Prevention of organ failure in hereditary haemochromatosis

J.J.M. Marx

Eijkman-Winkler Centre for Microbiology, Infectious Diseases and Inflammation, University Medical Centre Utrecht, G04.614, PO Box 85500, 3508 GA Utrecht, the Netherlands, tel.: +31 (0)30-250 73 94, fax: +31 (0)30-254 17 70, e-mail: jmarx@azu.nl

ABSTRACT

In this editorial the dominant sites of organ manifestations in hereditary haemochromatosis are discussed as well as conditions that can occur as a result of iron-mediated manifestations: liver disease, diabetes mellitus, arthritis, and cardiomyopathy. The incidences of these organ manifestations and their well-known typical symptomatology are mentioned, in order to investigate hereditary haemochromatosis as a possible (missed?) cause of the chronic fatigue syndrome. In particular the limitations of most studies about the prevalence of hereditary haemochromatosis in patients with the chronic fatigue syndrome are clearly summarised.

Hereditary haemochromatosis (HH) is a common genetic disorder in subjects of European descent which causes end-organ damage as iron overload progresses. Important end organs are the liver, pancreas, joints and heart. In addition, other endocrine organs and the vascular endothelium should be considered as sites for iron-mediated damage.

Many investigations have revealed detailed knowledge of organ damage in advanced haemochromatosis. A timely diagnosis is important as early treatment will lower mortality and improve the quality of life. Clinical and pathological findings are not always specific for HH, which is why clinicians often miss the correct diagnosis and fail to treat patients with phlebotomy. In a large international study among 2851 haemochromatosis patients it was found that the mean age of symptom onset was 41 years, while the mean age of diagnosis was 50 years. This means that physicians could have diagnosed the disease much earlier, and in many cases prevented irreversible organ damage. The most common symptoms were extreme fatigue (46%), arthralgia (44%), loss of libido (26%), skin bronzing (26%), heart fluttering (24%), depression (21%), and abdominal pain (20%). The reasons for performing relevant laboratory tests were symptoms (35%), an abnormal laboratory test (45%) or diagnosis of HH in a family member (20%).

The problem with most ‘typical’ symptoms of HH is that they are common in the general population, in particular among the elderly in whom symptoms of advanced haemochromatosis may also become manifest. Several studies reported no significant difference in fatigue frequency between the general population and haemochromatosis patients. On the other hand, many patients with symptoms ascribed to haemochromatosis improve dramatically after and even during phlebotomy treatment. Current knowledge about clinical manifestation of HH is mostly based on reports from referral centres, and favourable therapeutic effects are biased by a positive interpretation by patients as well as physicians. To find out whether common clinical manifestations are aetiologically related to HH, rigorous population-based studies are needed, including a control population that is not biased by overrepresentation of pathological symptoms (study in a clinical setting) or of healthy subjects (screening of asymptomatic adults or blood donors).

In this issue of the Journal a group from Nijmegen, investigating the importance of fatigue as a haemochromatosis symptom, followed an interesting approach.
They tested the hypothesis that there are many undiagnosed haemochromatosis patients among subjects with chronic fatigue syndrome (CFS). In a group of 88 CFS patients no overrepresentation of haemochromatosis patients could be found. The studied population, however, might have been too small to reach any significant results, and some bias was introduced because fatigue patients in whom haemochromatosis was already detected could not qualify for the diagnosis of CFS and were not included in the study. Following a different approach, an Irish group demonstrated the non-specific nature of fatigue as an early symptom of HH. They investigated 30 HH probands (all C282Y homozygous) and 79 C282Y homozygous family members. For identification of so many probands it would have been necessary to screen between 7000 and 9000 individuals. The percentage of subjects with fatigue was higher in probands compared with HH family members, and also higher in family members with iron overload compared with those with (as yet) normal iron parameters. A significant difference with respect to fatigue could only be established between female probands (100%) and homozygous female family members with iron overload (43%), p=0.041.

Previous investigators chose an approach similar to the group from Nijmegen to detect haemochromatosis among patient groups with typical end-organ damage. The problem with the association of liver disease, diabetes, joint complaints and cardiomyopathy with HH is that there are – similar to fatigue – so many other causes for such disorders, some of which even more frequent than HH. It is, therefore, important to know what proportion of liver disease, diabetes, joint disorders and cardiomyopathy can be attributed to HH.

LIVER DISEASE

Accumulation of iron in hepatocytes occurs early in the development of haemochromatosis, followed by leakage of aminotransferases, and finally cirrhosis, which is an important risk factor for hepatoma. Investigations on the prevalence of HH in liver disease may focus on one of these entities. There is a controversial relation between haemochromatosis and alcoholism, as in some studies patients with siderosis related to alcohol or to cirrhosis are interpreted as HH. Quantification of total liver iron and recognition of typical pathological features of alcohol misuse can solve this problem. Chapman and co-workers found the following mean values for liver iron concentration (g/100 mg dry weight): 156 in 60 alcoholics, 2095 in 15 patients with untreated HH, and 53 in 16 controls with biliary tract disease. The prevalence of haemochromatosis in asymptomatic patients (n=149) with moderately but persistently elevated activities of serum aminotransferases was studied by Hultcrantz and co-workers. The causes were 64% fatty liver, 20% chronic hepatitis, 6% cirrhosis, 4% α1-antitrypsin deficiency and 3.5% haemochromatosis.

Tissue iron was studied histologically and chemically in 447 cirrhotic livers. Despite the fact that a positive iron staining was reported in 32.4% and increased chemical hepatic iron concentration in 20.3%, including 8.5% in the haemochromatosis range, homozygous HH was detected in only 1.1%.

