Current Approaches to the Management of Hemochromatosis

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The term hemochromatosis encompasses at least four types of genetic iron overload conditions, most of them recently distinguished from one another as a result of the identification of a series of genes related to iron metabolism. At least three of these entities (HFE hemochromatosis, juvenile hemochromatosis and transferrin receptor 2 hemochromatosis) involve systemic hepcidin deficiency as a key pathogenetic factor. Major advances in the management of hemochromatosis influence the diagnostic approach to the disease, with the development of an overall non invasive strategy, mainly based on clinical, biological (iron parameters and genetic testing), and imaging (especially magnetic resonance imaging) data. Therapeutic management remains, on the curative side, dominated by phlebotomy (venesection), practical aspects of which have been recently revisited by the Guidelines Department of the French "Haute Autorité de Santé." However, innovative treatment approaches, based on the improved pathophysiological understanding of these diseases and the progress in iron chelation therapy, are emerging. Preventive therapy, focused on family screening, remains a key part of the management of hemochromatosis.

1. Definition and Classification

The term hemochromatosis encompasses a variety of chronic iron overload syndromes of genetic origin.[1] In light of the identification of the respective mutated genes, the following classification—mainly based on OMIM proposals[2]—can be proposed:

1. HFE hemochromatosis is by far the most frequent form, representing more than 90% of hemochromatosis cases. It is related to mutations of the HFE gene and corresponds to the "classic" adult hemochromatosis[3] (also called type 1 hemochromatosis). It affects only Caucasian populations.

2. Juvenile hemochromatosis (also named type 2) results from mutations in the hemojuvelin (*HJV*) gene[4] (type 2A) or of the hepcidin (*HAMP*) gene[5] (type 2 B).

3. Transferrin receptor 2 (TFR2) hemochromatosis (= type3 hemochromatosis) is caused by mutations in the TFR2 gene.[6,7] It clinically mimics HFE hemochromatosis.

4. Ferroportin disease results from mutations of the ferroportin (*SLC40A1*) gene.[8-12] It is also named type 4 hemochromatosis and can be subdivided into 2 forms: subtype "A," characterized by low transferrin saturation and macrophage iron deposition, and subtype "B," which mimics HFE hemochromatosis with high transferrin saturation and hepatocytic iron deposition.

5. Other rare forms of genetic iron overload—due to mutations in the ceruloplasmin gene[13] (with hematological and/or neurological presentation), the transferrin gene (atransferrinemia, expressed by severe iron deficiency anemia and parenchymal iron overload)[14] or, recently, in the DMT1 (Divalent Metal transporter 1) gene,[15] also responsible for iron deficiency anemia and hepatic iron excess—have been reported.

In reviewing the pathophysiology underlying the phenotypic manifestations of hemochromatosis, several factors must be considered: the major role of hepcidin deficiency in the pathophysiology of hemochromatosis types 1,[16,17] 2,[4] and 3;[18,19] the type of mutation involved, although genotype-phenotype correlations remain most often difficult to establish; and external (acquired) factors, such as chronic alcoholism and the dysmetabolic syndrome, that are important modifiers of iron metabolism. Because of the high frequency of type 1 (HFE-related) hemochromatosis, the discussion of diagnostic and therapeutic management will be focused on this classic form of hemochromatosis. Other forms of hemochromatosis will be discussed in the context of the differential diagnosis of type 1.

2. Diagnosis of HFE (Type 1)-Hemochromatosis

The diagnosis of hemochromatosis follows five successive steps:[20,21]

1. Consider the diagnosis of HFE hemochromatosis in evaluation of a patient with various presenting features: chronic asthenia, arthropathies, impotence, hyperpigmentation, liver abnormalities (hepatomegaly,

slight hypertransaminasemia), diabetes, cardiomyopathy, and hyperferritinemia. One should be aware that these features usually recognize more common causes, but it is essential to keep in mind, after having ruled out these usual causes, the possibility of their hemochromatosis nature.

2. Evaluate for an increased transferrin saturation (often > 80%). This is essential since it is the earliest biochemical parameter to be increased in this disease. In practice, except in the setting of a coexisting inflammatory syndrome, a normal transferrin saturation excludes the diagnosis of HFE hemochromatosis. To rule out underlying inflammation, a plasma CRP (C reactive protein) should be checked with the transferrin saturation.

3. Perform HFE testing. Typically, a homozygous C282Y mutation (now called p.Cys282Tyr) will be found (C282Y/ C282Y). The diagnosis of type 1 hemochromatosis is then established, and no further investigations are required to confirm the diagnosis.

