

Clinical management of hemochromatosis: current perspectives

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Abstract: Hemochromatosis (HC) corresponds to systemic iron overload of genetic origin. Its spectrum covers *HFE*-related HC, a frequent disease exclusively present in Caucasians; however, several entities of non-*HFE*-related HC, which correspond to very rare disorders, have been observed in both Caucasian and non-Caucasian populations. In most HC forms, iron overload is explained by hepcidin deficiency, which increases iron delivery into the plasma from both duodenal and splenic sources, with subsequent organ iron deposition. The diagnosis depends on a noninvasive approach combining clinical, biological, and imaging data. The treatment remains largely based on phlebotomy therapy, which is rarely replaced with erythrocytapheresis or chelation therapy. Heparin supplementation represents the logical therapeutics of the future for all HC forms related to hepcidin deficiency.

Keywords: iron overload, *HFE*, ferroportin, hemojuvelin, transferrin receptor 2, hepcidin, phlebotomy

Nosological and pathophysiological background

Before considering the clinical management of hemochromatosis (HC), it is of interest to update the following aspects.

Terminology

HC refers to systemic iron overload of genetic origin. Therefore, the term should not be applied to nongenetic forms of chronic iron overload, which occur in hematological situations, especially congenital anemias,^{1,2} due to multiple transfusions (and dyserythropoiesis) or following excessive parenteral iron supplementation.³ These disorders correspond to acquired forms of iron overload. Similarly, the term “hemosiderosis” should no longer be used for any form of iron overload.

HC spectrum

Following the discovery of the *HFE* gene in 1996,⁴ the nosological frame of HC has changed dramatically in two main aspects. First and foremost, it appeared that most previously reported HC cases were related to homozygosity of the *HFE* mutation *C282Y* (*p.Cys282Tyr*) defining type 1 HC, but it also rapidly turned out that rare HC cases were non-*HFE* related, and today four main types of non-*HFE* HC can be individualized.⁵ Type 2 HC relates to mutations of the hemojuvelin (*HFE2* or *HJV*) gene (type 2A HC) or of the hepcidin (*Hamp*) gene (type 2B HC). Type

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3 HC refers to mutations of the transferrin receptor 2 (*TFR2*) gene. Type 4 HC (also called ferroportin disease) corresponds to mutations of the ferroportin gene (*SLC40A1*). Hereditary aceruloplasminemia (HA), due to mutations of the ceruloplasmin (*CP*) gene, should, in our view, be added to the scope of HC entities. It should be stressed that types 1–3 HC are very rare compared to HFE HC. The predictive frequency of *HFE* pathogenic genotypes has been estimated at 1/1,000 vs 1/5,000,000 for type 2A HC, vs 1/6,000,000 for type 3 HC, and vs 1/180,000,000 for type 2B HC. However, the frequency for type 4 HC was close to that for type 1 HC (1/1,300), probably due to the dominant nature of the disease (whereas all other HC forms are recessive diseases).⁶

Pathophysiology

When considering the mechanism of iron overload, the different HC forms can be divided into the following two main opposing categories (Figure 1).

Iron overload due to increased plasma iron

This mechanism, whose common denominator is hepcidin deficiency, applies to types 1–3 HC. In these settings, the corresponding mutations either decrease the hepatic production of hepcidin by altering the molecular cascade involved in its

synthesis (types 1, 2A, and 3 HC) or totally prevent hepcidin synthesis (type 2B HC). Hepcidin is a small peptide, essentially produced by the liver,⁷ that is considered as the “iron hormone” since it regulates systemic iron homeostasis.^{8,9} A decrease in plasma hepcidin concentration leads to an increased plasma iron concentration by a double mechanism, enhanced intestinal absorption of iron, and enhanced release by the spleen of the iron originating from the normal degradation of old red blood cells (erythrophagocytosis). This double source of increased iron delivery into the plasma is due to the “activation” (caused by hepcidin deficiency) of the cell iron exporter function of ferroportin (particularly present at the duodenal and spleen levels). When the transport capacity of the plasma iron carrier transferrin (corresponding to the notion of transferrin saturation [TfSat]) is exceeded by the large amount of iron reaching the plasma, new forms of circulating iron appear. Plasma non-transferrin bound iron (NTBI) has the kinetic property to be very avidly uptaken by various organs (liver, pancreas, and heart), in contrast with transferrin-bound iron whose target is essentially the bone marrow (in order to produce new erythrocytes).¹⁰ NTBI is therefore likely to be responsible for the type of iron overload distribution occurring in hepcidin deficiency-related HC. Labile plasma iron (LPI) is an NTBI form defined by