The most important complication of HH, once cirrhosis has developed, is hepatocellular carcinoma (HCC), which can also occur long after effective phlebotomy treatment. Worldwide, chronic hepatitis C and B are the main causes of HCC. As the distribution of these forms of hepatitis is unequal in northern and southern Europe, this situation will highly influence prevalence numbers of haemochromatosis in HCC. A German study revealed that in 100 consecutive patients with HCC, only 2% had HH. In a French study from the department of Calvados, among 213 patients with HCC, 4.7% had HH.

DIABETES MELLITUS

Diabetes mellitus (DM) type 2 has been recognised as a complication of HH for many years now. It may be a result of iron accumulation in pancreatic islands and/or of HH-associated cirrhosis of the liver. Although the frequency of diabetes is high in advanced stages of iron overload, it may also occur in non-cirrhotic HH patients.

Of larger studies in patients with diabetes mellitus only a few allow conclusions to be drawn regarding the prevalence of HH in patients treated for DM. One group found a high prevalence of HH in DM of 1.34%, advocating case finding in diabetics, while another reached the opposite conclusion, finding only 0.42% subjects with HH. In a meta-analysis of 2630 type 2 DM patients no significant association between C282Y mutation homozygosity and diabetes was found. A large Danish investigation on the prevalence of HH in late-onset type 1 DM, including 716 unselected patients and 9174 controls from the general Danish population, performing HFE genotyping of all these subjects, revealed that more patients with diabetes than controls were homozygous for the C282Y mutation (odds ratio 4.6; 2.0-10.1, p=0.0001). In a study by Chapman and co-workers, apparently there is no consensus on the frequency of HH in subjects with DM. However, there is no uniformity in the criteria for HH and type of DM. Often, screening for...
HH is performed by serum iron concentration, transferrin saturation, serum ferritin, and/or genotyping. Subjects with suspected values were usually screened twice, and were further investigated by assessment of liver iron accumulation, which is often refused despite suspicious liver enzymes. Along the road several subjects are lost for more precise evaluation, and as a consequence the frequency of HH in DM populations seems to be underestimated. To allow scientific conclusions a population screening should include serum ferritin, serum iron saturation and HFE mutation detection.

**ARTHROPATHY**

Arthropathy is a common finding in HH, and arthritis is often the presenting symptom. The incidence of joint disease in haemochromatosis is estimated to be more than 50%, and even 63% in another study. In an Italian study of 32 HH patients radiological signs of arthropathy were observed in 81.3% of the cases. Evaluation of about 5000 German patients referred to a rheumatology outpatient clinic detected 11 with typical signs of haemochromatotic arthropathy. In all subjects the diagnosis of HH was missed for several years. In an Australian study 339 consecutive patients, attending a rheumatology clinic, were screened for iron overload. Twelve patients (3.5%) had persistently high transferrin iron saturation values and high serum ferritin concentrations.

Although arthropathy is well recognised as a leading symptom, its prevalence in HH is probably biased by the population studied as many publications come from departments of rheumatology.

**CARDIOMYOPATHY**

Cardiomyopathy with cardiac arrhythmias and congestive heart failure occurred in about one third of HH patients described in early studies. In more recent investigations a much lower incidence has been reported, for example 2.4% and 1.8%. Cardiomyopathy complicates advanced iron storage, and phlebotomy treatment ameliorates cardiac pathology. It remains, however, an important cause of death in HH. In a study on mortality rates in the US for the years 1979 to 1992 for all records listing haemochromatosis, decedents with haemochromatosis were five times more likely to have cardiomyopathy than decedents without haemochromatosis. Conversely, decedents with cardiomyopathy were also five times more likely to have haemochromatosis than those without cardiomyopathy.

Information on prevalence of HH in patients with cardiomyopathy comes from Sweden. Serum ferritin was determined in 232 men with a permanent pacemaker. Iron overload of the liver was found in three men (1.3%).

In a study of 462 endomyocardial biopsies performed in patients with native heart disease 65.5% were abnormal. In two subjects (0.4%) haemochromatosis was found. The only study that could be found which tried to determine the prevalence of HH in patients with symptoms that can be related to cardiomyopathy comes from Sweden. Serum ferritin was determined in 232 men with a permanent pacemaker. Iron overload of the liver was found in three men (1.3%).

**CONCLUSION**

Most studies reporting the prevalence of HH among patients with chronic fatigue and symptoms of end-organ damage do not allow solid conclusions for several reasons:

- There is no conformity in diagnostic criteria for HH; only investigations published after 1996, when the HFE gene was detected, can use valid genetic criteria.
- Genotyping for HFE is necessary but will not detect 15% (northern Europe) to 50% (southern Europe) of patients with primary haemochromatosis phenotypes, who have mostly unknown mutations of other genes.
- The investigators often do not detect early and mild phenotypic expression of HH.
- On the other hand, if there is no advanced disease in a subject identified as having HH, then there should be no causal relation with manifestations of end-organ damage.
- The epidemiology of other causes of organ damage (e.g. use of alcohol, hepatitis) has an important effect on the relative prevalence of HH manifestations, which will highly influence the outcome of studies in different populations.
- Variables of iron metabolism can be influenced by inflammation and cellular damage related to the specific disorder, and comorbidity of other causal factors may occur.
- Large numbers of patients, with appropriate controls, should be studied because ‘typical’ symptoms and signs of HH, and related end-organ damage, have many other causes, while patients with detectable homozygous HH organ damage are scarce.

The aim of the diagnostic strategy in haemochromatosis should be prevention of end-organ failure leading to
morbidty and early mortality. A negative outcome of inconclusive investigations that tries to link signs and symptoms of HH to objective laboratory criteria for HH should not frustrate physicians' awareness and willingness to initiate necessary laboratory tests.

REFERENCES