4. Quantify iron overload. This is performed by assessing the plasma ferritin level (N < 300 μg/L in men, < 200 μg/L in women). In HFE hemochromatosis, there is a close correlation between the level of hyperferritinemia and the degree of body iron excess. Mild iron excess corresponds to values < 500 μg/L, medium to 500-1000, and severe > 1000. This threshold of 1000 should be kept in mind since, beyond this value, severe clinical complications become very likely.

5. Stage the phenotypic manifestations of HFE hemochromatosis. This is important in order to define the most appropriate measures for both treatment and follow-up.

A five-grade scale has recently been proposed[22] and adopted by Haute Autorité de Santé (HAS)[23] in France as a basis for its clinical recommendations on the management of HFE hemochromatosis (**Figure 1**):

- Stage 0 = C282Y homozygosity without biochemical (normal plasma transferrin saturation and ferritin) or clinical symptoms.
- Stage 1 = C282Y homozygosity with increased transferrin saturation (> 45%) but normal serum ferritin values and no clinical symptoms.
- Stage 2 = C282Y homozygosity with both increased transferrin saturation and ferritin (> 300 μg/L in men; > 200 μg/L in women) but no clinical symptoms.
- Stage 3* = C282Y homozygosity with increased transferrin saturation, increased ferritin, and clinical symptoms affecting the quality of life (asthenia, impotence, arthropathies, etc.).
- Stage 4* = C282Y homozygosity with increased trans-

ferrin saturation, increased ferritin, and clinical symptoms manifesting organ damage predisposing to early mortality (cirrhosis with the risk of hepatocellular carcinoma, insulin-dependent diabetes, cardiomyopathy).

Interpretation of laboratory parameters of hemochromatosis

There are several caveats to the interpretation of laboratory signs of iron overload:

1. Increased plasma transferrin saturation: An increased transferrin saturation is not specific for HFE hemochromatosis. It can be found i) in other types of genetic iron overload conditions (juvenile hemochromatosis, TFR2 hemochromatosis and type B ferroportin disease), as well as in post-transfusional iron excess; and ii) in non-iron overload conditions: marked cytolysis (as seen in acute hepatitis and reflected by major transaminasemia) through increasing plasma serum iron level and/or hepatic failure through decreasing plasma transferrin concentration can generate very high levels of transferrin saturation. In practice, when interpreting the significance of high transferrin saturation, one needs to rule out chronic anemia requiring transfusions as well as severe hepatic failure. In the absence of a recognized clinical condition, one should evaluate for laboratory evidence of unsuspected disease by checking hemoglobin (in order to eliminate chronic anemia) and transaminases plus prothrombin index (to exclude hepatic disease). To rule out non-HFE genetic hemochromatosis may be more problematic and require complementary specific genetic testing.

2. HFE status: Some results of genetic testing for hemochromatosis may raise diagnostic difficulties: i) Compound heterozygosity (C282Y/H63D) (new denomination: p.Cys282Tyr/p.His63Asp) is generally considered to be associated with a mild variant of HFE hemo-
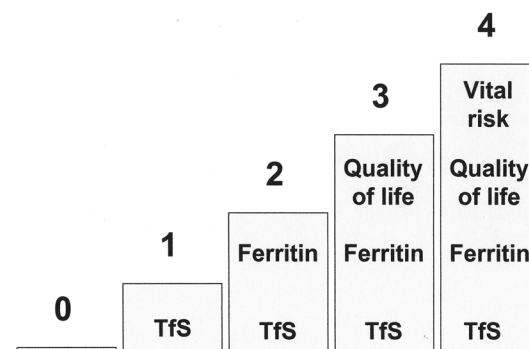

Figure 1. Classification of phenotypic expression of C282Y/C282Y subjects.
Tfs = Transferrin saturation > 45%; Ferritin means ferritinemia > 300 μg/L in men and > 200 μg/L in women; Quality of life means symptoms such as asthenia, impotence, arthropathies; Vital risk means symptoms compromising the lethal prognosis (cirrhosis, cardiomyopathy). After Brissot et al[22] and HAS.[23]

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* As previously indicated (paragraph 2.1) none of these clinical syndromes being specific, a careful clinical interpretation is needed before ascribing them to a putative hemochromatotic nature.

