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EDITORIAL

Hereditary haemochromatosis

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In the current issue of the Netherlands Journal of Medicine, some new developments in the field of hereditary haemochromatosis (HH) are discussed. Swinkels *et al.* publish the recently developed guidelines for diagnosis and management of HH on behalf of the Dutch Institute for Healthcare Improvement, the CBO.[1] Jacobs *et al.* review changing aspects of *HFE*-related HH[2] and report the results of family screening.[3] HH is one of the most common inherited disorders with an autosomal recessive inheritance pattern. Initial clinical symptoms are relatively aspecific, making it difficult to recognise them as related to iron overload. In later stages, disease manifestations may include arthropathy, diabetes mellitus, hypogonadism and other endocrinopathies, liver cirrhosis, cardiomyopathy, skin pigmentation, and in cirrhotic patients, increased susceptibility to liver cancer. Early diagnosis and therapeutic phlebotomy can prevent the development of tissue damage, reducing morbidity and mortality, and providing long-term survival similar to the general population. Unfortunately, vague symptoms such as athropathy and tiredness often persist after therapy.

In 1996, Feder *et al.* identified the haemochromatosis *(HFE)* gene (previously called HLA-H gene). They attributed the most common form of HH to homozygosity for the C282Y sequence variation of this gene. Since then, it rapidly became clear that the situation was much different than previously thought: despite its remarkably high prevalence C282Y homozygosity was characterised by relatively low penetrance. Recent surveys involving *HFE* genotyping of nonclinically selected populations found that a large number of C282Y homozygotes had no symptoms of disease. Heterogeneity of clinical presentation, even within families, is reported, suggesting that there is a role for other unknown genetic and environmental factors.

HFE genotypes other than C282Y homozygosity rarely cause clinically significant iron overload. C282Y heterozygotes usually do not develop iron overload unless they have associated conditions, such as environmental factors (alcohol, viruses, hepatic disease) or variant forms of other genes. A particular group of *HFE* genotypes consists of persons who are compound heterozygous for C282Y and H63D. These individuals have been described as being at higher risk to develop iron overload, but generally in a much milder form than in C282Y homozygotes. However, given the fact that the clinical penetrance of C282Y homozygosity is low, compound heterozygotes with clinical disease will be scarce. A third sequence variant, S65C, with an allele frequency as low as 1.6 to 2.0%, was found to exert a consistent but small effect on serum iron indices, particularly when present in combination with other *HFE* genotypes, such as C282Y and H63D.

The molecular function of HFE in iron metabolism has long been attributed to the *crypt hypothesis*. However, it is mainly since the discovery of hepcidin that the crypt model has been replaced by the *hepcidin model* as the prevailing hypothesis. The recently identified β-defensin-like antimicrobial peptide hepcidin is thought to be the long-anticipated regulator that controls iron absorption and macrophage iron release. Hepcidin is synthesised in the liver when changes occur in body iron needs, such as in anaemia, hypoxia and inflammation, and is secreted in the circulation. Recently, light was also shed on how hepcidin exerts this regulatory function; it was reported to counteract the function of ferroportin, a major cellular iron-exporter protein in the membranes of macrophages and the basolateral site of enterocytes, by inducing its internalisation and degradation. Sequence variations in *HFE* were shown to lead to inappropriately low concentrations of hepcidin, suggesting that *HFE* is involved upstream in the regulation of hepcidin expression. In the future, determination of hepcidin might be a valuable tool in the diagnosis of atypical cases of anaemia and haemochromatosis.

According to the guideline, elevated serum ferritin in combination with transferrin saturation (TS) above 45% is suggestive of the presence of primary iron overload. Discussion is going on about the exact reference values, due to the different populations examined and the variability of normal ferritin values between laboratories. Unfortunately,

an increasing number of patients undergo molecular testing just because plasma ferritin *or* TS is increased. Often this leads to an unnecessary search for hereditary defects in individuals with various common, nonhereditary conditions that are characterised by similar abnormalities in serum ferritin and/or TS, such as hepatitis, excessive alcohol consumption and secondary forms of iron overload. There is increasing evidence concerning the relation between elevated serum ferritin levels and the metabolic syndrome, but the pathophysiology and clinical consequences are not clear yet. In these cases TS is generally normal.

The gold standard for diagnosis of liver iron overload remains a liver biopsy. According to the guideline (which is mainly expert-opinion based) a liver biopsy is indicated in the following cases: 1) elevated liver enzymes in combination with HH and 2) serum ferritin above 1000 µg/l. A relatively new diagnostic tool for the presence and severity of iron overload is magnetic resonance imaging (MRI). In case of elevated ferritin levels in the absence of homozygosity for C282Y / compound heterozygosity for C282Y/H63Asp hepatic iron quantification with MRI might be helpful. However, consensus has not been reached yet regarding the technique or the possibility to reproduce the same method of calculus in different machines. Of course, the advantage of a biopsy is that histology may show cirrhosis and fibrosis, which may change the prognosis of the patient.

Treatment of HH is relatively simple, reducing iron accumulation by phlebotomy. With removal of 500 ml of blood, 200 to 250 mg iron is removed from the body. Treatment starts with intensive phlebotomy, weekly phlebotomy until a serum ferritin level of 50 µg/l is reached. Thereafter it is not clear whether one should hold on to a ferritin level of 50 µg/l or a higher level. Red cell apheresis is considered to be an alternative procedure; it is suggested that it removes excess iron twice as fast as manual whole blood phlebotomy. Currently this method is being evaluated as treatment of HH in the Netherlands.

It is suggested that the majority of relatives found to be homozygous for the C282Y mutation will have biochemical evidence of iron overload and 10 to 38% may have HH-associated liver disease or arthropathy. Siblings of a subject homozygous for the C282Y mutation have a one in four chance of inheriting the same mutation if both parents are heterozygous, or a one in two chance if one parent is homozygous and one is heterozygous. Therefore, family screening has been proposed, since this has proven efficacy in the detection of latent homozygotes for frequent recessive mutations. In the Hemochromatosis Family Study (HEFAS) study Jacobs *et al*. describe that morbidity among first-degree family members of C282Y-homozygous probands previously diagnosed with clinically proven HH is higher than that in an age- and gender-matched normal population.[3]

For clinicians, the challenge is now to diagnose *HFE*-related HH before irreversible tissue damage appears and at the same time to distinguish HH from increasingly common diseases that lead to only moderately increased body iron stores, such as the metabolic syndrome. The other challenge is to optimally use both conventional and innovative laboratory tests to differentiate between the various causes of iron overload. After initial clinical and laboratory investigations and exclusion of acquired causes of hyperferritinaemia, atypical patients should be referred to specialised centres that can perform investigations with an up-to-date, targeted approach. However, the strategy proposed may change in time with advances in noninvasive techniques for the assessment of hepatic iron and tissue damage, the availability of hepcidin measurements in both urine and serum, and the identification of new key players in iron homeostasis.

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