DIAGNOSTIC AND TREATMENT OF INHERITED HAEMOCHROMATOSIS

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The management of haemochromatosis has recently benefited from major improvements on both diagnostic and therapeutic sides.

The New Spectrum of Haemochromatosis

Haemochromatosis can be defined as chronic iron overload of genetic origin. Although the most frequent form remains, by far, HFE related haemochromatosis (C282Y/C282Y or type 1 haemochromatosis), several other entities have been identified : i) Juvenile (or type 2) haemochromatosis with 2 subtypes, subtype A due to mutations of the hemojuvelin gene and subtype B due to mutations of the hepcidin (or HAMP) gene ; ii) Type 3 haemochromatosis due to mutations of the transferrin receptor2 gene ; iii) Type 4 haemochromatosis also named ferroportin disease, due to mutations of the ferroportin gene. It is the only form of haemochromatosis with a dominant pattern of inheritance. It has 2 subtypes: subtype A whose phenotype is characterised by normal plasma transferrin saturation and predominant iron deposits within macrophages, and subtype B which mimicks type 1 (or type 3) haemochromatosis ; iv) Hereditary aceruloplasminemia characterized by low transferrin saturation, anemia and neurological symptoms.

New Diagnostic Aspects

The diagnostic management of haemochromatosis is essentially based on a non invasive approach.

The clinical background remains an essential prequisite for suggesting haemochromatosis. Potential symptoms are miscellaneous and diversely associated: chronic asthenia, arthropathy, hepatomegaly, diabetes, impotence, skin hyperpigmentation, osteoporosis, cardiac symptoms, etc.

Increased plasma ferritin level (>300µg/L in men, >200µg/L in women), checked on the basis either of suggestive clinical symptoms or of a systematic biochemical check-up, is the major biological parameter indicating the possibility of iron excess. Hyperferritinemia must, however, be interpreted with caution before accepting that it directly reflects iron excess, due to four possible confounding situations: i) major inflammatory syndrome (as expressed by pronounced CRP increase); ii) major hepatic cytolysis (as expressed by marked serum transaminase increase); iii) the polymetabolic syndrome: in this setting, characterized by, more or less, increased body mass index, increased blood pressure, non insulin dependent diabetes, hyperlipidemia, hyperuricemia, serum ferritin levels are often increased (500-1000µg/L) contrasting with normal transferrin saturation (<45%) and mild visceral iron excess (in marked contrast with the degree of hyperferritinemia); iv) alcoholism: interest of controlling especially the absence of macrocytosis and of elevated plasma GGT activity.

Plasma transferrin saturation is a pivotal parameter for diagnosing the haemochromatosis type. It is markedly elevated (usually >60% in men, and 50% in women) in types1, 2A, 2B, 3, and 4B haemochromatosis whereas it is normal or low in type 4A haemochromatosis and in hereditary aceruloplasminemia.

Hepatic and splenic MRI (Magnetic Resonance Imaging) is a valuable procedure for the following two main reasons : i) it directly visualizes and quantifies visceral iron excess ; ii) it indicates the respective involvement of liver and spleen, which provides an important clue to the etiology of haemochromatosis (in type 4A haemochromatosis – i.e. the usual form of ferroportin disease- iron deposits touch essentially the macrophages and therefore the spleen at variance of the other types of haemochromatosis where iron overload concerns essentially parenchymal cells, i.e. the liver and at a lesser degree the pancreas.

Genetic testing, performed from blood, cheek-brush or saliva samples, is of course the key step for identifying haemochromatosis. The following strategy can be adopted in practice for an efficient diagnostic process: i) in case of iron overload with increased transferrin saturation: to look first (especially in Caucasian individuals) for C282Y homozygosity (=C282Y/C282Y) which proves type1 haemochromatosis ; if there is no C282Y homozygosity, the genetic search must be followed in a young patient (<30 years old) by mutations of hemojuvelin and hepcidin genes (=types 2A and 2B haemochromatosis, respectively); in an older patient, to look for mutations of the ferroportin gene (= subtype B ferroportin disease) and, if negative, for mutations of transferrin receptor2 gene (=type 3 haemochromatosis); ii) in case of iron overload with normal or low transferrin saturation, after having ruled out hereditary aceruloplasminemia by simply verifying that plasma ceruloplasmin level is normal, the genetic search must concern mutations of the ferroportin gene for diagnosing subtype A ferroportin disease.