chromatosis. It should be pointed out, however, that a) in the vast majority of cases compound heterozygosity does not lead to significant disease manifestations, and b) when it presents with signs of disease, it is usually associated with conditions such as alcoholism or the dysmetabolic syndrome;[24,25] ii) H63D homozygosity has been reported to be associated with a phenotypic picture of hemochromatosis in rare cases, but here again, this is usually in association with other comorbidities (alcoholism, dysmetabolic syndrome); iii) It must be emphasized that simple C282Y heterozygosity and simple H63D heterozygosity virtually never cause phenotypic type 1 hemochromatosis; iv) The clinical utility of searching for further HFE mutations (especially p.Ser65Cys [26]or p.Gin283Pro[27]—previous names S65C and Q283P, respectively) in the case of simple C282Y heterozygosity or to search for associated non-HFE mutations (hemojuvelin, ferroportin, transferrin receptor 2, hepcidin) in patients with C282Y homozygosity[28-30] and major clinical abnormalities remains to be documented.

3. Increased plasma ferritin: Plasma ferritin values must be interpreted with respect to three main confounding situations, namely, inflammation, alcoholism and the dysmetabolic syndrome. In practice, whenever a C282Y/C282Y patient presents with an associated factor likely to lead to an overestimation of ferritinemia as an index of body iron level, it is important to perform direct quantification of visceral iron deposition. This can be done by hepatic MRI, which enables the calculation of liver iron concentration without special equipment (using, for example, the algorithm presented on http://www.radio.univ-rennes1.fr[31]). In this setting, liver biopsy may also be helpful, since, in addition to quantifying iron excess, it can provide valuable information about the cellular distribution of iron (hepatocyte versus macrophage) and also provide diagnostic information regarding associated abnormalities (fatty liver, steato-hepatitis, alcoholic hepatitis).

Differential diagnosis of iron overload syndromes: Evaluation of patients with iron overload with increased transferrin saturation and negative HFE testing

In the patient with unexplained iron overload, further testing is largely guided by the patient's age. If the patient is less than 30 years old, two main diagnoses should be considered. The first one is juvenile hemochromatosis (or type 2 hemochromatosis), characterized by massive iron overload associated with prominent endocrine (hypogonadotrophic hypogonadism) and/or cardiac disease (cardiomyopathy). Genetic testing should be performed to evaluate for hemojuvelin mutations (type 2A hemochromatosis) and, if negative, for hepcidin mutations (type 2B hemochromatosis). The second possible diagnosis is TFR2 hemochromatosis (= type 3) that has also been reported in adoles-

cents[27] and even in a young child.[27]

If the patient is more than 30 years old, one should consider both the diagnosis of TFR2 hemochromatosis and of ferroportin disease (in its B form). TFR2 hemochromatosis mimics HFE hemochromatosis, with an overall phenotypic severity that is intermediate between juvenile hemochromatosis and HFE hemochromatosis.[7] Specific genetic testing for TFR2 mutations will confirm the diagnosis. Ferroportin disease in its "B" form also mimics classic (HFE) hemochromatosis.[32] Since it is a dominantly inherited disease, diagnosis may be facilitated by the documenting hyperferritinemia among first-degree relatives. Genetic testing will confirm the diagnosis. In practice, the genetic detection of TFR2 mutations is difficult and time consuming. Consequently, it is better to search first for type "B" ferroportin disease, confining the search for potential TFR2 mutations to those patients with negative results for ferroportin mutations.

Evaluation of the patient with iron overload with normal or low transferrin saturation

An elevated serum ferritin in association with low transferrin saturation may occur in three pathological states: "dysmetabolic" hyperferritinemia, ferroportin disease (in its A form) and aceruloplasminemia.

Dysmetabolic hyperferritinemia (or dysmetabolic hepatosiderosis), also termed insulin resistance–associated iron overload, is a common syndrome. It typically presents with the following signs[24]: i) multiple metabolic abnormalities, including increased body mass index, high blood pressure, hyperlipidemia, noninsulin-dependent diabetes, and hyperuricemia (with sometimes overt clinical gout); ii) hyperferritinemia, which may exceed 1000 µg/L; iii) normal transferrin saturation (i.e., < 45%) ; iv) mild hepatic iron excess (especially as compared to plasma ferritin levels), usually less than 3 times the upper normal limit of hepatic iron concentration (as judged by biochemical assay on the liver biopsy or, more frequently, on MRI measurements); v) mixed (i.e., both hepatocyte and macrophage) iron deposition whenever a liver biopsy is performed.

Ferroportin disease in its "A" form presents with low transferrin saturation (and sometimes mild anemia), predominant macrophage iron excess and absent or mild iron-related complications (even in the presence of severe iron burden, liver disease may be limited to sinusoidal fibrosis[12]).

