Treatment of Haemochromatosis

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***Dr Suzanne Norris says the cornerstone of treatment is phlebotomy and while a strict iron deficient diet is not necessary, iron rich foods or beverages are out.**

Hereditary Haemochromatosis (HH) is a common inherited disorder of iron metabolism, and is the most common genetic disorder in Caucasians, with a prevalence rate of 1 in 250 reported for those of Nordic or Celtic ancestry, it is perhaps no surprise that the highest frequency of C282Y alleles worldwide has been reported in the Irish population.

Data from studies performed in this country indicate that one in 80 people are C282Y homozygous; one in 25 are C282Y/H63D compound heterozygous, and one in five carry one copy of the C282Y mutation (C282Y heterozygous).Given the high prevalence of the disorder in this country, the silent accumulation of iron for many decades, and the potentially life-threatening clinical outcomes for those who remain undiagnosed , screening for the condition and early diagnosis remain a high priority.

Genetic aspects

In 1996, a candidate gene for HH was identified, the HFE gene on chromosome 6. A single mutation in the HFE gene results in the substitution of tyrosine for cysteine at amino acid 282, the C282Y mutation. A second mutation in the HFE gene results in the substitution of aspartate for histidine at amino acid 63 and is termed the H63D mutation. Homozygosity (two copies of the affected gene) for the C282Y mutation is found in 85-90 per cent of individuals of north European origin who have HH, while the H63D mutation is found in four to six per cent of patients. Compound heterozygosity (one copy of C282Y and one copy of H63D) has been reported in three to five per cent of published series.

Recent evidence suggests that other mutations, such as ferroportin, may account for those individuals who have clinical evidence of iron overload but negative genetic testing (C282Y negative genetic testing, H63D negative), as is common in northern Italy.

Clinical aspects

Clinical manifestations of HH relate to the level of iron accumulation, which is progressive with age, and thus the condition develops in a series of stages. Clinically insignificant accumulation occurs over the first 20 years of life (0-.5g parenchymal iron storage).This evolves to a stage of iron-overload without disease (approximately 20-40 years of age; 10-20g iron storage), which, if left untreated, may progress to a stage of iron overload with organ damage (older than 40 years; >20g iron storage).The degree of iron overload has a direct impact on life expectancy of the HH patient. The major causes of death are decompensated cirrhosis, HCC, cardiomyopathy and diabetes, which occur at a frequency of 10 to 119 fold higher than expected in age and sex-matched population without HH. However, survival is normal in HH patients in whom treatment is initiated before the development of cirrhosis, emphasising the importance of early diagnosis and

treatment. The commonest presenting symptom is fatigue which affects more than60 per cent of patients. Other common signs and symptoms are listed in *Box 1.*

However, not all C282Y homozygotes develop clinically apparent disease. In a population-based study of 5,000 Australians, only half of those who were homozygous had clinical features of HH, and 25 per cent had serum ferritin levels that remained in the normal range over a four-year follow-up period. This suggests that clinical expression (or phenotype) of the condition is variable and incomplete, and that despite their genetic predisposition to iron overload, some HH individuals will not accumulate iron sufficient to cause end-organ damage. Factors which influence iron absorption or accumulation are listed in *Box 2.*

Increasing evidence from varying disciplines indicates that some individuals have a greater or lesser susceptibility to develop fibrosis as a result of liver injury(profibrogenic versus antifibrogenic genotype) which may contribute to the rate of liver fibrosis and ultimately cirrhosis. However, in the absence of readily available tests to identify this subgroup of HH patients, it seems sensible to monitor all HH patients for iron accumulation on a regular basis. In addition, a four-year period is probably insufficient to judge the rate of iron accumulation, and longer follow-up would be needed to support the conclusion that the clinical penetrance of the C282Y mutation is low.

Diagnosis and Screening

The diagnosis of HH is based on biochemical evidence of iron overload (elevated serum ferritin level and serum transferrin saturation), and where indicated, characteristic liver biopsy findings with elevated hepatic iron levels. Measurement of transferrin saturation (TS) is the single best screening test. When the fasting TS exceeds 45 per cent,TS has a sensitivity of 94 per cent for the diagnosis of HH. Overnight fasting avoids circadian or postprandial variations and eliminates 80 per cent of false-positive TS results. In at least three population-based studies, a TS cutoff value of 45 per cent identified greater than 98 per cent of homozygote HH patients. However, fewer than half those with elevated TS values were homozygote for HH (positive predictive value 44 per cent), reflecting other possible diagnosis with secondary iron overload (*Box 3*).