The place of liver biopsy has become very limited, mainly confined to the search of iron-related cirrhosis, which –once diagnosed- requires a special follow-up (by checking every 6

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months serum alpha-foetoprotein and hepatic echography) in order to detect an emerging hepatocellular carcinoma. In practice, liver cirrhosis should be suspected whenever serum ferritin is >1000µg/L and/or there is hepatomegaly and/or there is transaminase increase. In fact, even for this purpose, liver biopsy might, in the near future, be replaced by non invasive approaches for predicting hepatic fibrosis, using various isolated or combined blood parameters and/or hepatic elastography.

New Therapeutic Aspects

Family Screening

All these genetic diseases require family screening once the diagnosis has been done in a given family member (=the proband). This screening is at best performed by specific structures devoted to contact the members (through the proband in France), and to explore, mainly through general practitioners, their iron and genetic status. For this screening, the exploration of ferroportin disease is peculiar since it is the only form of genetic haemochromatosis with a dominant mode of transmission.

Iron Overload Treatment

Venesections remain the main therapeutic approach. The practical management of phlebotomies has been recently revisited in France. Although it was specifically proposed for type1 (= "classical") haemochromatosis, it may be valid for every other type of haemochromatosis requiring venesections (i.e. corresponding to haemochromatosis forms in which iron excess is related to hepcidin deficiency). Briefly, venesections are indicated when serum ferritin levels are above the upper normal limits (300µg/L in men, 200 µg/L in women); the recommended substracted volume per venesection is 7mL/kg body weight (without exceeding 550mL); phlebotomies are performed usually on a weekly basis, with serum ferritin being checked every month until ferritin levels reach the upper normal limits, and bimonthly thereafter until the level is ≤50µg/L. During maintenance therapy (one phlebotomy every 1 to 4 months according to the patients), ferritin should remain ≤50µg/L. Whether, in case of maintenance treatment for type1, 2, 3 or 4B haemochromatosis, transferrin saturation should also be periodically checked remains debated. It may be useful to check twice a year this parameter in order to ensure that its value remains <75%, a threshold above which there is appearance of plasma non-transferrin bound iron (which is a potentially toxic iron species).

Therapeutic Perspectives

Oral chelation. The new once-daily oral chelator deferasirox (Exjade®) may be especially useful in case of haemochromatosis with low transferrin saturation, given the risk of anemia under phlebotomy (ferroportin disease subtypeA) or pre-existing anemia contra-indicating venesections (hereditary aceruloplasminemia). In type1, 2 and 3 haemochromatosis, deferasirox could be useful, alone or as an adjunct to venesections (in case of poor venous or psychological tolerance). Preliminary results from a phase I/II, dose-escalation trial, in type1 haemochromatosis suggest that deferasirox is effective at reducing iron burden with an acceptable safety profile.

Molecular targeting approach. The identification of numerous new proteins involved in transmembrane iron transport could be used to inhibit excessive iron entry from the duodenum into the plasma and/or from the plasma into the main storage organs. But the most promising pharmacological perspective is certainly represented by counteracting hepcidin deficiency which forms the key pathophysiological basis for the majority of genetic iron overload entities, and especially for types 1, 2 and 3 haemochromatosis.

In conclusion, the world of haemochromatosis has greatly changed over the recent period. Besides the identification of numerous novel genetic entities, the diagnosis has become mainly a non invasive one, essentially based on biological and imaging techniques. The practical management of venesection therapy has been revisited and very promising innovative therapeutic approaches are emerging. They are the direct consequence of the astonishing improved knowledge of the molecular mechanisms accounting for these genetic iron overload disorders.

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