes may also carry an unidentified second mutation.

Children of hemochromatosis patients are at the highest risk of disease

The misconception that children of hemochromatosis patients are at the highest risk of disease arises because of a misunderstanding by patients and physicians of the concept of autosomal recessive inheritance. Usually a typical C282Y homozygote has heterozygous parents and so there is a higher risk for siblings. The risk is slightly higher than 25% because there is a possibility that one of the parents is a homozygote. Children of homozygotes are at a much lower risk because the partner must also carry the C282Y mutation. Among Caucasian couples, the risk to children is approximately 5% (18). Genetic testing of children younger than 18 years of age is not recommended because of a number of potential concerns about informed consent and genetic discrimination.

Genetic testing for hemochromatosis is a research tool

Genetic testing for hemochromatosis has a number of unique characteristics. Unlike most genetic diseases, in hemochromatosis there is a single genetic mutation (C282Y) that explains most typical cases. The test is widely available and can be performed at a relatively low cost. There have been a number of studies (19-21) that have assessed the psychosocial impact of genetic testing for hemochromatosis which have concluded that the test is well accepted by patients and has rarely been associated with insurance discrimination. For these reasons, the genetic test has become one of the most commonly requested tests and is a powerful diagnostic tool that is accessible to most physicians.

Hemochromatosis patients should be on a low-iron diet

Although dietary iron is the source of excess iron in hemochromatosis, a decrease in dietary iron has not been shown to decrease iron stores in hemochromatosis. All food groups contain iron and most humans will absorb only a small fraction of orally ingested iron. Iron absorption includes

components from heme and nonheme iron sources (22), and the control or lack of control over these regulatory mechanisms is incompletely understood in hemochromatosis. It has been speculated that a defect in hepcidin, a circulating peptide produced by the liver, is a fundamental defect in hemochromatosis which results in an increase in intestinal iron absorption (23). Iron supplementation of food was introduced in the 1950s as a marketing tool, and the added iron has poor bioavailability. Generally, vegetarians have lower serum ferritin levels than meat-eating patients but this does not translate into a dietary recommendation (24). The description of bacterial infections from *Yersinia* (25) and other *Vibrio* species has led to recommendations to avoid raw shellfish which may be appropriate for all patients rather than just hemochromatosis patients. Hemochromatosis patients are advised to avoid iron supplementation and large doses of supplemental oral vitamin C which may adversely affect some patients with iron overload (26).

Hemochromatosis is a progressive disease

Because hemochromatosis patients presumably begin absorbing excess iron at birth, it seems intuitive that progressive iron overload over time would occur. However, it has not been possible to show a correlation between liver iron concentration and age in hemochromatosis (27). It has become apparent through various studies, in which genetic testing was performed after many years of observation such as in the Copenhagen Heart Study (28), that many C282Y homozygotes do not have a progressive rise in serum ferritin levels, even without phlebotomy treatment. This is the most likely explanation for the discordance between the high frequency of the hemochromatosis genotype and the relatively low representation of hemochromatosis in liver transplant registries (29) or in death certificate data (30). There have been patients who have refused phlebotomy therapy and have been observed over many years to not have any changes in their serum ferritin levels. Phlebotomy therapy has never been subjected to a randomized trial. The strongest supporting evidence for a beneficial effect of phlebotomy is the improvement of liver fibrosis that has been demonstrated on serial liver biopsies in hemochromatosis patients (31). Maintenance therapy is even less established following iron depletion, and many patients will not demonstrate any evidence of iron reaccumulation after many years of observation (32). Many patients enjoy the concept of continuous therapy for hemochromatosis and these patients can be encouraged to be voluntary blood donors several times per year (33). If they are ineligible, an annual ferritin determination is a reasonable alternative to guide maintenance therapy.

SUMMARY

Hemochromatosis is a common and relatively simple genetic disease to diagnose and treat. It can be diagnosed and treated by family physicians using transferrin saturation, serum ferritin and C282Y genetic testing. Physicians who are not comfortable with interpretation of the genetic test and subsequent family counselling should refer to local specialists and try to avoid any perpetration of misinformation.

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