Screening, investigating and managing haemochromatosis

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Usually developing in patients aged between 30 and 60 years, haemochromatosis can lead to severe systemic complications if untreated. Here, Dr Watson outlines his approach to this condition.

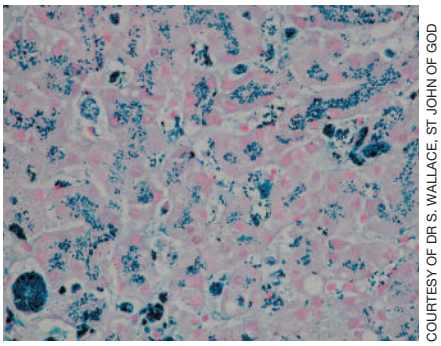

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Figure. Liver biopsy from a haemochromatosis patient with grade 4 haemosiderosis.

Remember

- Hereditary haemochromatosis is the most common inherited disease in Australia in people of Northern European descent. It is characterised by the deposition in various organs of excess iron (in the form of the iron-protein compound haemosiderin, formed by the polymerisation of ferritin). This leads to eventual fibrosis and functional organ failure.
- Great advances have been made in recent years in our understanding of the genetics of hereditary haemochromatosis, and it is now recognised as a common phenotype resulting from mutations in at least five unique genes.
- In practical terms, the commonest genotype encountered on a day to day basis is type 1 hereditary haemochromatosis arising from mutations in the *HFE* gene. *HFE* is inherited as an autosomal recessive trait. C282Y is the most common mutation in this gene and is present in about 12% of the Australian population. The H63D mutation is the next most common mutation. The frequency of C282Y homozygosity is approximately 1:300. Only individuals who are C282Y homozygous or C282Y/H63D compound heterozygous express iron overload secondary to hereditary haemochromatosis.
- An important clinical issue that has arisen with our increased understanding of the genetics of the disease is the phenomenon of incomplete penetrance. Fewer than 1% of individuals who are C282Y homozygous and even fewer of those who are C282Y/H63D compound heterozygous are thought to phenotypically express the disease. Incomplete penetrance may in part be explained by other conditions that contribute to blood loss.

Assessment

- Investigation for haemochromatosis should be performed when clinical suspicion exists (symptoms and signs are discussed below) or when relatives of an index case present for screening. Siblings of a C282Y homozygous patient have a 25% chance of C282Y homozygosity and a 50% chance of heterozygosity. Parents are almost always carriers but may occasionally be undiagnosed homozygotes and should, therefore, be screened. Children of index patients should also be screened; assuming random association of sexual partners they have about a 5% chance of being homozygous. Individuals found to be homozygous for C282Y should have blood tests for iron stores, and also liver function tests. If all the results are normal, the tests should be repeated every one to three years, depending on the person's age and sex.
- Symptoms of haemochromatosis can develop at any age but usually develop between the ages of 30 and 60 years. Symptoms include lethargy and weakness, arthralgia, loss of libido and upper abdominal discomfort. Physical examination may be normal but can reveal hepatomegaly, skin pigmentation (characteristic 'bronzed' or slate grey appearance), testicular atrophy and joint swelling and tenderness. The most commonly affected organ is the liver, but excess iron deposition can also occur in the pancreas, heart, joint synovia and anterior pituitary, thyroid, parathyroid and adrenal glands.
- It is important to check serum ferritin and iron studies in the morning, after an overnight fast. Serum ferritin concentrations are related quantitatively to total body iron, and increased concentrations are good evidence of excess iron stores. Remember, however, that serum ferritin can be raised nonspecifically in other

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inflammatory conditions. The serum iron almost always exceeds 36 mmol/L in haemochromatosis (normal range, 10 to 38 mmol/L). A transferrin saturation of greater than 60% (normal range, 15 to 58%) accurately predicts the homozygous genotype in more than two-thirds of patients presenting with hereditary haemochromatosis, and constitutes strong evidence of iron overload.

- Liver biopsy establishes the extent of liver damage and the presence of excess iron (see Figure). It remains an important diagnostic test in patients in whom hereditary haemochromatosis is suspected, but carries a morbidity of approximately 1% and a mortality of between 0.01 and 0.1%. Recent research has suggested that the combination of a ferritin level of above 1000 mg/L (normal range, males 20 to 300 mg/L, females 15 to 200 mg/L), the presence of hepatomegaly, and an aspartate aminotransferase level greater than the upper limits of normal (normal range, 5 to 55 U/L) is highly predictive of cirrhosis.

Management

- Untreated haemochromatosis can lead to severe systemic complications, including liver disease with cirrhosis or hepatocellular carcinoma, arthritis, gonadal failure, diabetes mellitus, cardiac failure and arrhythmias.
- The treatment of hereditary haemochromatosis is to remove the excess body iron. This is done by weekly phlebotomy of 500 mL of blood (which will contain approximately 250 mg of iron). As the total body iron varies from 10 to 40 g, this regimen may have to be continued for one to three years. In some patients the frequency of phlebotomy may have to be reduced if the haemoglobin level drops below 10 g/L (normal range, males 13.0 to 17.0 g/L, females 11.5 to 15.0 g/L). Serum ferritin should be monitored regularly.
- When the iron stores have been removed, reaccumulation is prevented by phlebotomy at regular intervals. As different patients reaccumulate iron at different rates, serum iron stores need to be monitored frequently for the first year after depletion was achieved. Once an acceptable phlebotomy frequency has been established, annual monitoring of serum iron stores and ferritin is appropriate.
- An iron free diet is unnecessary as the amount of iron absorbed from a normal diet is small relative to that lost by phlebotomy. However, patients should be advised against taking multivitamin preparations that contain iron or vitamin C.
- In patients with hereditary haemochromatosis in whom advanced liver disease has already developed, screening three-monthly for alpha-fetoprotein and six-monthly with ultrasound are recommended for the early detection of hepatocellular carcinoma. Orthotopic liver transplantation remains an important treatment option both in end stage liver disease and in cases of early hepatocellular carcinoma.
- Those patients with haemochromatosis who do not have cirrhosis have the same life expectancy as the normal population. Those who have already developed cirrhosis at the time of diagnosis have a 5.5-fold increased mortality. The main causes of death are hepatocellular carcinoma, liver failure, variceal bleeding, cardiac failure and the consequences of diabetes mellitus. MT

Further reading

1. Korenblat KL, Schilsky ML. Inherited metabolic liver disease. Curr Opin Gastroenterol 2003; 19: 194-202.

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DECLARATION OF INTEREST: None.