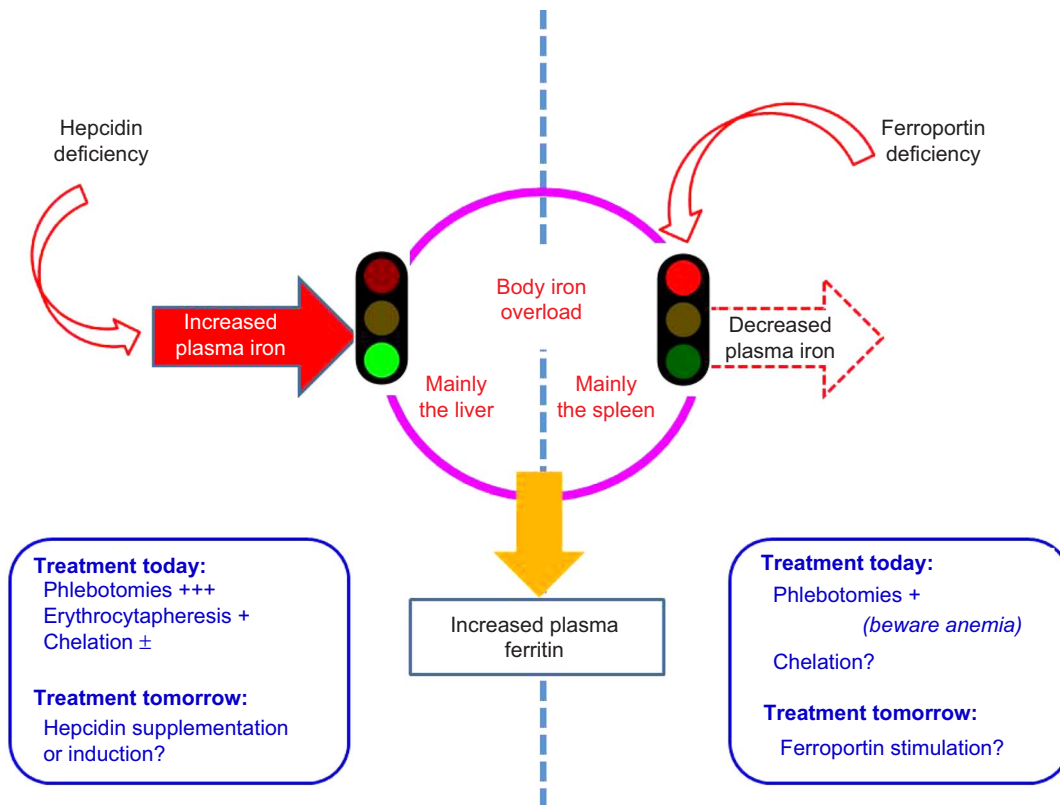


Figure 1 Pathophysiological and therapeutic aspects for the two most common forms of hemochromatosis.

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its potential cellular toxicity through its high propensity to generate reactive oxygen species¹¹ and might be involved in HC tissue toxicity.¹² A peculiar situation is hepcidin cell deprivation that is caused by mutations of the ferroportin gene affecting its other function, similar to that of hepcidin receptor, and not by decreased plasma hepcidin concentration. Then, a hepcidin resistance state develops¹³ whose consequences are similar to those following true plasma hepcidin deficiency (type 4B HC).

Iron overload due to decreased plasma iron

The typical situation is type 4A HC, which is the most frequent form of ferroportin disease.^{14,15} The involved mutations affect the cell iron export function of ferroportin. Therefore, there is decreased cell iron delivery into the plasma causing iron overload by intracellular iron retention. Since ferroportin activity is especially pronounced in macrophages, iron overload will be mainly located in the spleen and within hepatic macrophages (Kupffer cells). This location (considered as less toxic than parenchymal iron overload), combined with the fact that neither NTBI nor LPI are expected to appear in the plasma (since TfSat is not increased and is in fact often decreased), accounts for the low damaging effects of this type of iron overload.¹⁶

The case of HA

It has been proposed that iron overload is due to cellular iron retention related to a decreased ferroxidase activity of CP, which, in turn, would alter the cell export function of ferroportin, according to a mechanism similar to that involved in type 4A HC.¹⁷ This view fits with the decreased plasma iron levels with low transferrin saturation levels observed in this disease. However, it may not be the sole explanation when considering especially that, in HA, iron overload is mainly present in the liver and spares the spleen, an organ iron distribution that does not fit with the prevailing localization of ferroportin in the reticuloendothelial (macrophagic) system. Moreover, iron deposition occurs within the brain, in contrast with the other HC types.¹⁸

Clinical management

Diagnostic aspects

Clinical situations

Individuals of both sexes aged >30 years or younger (adolescents or adults <30 years) may be affected. The symptoms are as follows: chronic fatigue, impotence, arthropathies, osteoporosis, increased skin pigmentation, hepatic signs (hepatomegaly, mild cytolysis, sometimes cirrhosis, or

hepatocellular carcinoma), diabetes, cardiac symptoms (rhythm disturbances and cardiac failure), rarely (limited to HA) anemia and neurological (extrapyramidal) symptoms.