Hereditary aceruloplasminemia is a very rare disease that is due to mutations in the ceruloplasmin gene located on chromosome 3. It mimics HFE hemochromatosis in that it is familial and can be associated with major hepatocyte iron overload and diabetes mellitus. However, besides the finding of a low transferrin saturation, two main features suggest this disease: (i) The finding of low TS (and often anemia) in the face of marked hyperferritinemia in the absence of features suggesting an inflammatory syndrome; and (ii) the presence of a neurological syndrome (extrapyramidal syndrome, cerebellar ataxia, retinal degeneration, dementia),

which is never encountered in other types of hemochromatosis. The confirmation of this diagnosis depends on documenting undetectable levels of serum ceruloplasmin.

3. Therapeutic Management of HFE (Type 1) Hemochromatosis

We will focus here on correction of iron overload, since no specificity exists as to the management of the various visceral complications which can be observed in this disease.[21,22]

Venesection

Venesection (phlebotomy) constitutes the primary modality for reducing iron overload. Although patients should be advised to avoid ingesting large quantities of vitamin C–containing food (since ascorbic acid can both increase iron intestinal absorption and facilitate the release of iron from the storage sites, which has been responsible for rare instances of lethal cardiac failure), nutritional advice otherwise has little place. Chelation therapy using long-term subcutaneous infusions of desferrioxamine (Desferal®) is indicated only in the very rare setting of significant contraindications to venesection (technical impossibility of blood withdrawal due to the venous status, coexisting anemia).

Management of venesection (as proposed by HAS[23])

1. Induction Phase

i) Indication. Venesection therapy should be started at stage 2 of the phenotypic classification of HFE hemochromatosis, corresponding to increased plasma ferritin levels (**Figure 2**).

ii) Withdrawal schedule. The venesections are usually performed on a weekly basis, although their frequency can be adapted to both the initial levels of hyperferritinemia and to the patient's tolerance. The volume should be adapted to body weight: 7 mL/kg body weight, not exceeding 550 mL per phlebotomy.

iii) Aim. The goal is to obtain ferritinemia ≤ 50 μg/L.

iv) Follow-up. Efficiency is based on serum ferritin, checked on a monthly basis as long as ferritin levels remain above the upper normal limits (300 μg/L in men, 200 μg/L in women). Thereafter, testing should be performed every two venesections. Tolerance is based clinically on general assessment (with blood pressure surveillance) at each withdrawal. Venesections should be held whenever hemoglobin values are < 11 g/dL.

2. Maintenance therapy

Following the induction phase, maintenance treatment is based on phlebotomy every 1-4 months, according to the patient's needs, and aims at maintaining the serum ferritin level ≤ 50 μg/L. The patient should understand that the management is based on ferritin values, which reflect the amount of stored iron, and that transferrin saturation levels can fluctuate and (probably) be acceptable as long as values remain $< 75\%$ (when the TS is below this thresh-

old, no potentially toxic iron species are expected to be present in the circulation[33]). This addresses a common misconception that transferrin saturation reflects the degree of saturation of the overall body in iron. Serum ferritin levels should be checked at least every two venesections and hemoglobin monitored within the 8 days preceding each phlebotomy (checking this parameter immediately prior to the venesection may be of course the most simple procedure). Venesections can be performed in the hospital, in a blood transfusion center, by the general practitioner, or at home by a nurse provided a good network and written guidelines have been set up between the various medical and non-medical partners.

Results of venesection

General health is improved after several weeks of venesections, transaminases return to normal, and hyperpigmentation lessens. Arthralgias may disappear, but the patient should be aware that this is not always the case, and that joint symptoms may actually worsen during the venesection induction phase. In the setting of stage 4 complications, some manifestations of disease may be irreversible. Despite correct elimination of the iron burden, insulin-dependent diabetes will not resolve, and the risk for hepatocellular carcinoma remains if cirrhosis was present prior to venesection therapy. Although regression of cirrhosis is sometimes observed following venesection therapy,[34] whether this decreases the risk for the development of hepatocellular carcinoma requires further study.
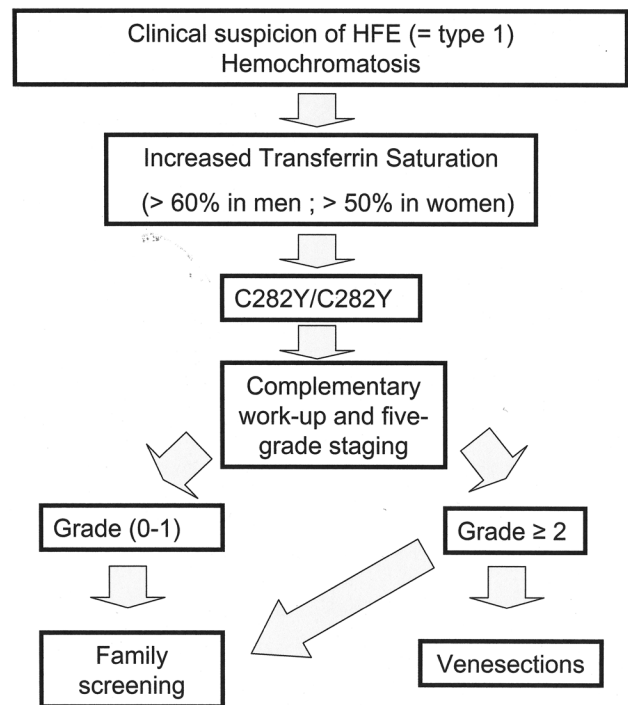

