Patients with presumed iron overload

Commentary by **LAWRIE POWELL** MD, PhD, FRACP, FRCP

Treatment of patients with an iron overload who are homozygous for the C282Y mutation is straightforward, but how does treatment differ for patients who are heterozygous for the C282Y or H63D mutation?

Case scenario

The treatment of patients with haemochromatosis and iron overload who are homozygous for the C282Y mutation is straightforward. Treatment includes venesections until patients' iron levels are reduced to within the normal range.

What is your approach to patients with presumed iron overload (e.g. ferritin levels >600 µg/L and transferrin saturation >60%) who are heterozygous for the C282Y or H63D mutation? Is the treatment endpoint for patients who are heterozygous for the C282Y or H63D mutation the same as for those who are homozygous for the C282Y mutation, or are these patients classed into different treatment subgroups?

Commentary

These are very pertinent and important practical questions. To put the answers in perspective it is appropriate to provide a little relevant background.

Haemochromatosis is a common disorder of iron storage in which an inappropriate increase in absorption of intestinal iron results in the deposition of excessive amounts of iron in the parenchymal cells. This leads to eventual tissue damage and impaired function of organs in affected patients.

The most common form of haemochromatosis in Australia is by far HFE-associated haemochromatosis, which accounts for over 95% of cases in this country (*HFE* is a gene located on chromosome 6). Haemochromatosis is one of the most common genetic disorders in populations of European extraction, although the prevalence can vary. Australia has one of the highest incidences worldwide: approximately one in 10 persons are heterozygous carriers for the common *HFE* mutation C282Y and one in 200 persons are homozygous for this mutation (two copies). Expression of the disease is modified, however, by several factors, especially alcohol consumption, dietary iron intake, blood donation and blood loss associated with menstruation and pregnancy. The clinical expression of the disease is five to 10 times more common in men than in women. The disease is rarely evident before the age of 20 years, and nearly 70% of affected patients develop their first symptoms between the ages of 40 and 60 years. Common symptoms include lethargy, arthralgia and features of diabetes. However, appropriate controlled studies have not yet been undertaken to determine whether these nonspecific symptoms are more common in patients with haemochromatosis than in the general population. Thus a high index of suspicion is needed on the part of the clinician. With family screening and periodic health examinations, however, asymptomatic patients with iron overload (including young menstruating women) can be identified.

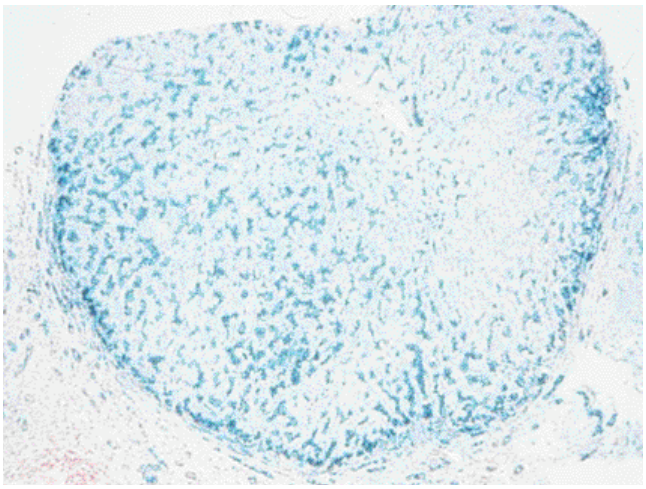

Figure. An advanced stage of cirrhosis in a patient with haemochromatosis.

Recent studies in non-blood bank populations have revealed that at least 30% of homozygous individuals do not have evidence of iron overload. The penetrance of the mutation is, therefore, very variable. Indeed most population studies have shown that approximately 70% of men who are homozygous for the C282Y mutation have an elevated serum ferritin level compared with 30 to 40% of homozygous women. However, only about 20% of all homozygous patients have significant elevations of hepatic iron levels, and fewer than 10% of homozygous patients will develop cirrhosis or other complications, including arthritis, diabetes and cardiomyopathy (see Figure). The factors that determine expression in homozygous patients are unclear, but include the factors mentioned above, in addition to as yet undetermined genetic modifiers.

A second more minor mutation of the *HFE* gene (H63D) has also been described. H63D and C282Y do not occur together on

Professor Powell is Professor of Medicine, University of Queensland, and Director of Research, Royal Brisbane and Women's Hospital, Herston, Brisbane, Qld.

the same chromosome so a person might have one copy of either mutation, two copies of either mutation or one copy of each (known as a H63D/C282Y compound heterozygote). The H63D mutation is quite common in populations of European extraction: approximately 20 to 25% of individuals have a single copy and 5 to 10% of individuals have two copies.

The statements that follow specifically answer the questions raised above.

- Patients who are heterozygous for the C282Y mutation might have slight elevations in levels of serum ferritin or a high percentage of plasma transferrin saturation, but do not develop progressive iron overload and need only reassurance that they will not suffer any consequence of having the genetic mutation.
- Patients with the H63D mutation (one or two copies) might have some elevation in levels of serum ferritin and/or a high percentage of plasma transferrin saturation, but again do not require venesection because they will not develop progressive iron overload.
- Patients who have one copy each of the C282Y and H63D mutation (compound heterozygotes) might develop progressive iron overload, but to a lesser degree than patients who are homozygous for the C282Y mutation. It is common practice to venesect such patients until iron levels are within the normal range as determined by measurement of serum ferritin levels. Venesection is performed on a regular basis (for example, weekly) until serum ferritin levels fall to within the normal range and preferably under 100 μg/L to ensure that all excess iron is removed from the liver. Serum ferritin levels should be measured every one or two months during active venesection therapy, but only approximately once or twice per year thereafter.

It is important to emphasise that all of the patients included in the above statements are ideal candidates for blood donation if there is no contraindication. This should be kept in mind when advice is given to them as Australia uses blood from individuals with haemochromatosis for blood transfusion. Since blood is urgently required, it is a shame to see such 'normal' blood thrown away after venesections. MT

Further reading

1. Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, eds. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill; 2005.

DECLARATION OF INTEREST: None.