Hereditary Hemochromatosis Types 1, 2, and 3

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Hereditary hemochromatosis (HH) is now recognized to comprise a number of inherited disorders that can lead to progressive iron loading. Patients with excessive iron loading are at risk of developing cirrhosis, hepatocellular cancer, cardiomyopathy, diabetes mellitus, hypogonadism, and arthropathy.¹ Advances in molecular testing have allowed better refinement of the underlying genetic defects that cause iron overload disease. The classification of these disorders is now largely based on the nature of this genetic defect.

Mutations in the *HFE* gene (type 1) are responsible for the majority of cases of hemochromatosis. Although the prevalence of the C282Y mutation in the *HFE* gene is common in Caucasian populations, the penetrance and clinical expression of the disease is highly variable.² This variation is attributable to other genetic factors as well as exposure to environmental factors that increase the risk of liver injury—particularly alcohol, viral hepatitis, and nonalcoholic fatty liver disease. The diagnosis of HH is usually straightforward. A high index of suspicion is required in patients with symptoms related to iron overload, and subsequent testing for transferrin saturation and serum ferritin concentration may reveal elevations in either or both of these two parameters. If either of the two indices is elevated, genetic testing for mutations in *HFE* is warranted. An elevated serum ferritin is seen in many other conditions and is often present in patients with nonalcoholic fatty liver disease or alcohol-related liver injury—presumably due to necroinflammation. Systemic inflammatory diseases and various neoplastic processes can also be associated with an elevated serum ferritin concentration. Usually the transferrin saturation is within normal limits in these situations. The serum ferritin concentration in non-alcoholic fatty liver disease only occasionally is $>1000 \mu\text{g/L}$. If genetic testing reveals no apparent mutations, then the diagnosis of iron overload is unlikely, and the serum ferritin falls with risk factor modification. A serum ferritin concentration of $>1000 \mu\text{g/L}$ in patients with type 1 HH is associated

with a much higher risk of advanced fibrosis and cirrhosis, and patients with this degree of liver injury are at a markedly increased risk of hepatocellular carcinoma.³ Thus, some assessment of the extent of fibrosis is warranted in these patients, as HCC surveillance may form an important element of their ongoing management plan. The indications for liver biopsy in HH are well established. Prior to the identification of the genetic defects, liver biopsy with concomitant Perls staining and measurement of hepatic iron concentration was an important component of the diagnostic strategy. The widespread availability of *HFE* testing has largely replaced liver biopsy as a diagnostic tool, and the conduct of liver biopsy is usually to determine the extent of fibrosis. Serum ferritin is the single most important predictor of cirrhosis and is recommended in patients if the serum ferritin concentration is $>1000 \mu\text{g/L}$.⁴ The role of noninvasive strategies such as serum biomarkers, including hyaluronic acid and transient elastography, is yet to be fully clarified; however, both strategies are promising alternatives that may further obviate the need for liver biopsy in many patients.⁵ Although the evidence base for treating patients with only modest iron burdens is limited, it is generally accepted that all patients with HH type 1 should commence phlebotomy once the serum ferritin exceeds the normal range. In the initial stages, phlebotomy is conducted on a weekly to fortnightly basis to bring serum ferritin concentration into the range of $50\text{--}100 \mu\text{g/L}$.⁴ Maintenance venesection to keep the serum ferritin concentration within this range follows. The frequency of venesection varies between individuals depending on the penetrance of the disease, sex, and other factors. Occasionally venesection requirements may reduce even in the absence of identified blood loss, and the basis for this observation is unexplained.

Type 2 hemochromatosis or juvenile hemochromatosis is subclassified into type 2a, which is associated with mutations in hemojuvelin, and type 2B, which is associated with mutations in hepcidin.⁶ Both conditions can present before

Abbreviation: HH, hereditary hemochromatosis.

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the third decade, and affected patients are at high risk of developing target organ damage, including cardiomyopathy. Although often more severe, the phenotype of type 2 HH closely resembles that of type 1, since both conditions are associated with reduced expression of the master iron regulatory protein hepcidin.⁷ Both conditions are inherited as autosomal recessive traits, with increased transferrin saturation and serum ferritin and parenchymal iron deposition. The response to phlebotomy is excellent.⁶

Type 3 HH is characterized by mutations in transferrin receptor 2. The clinical presentation closely resembles that of HH type 1. The onset of organ dysfunction usually occurs in the fourth decade. The rate of disease progression and overall phenotype therefore is less severe than type 1 disease. Iron loading is parenchymal in nature, and progression to cirrhosis has been documented in some cases. Response to phlebotomy is excellent.⁸

Once a patient with hemochromatosis types 1, 2, and 3 has been identified, family screening of all first-degree

relatives should commence. It is recommended that biochemical and genotypic analyses be performed. If the genetic basis of the iron loading can be characterized, the testing of the other parent may preclude the need for further testing in offspring of probands. If the other parent's test is normal, then the child is an obligate heterozygote, and no further testing is required.

In summary, this brief review aims to translate recent genetic discoveries into a clinical context and provide the practicing clinician with some guidance on the common clinical questions that arise when caring for patients with disorders of iron overload. A high index of suspicion, incisive knowledge of diagnostic strategies, awareness of the range of genetic mutations that can be associated with iron overload, and a common sense approach to management are the hallmarks of quality care of affected patients.

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