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Revisited Haemochromatosis

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Abstract

Haemochromatosis is a genetic disease caused by hepcidin deficiency, responsible for an increase in intestinal iron absorption. Haemochromatosis is essentially associated with homozygosity for the *HFE* p.Cys282Tyr mutation. However, rare cases of haemochromatosis (non-*HFE* haemochromatosis) can also be caused by pathogenic variants in other genes (such as *HJV*, *HAMP, TFR2*, and *SLC40A1*). A working group of the international society for the study of iron in biology and medicine (BIOIRON Society) concluded that the classification based in different molecular subtypes is difficult to be adopted in clinical practice and proposed a new classification approaching clinical questions and molecular complexity. The aim of the present review is to provide an update on classification, pathophysiology, and therapeutic recommendations.

Keywords: haemochromatosis; iron overload; *HFE*; molecular diagnostic; hepcidin.

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Core Tip: Haemochromatosis is a genetic disease caused by hepcidin deficiency, responsible for an increase in intestinal iron absorption. Haemochromatosis is essentially associated with homozygosity for the HFE p.Cys282Tyr mutation. However, rare cases of haemochromatosis (non-HFE haemochromatosis) can also be caused by pathogenic variants in other genes (such as HJV, HAMP, TFR2, and SLC40A1). A working group of the international society for the study of iron in biology and medicine (BIOIRON Society) concluded that the classification based in different molecular subtypes is difficult to be adopted in clinical practice and proposed a new classification approaching clinical questions and molecular complexity. The aim of the present review is to provide an update on classification, pathophysiology, and therapeutic recommendations.

INTRODUCTION

Haemochromatosis is characterized as systemic iron overload of genetic origin caused by hepcidin deficiency, including decreased production of this hormone or decreased activity of hepcidin-ferroportin binding (1) (Figure 1). Iron overload leads to damage such as liver cirrhosis, cardiomyopathy, diabetes, arthritis, hypogonadism and skin pigmentation. However, the treatment, therapeutic phlebotomy, is efficient and safety (2). Iron chelation, mostly confined to iron overload related to chronic anaemias needing repeated transfusions, is exceptionally an alternative treatment (or adjuvant) in haemochromatosis, especially when phlebotomies are medically contraindicated (3) or iron overload is so massive that iron depletion is urgently needed.

Mostly, the disease is related to homozygosity for the gene *HFE* p.Cys282Tyr genetic alteration (which is a classical type 1 haemochromatosis). But p.Cys282Tyr/p.His63Asp compound heterozygosity has been reported to be linked to haemochromatosis. Rarely the cases of haemochromatosis can be caused by pathogenic variants in the other genes (called non-*HFE* haemochromatosis). Juvenile haemochromatosis corresponds classically to type 2, which can be subdivided into type 2A, that is related to mutations in the hemojuvelin gene, and type 2B, related to mutations in the hepcidin gene. Furthermore, mutations in the *TFR2* and *SLC40A1* genes can be associated to haemochromatosis (more details below) (4).

The clinical diagnosis of iron overload is of course the starting point before treating and monitoring the patient. Early diagnosis and treatment are essential for improving survival and for a better quality of life (5). The present review focuses on new information on classification, pathophysiology, and therapeutic recommendations.

CONCLUSION

It is strongly proposed to adopt, from now on, this new and more relevant classification of haemochromatosis which can be easily shared between practicing doctors and

reference centers and will contribute to facilitate the diagnosis and therefore to improve the therapeutic management of haemochromatosis patients.

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