Similar results have also been reported in the Irish setting. In a study of 330 fasting blood specimens received at the biochemical department at Portiuncula Hospital. A TS value of > 45 per cent identified all HH homozygotes (sensitivity 100 per cent, specificity 72.7 per cent).The current cost of a TS evaluation is approximately €1.70. Serum Ferritin,when used alone, has positive and negative predictive values for HH of 61 per cent and 87 per cent (where serum ferritin>300ng/ml is abnormal). But an elevated serum ferritin in combination with raised TS has a negative predictive value of 97 per cent. Thus, the message is clear : most people who are homozygous for the C282Y mutation can be reliably detected by measuring TS and ferritin(approximate total cost €5 per person).This view is consistent with the conclusions of a decision-analysis model that compared the cost effectiveness of genotyping all subjects in a blood donor population with that of genotyping only those with elevated TS values of initial screening. In one Australian study, screening by means of fasting Ts values would have averted the need for the more expensive genotyping in almost 99 per cent of the subjects with normal TS values after two measurements. Target populations for screening for HH are shown in *Box 4*. In the case of children of a known HH

patient, genotype analysis of the spouse will determine the need for mutation analysis in the children. If the spouse possesses no C282Y mutation, the children can only be heterozygous. If the spouse is heterozygous, each offspring has a 50 per cent chance of homozygous status. As organ damage has not been documented before adult life evaluation can be deferred until late teens.

The question as to whether general population screening is advisable and cost- effective is contentious.Genotypic screening (by mutation analysis of HFE gene) would be prohibitively expensive, a concern that may become less important as newer and less expensive technologies are developed. Technologies such as microarray gene analysis could allow for the simultaneous testing of a wide range of genetic mutations that could lead to iron overload. However, there is now a wealth of data confirming the sensitivity, specificity and positive predictive value of phenotypic screening tests(TS,ferritin) to support their use as baseline screening tools with subsequent genotypic confirmation offered to those with abnormal iron markers.

Some patients may need liver biopsy to assess the degree of liver injury, in particular fibrosis and cirrhosis. HH surveys in Canada and the US have reported that that women with HH with pre-treatment ferritin levels of greater than 1000 ng/ml were three times more likely to have serious liver disease , while men with pre-treatment ferritin levels of greater than 1000 ng/ ml were six times more likely to have serious liver damage.

As the iron burden in HH is progressive with age, those individuals less than forty years of age with no clinical evidence of disease (raised ALT, hepatomegaly, etc.) with serum ferritin values less than 1000 ng/ml are unlikely to have significant hepatic injury. However those with elevated ferritin levels more than 1000 ng/ml with abnormal liver enzymes, hepatomegaly or other clinical indicators of disease should be offered a liver biopsy. The presence of cirrhosis stratifies those at risk for complications of liver disease (ascites, varices, and HCC).

Treatment

The cornerstone of treatment is phlebotomy. One unit of blood (400-450mls, equivalent to 250mg of iron) should be removed once or twice weekly as tolerated and according to pre-venesection ferritin. In HH patients with total iron stores of more than 30 g iron, it may take 18-24 months to adequately reduce iron levels to the desired target of 50ng/ml. Maintenance phlebotomy to keep the serum ferritin below 50ng/ml may then be tailored to the individual by three- to- six –monthly assessment of fasting ferritin and TS. A strict iron deficient diet is not necessary but avoidance of iron- rich food or beverages is sensible. In addition, vitamin C supplements (which contain high levels of iron) should be avoided.

BOX 1: Symptoms and Signs of iron overload

Fatigue, loss of vitality
Arthralgia, arthritis (OA, chondrocalcinosis)
Sexual dysfunction (loss of libido, impotence)
Skin pigmentation
Endocrine dysfunction (diabetes,hypothyroidism)
Cardiac failure
Bone disease (osteoporosis)
Depression

BOX 2: Factors contributing to iron accumulation

Intake of iron-rich food
Intake of alcohol or other iron absorption enchancers
Blood transfusions
Gender-dependent iron loss (menstruation, child-birth)
Blood donation

BOX 3: non-HFE iron overload

Non-alcohol steatohepatitis (NASH)
HCV infection
Alcohol-related liver disease
Porphyria cutanea tarda
Thalassemia, hereditary spherocytosis
Chronic haemolytic anaemia

BOX 4: Target populations for HH screening

Asymptomatic;

First degree relative of confirmed HH

Individuals with unexplained elevation in liver enzymes

Individuals with unexplained abnormal serum iron markers

Symptomatic:

Type 11 diabetes (particularly with hepatomegaly or raised liver enzymes)

Unexplained manifestations of liver disease.

Early-onset sexual dysfunction.

Atypical cardiac disease.

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