Figure 2. Overall strategy for HFE hemochromatosis.

Role of venesection treatment in other forms of hemochromatosis

Phlebotomies remain the mainstay of the treatment for all other forms of hemochromatosis with the following nuances: i) in subtype A ferroportin disease a weekly venesection program may not be well tolerated and the therapeutic target of ferritin ≤ 50 µg/L not appropriate due to the risk of anemia;[12] and ii) in aceruloplasminemia, venesections are contra-indicated given the frequent anemia. Subcutaneous infusions of desferrioxamine have been, in individual cases, reported to be efficient.[35]

Perspectives on future therapy

Three main approaches are currently being explored: i) Oral chelation. So far, this approach has not been adopted because deferiprone (CP20 or Ferriprox®) presented the rare but unpredictable risk of agranulocytosis. This was felt to offer an unacceptable risk when compared to the innocuousness of phlebotomies. If deferasirox (or ICL670 or Exjade®),[36] which has recently been approved, proves to have no long-term problematic side effects, using this oral chelator could be an appealing adjunct to venesections during the induction phase and may serve as a possible substitute for phlebotomy during maintenance therapy. ii) Inhibition of cellular iron transport. Several iron transport molecules have been recently identified, opening the way to a therapeutic approach based on the design of iron transport inhibitors. iii) Correction of the systemic iron regulating defect. This approach is based on the understanding of the pathogenesis of the disease. Knowing that iron excess in HFE hemochromatosis is strongly related to insufficient hepcidin production by the liver,[37] the therapeutic challenge is now to find pharmacological agents to counteract this systemic hepcidin deficiency.[38]

3.2. Prevention

The potential severity of visceral and metabolic complications of hemochromatosis in the face of the efficacy and simplicity of disease treatment are powerful incentives to adopt high standards for disease prevention. These standards can be applied at three main levels:

1. Individual prevention. The determination of plasma transferrin saturation, followed by plasma ferritin determination, is indicated in all situations in which there is suspicion of hemochromatosis.[39]
2. Family Screening.[40] Upon diagnosis of the disease in a given individual (the proband), genetic counseling should be provided to the proband and his/her family. First-degree family members should be evaluated with measurement of their serum iron parameters (transferrin saturation, ferritin) and testing their HFE profile. In France, this procedure must be initiated by the proband him (her)self, who is the sole person legally allowed to inform the family members. Moreover, offspring who are younger than 18 years (age of legal majority) are not eligible for genetic testing since no therapeutic

consequences are expected until adulthood (HFE hemochromatosis having no significant phenotypic expression). The latter view, i.e., to delay genetic testing until late teenage years, is shared by others.[41]

3. Mass population screening.[40] The frequency of C282Y homozygosity, the potential severity of the disease, the noninvasive approach for diagnosing the disease, and the efficacy and simplicity of treatment constitute a solid rational basis for proposing general screening of the Caucasian populations, starting with the "filter" of increased transferrin saturation and confining genetic testing to those who have "passed" this first test[42] (i.e., their transferrin saturation levels are > 60% in men and > 50% in women). However, this policy has not yet been adopted in view of the following: i) the penetrance of C282Y homozygosity is much lower than previously thought,[43] and ii) the cost-effectiveness of such mass screening is much inferior to that of family screening. Pilot regional protocols are needed in order to document the degree of validity of such mass screening procedures.

In conclusion, hemochromatosis is an outstanding example of a set of genetic diseases whose clinical management has already, very quickly and profoundly, benefited, and will continue to benefit in the future, from basic—molecular, genetic and biochemical—pathogenetic discoveries.

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