Hyperferritinemia

Although low ferritin levels always rule out iron overload, hyperferritinemia is far from being synonymous of iron overload. It is therefore critical to exclude four main situations where hyperferritinemia is not (or only mildly) associated with iron overload. 1) Metabolic syndrome: ferritin levels can reach up to 1,000 µg/L (upper normal limits of the order of 300 µg/L in men and 200 µg/L in women). It can be recognized by the association of hyperferritinemia with one or more of the following dysmetabolic components: overweight, increased blood pressure, hyperlipidemia, diabetes, hyperuricemia (with sometimes gout), and hepatic symptoms related to steatosis (slight increase in plasma alanine amino transferase, aspartate amino transferase, and gammaglutamyltranspeptidase [GGT] activities associated with liver hyperechogenicity at ultrasound examination). Plasma transferrin saturation is normal (<45%). Hepatic iron overload is either absent or mild¹⁹ (contrasting with marked ferritin increase). 2) Chronic alcoholism: alcohol increases ferritin synthesis and should be especially evoked when ferritin levels show apparently spontaneous fluctuations, which are in fact explained by variations in the severity of alcohol consumption. It is therefore important to check biological signs of alcoholism such as increased GGT levels often associated with macrocytosis. 3) Inflammation: ferritin being an acute-phase reactant protein, it is good clinical practice to check CRP levels.

After exclusion of these confounding situations, hyperferritinemia can be considered as highly likely reflecting increased body iron stores.

Magnetic resonance imaging

Various techniques are available. Relaxometry approaches define indices called T2* and R2*.^{20,21} The simplest technique, in our practice, is based on the signal intensity ratio approach.²² It compares the magnetic resonance imaging (MRI) signal of the liver with that of the spinal muscles, which serve as the reference. This technique does not need any special MRI equipment, can refer to a diagnostic algorithm freely available on the web (<http://www.radio.univ-rennes1.fr/Sources/EN/HemoCalc15.html>), and has shown its reliability; the decrease in T2 signal is inversely proportional to hepatic iron concentration. It can also evaluate, in the same way, spleen and pancreas iron load.

MRI has largely replaced the liver biopsy, which is no more performed for the diagnosis of iron overload due to its invasiveness, except in case of MRI unavailability or contraindication or when liver biopsy could provide additional information, especially associated liver lesions or hepatic fibrosis (but even in the latter situation, biochemical tests of fibrosis²³ combined with transient elastography²⁴ are increasingly replacing histological determination).

Determination of the genetic origin of iron overload

Acquired iron overload should be excluded, which is usually easy by considering the following clinical background: chronic anemia necessitating numerous blood transfusions (mainly hemoglobinopathies such as thalassemia¹ and sickle cell disease²) and excessive parenteral iron supplementation.³

Arguments favoring genetic origin should be collected. They may consist of suggestive family data and/or the young age at which iron overload has developed.

Determination of the hemochromatosis type

Types of hemochromatosis must finally be defined. Demographic background, plasma iron concentration, and MRI distribution of iron overload are the key orientating factors (Figure 1).

Demographic background

In a non-Caucasian individual, *HFE* (type 1) HC can be excluded. In contrast, non-*HFE* HC can occur in both Caucasian and non-Caucasian populations.⁶ A severe phenotype (massive iron overload, hypopituitarism, cardiomyopathy, and cirrhosis) in an adolescent or an adult younger than 30 years must suggest juvenile HC (essentially types 2A and 2B HC but also possibly type 3 HC). In type 1 HC, severe clinical phenotype is usually expressed only after the age of 30 years.

Plasma iron concentration (or transferrin saturation) levels

High levels of plasma iron concentration are in favor of hepcidin-deficient (types 1–3) or hepcidin-resistant (type 4B) HC, whereas low or normal levels suggest type 4A HC or HA.

MRI distribution of iron overload

A “black” (implying massively iron overloaded) liver with a white spleen (implying no iron overload) points to hepcidin-deficient or -resistant HC. However, this imaging profile is also observed in HA. A black spleen and a “gray” (implying moderately iron overloaded) liver are in favor of ferroportin disease (type 4A).

Guided genetic testing definitely identifies the HC type

C282Y homozygosity (*C282Y/C282Y*) proves type 1 HC. It is no more recommended to search for the *H63D* (*p.His63Asp*) mutation. If nevertheless performed, *H63D* heterozygosity must be considered as a simple polymorphism without pathological meaning. *H63D* homozygosity and compound heterozygosity (*C282Y/H63D*) cannot lead to clinically significant iron overload (at most, they can be associated with an increase in transferrin saturation) but represent cofactors of hyperferritinemia and moderate hepatic iron overload in patients with alcoholism or metabolic syndrome.²⁵ The search for non-*HFE* mutations must be performed in highly specialized, accredited laboratories, following at best a prescription from a clinical reference center.²⁵

Therapeutic aspects

The therapeutic management²⁶ is focused, here, on the removal of iron overload (Figure 1).

Type 1 HC

Phlebotomies

Phlebotomies remain the mainstay of treatment and can be done in various settings (hospital, clinic, medical office, nurse office, and patient home²⁷), their primary objective being to remove iron overload (implying induction phase). Performed on a weekly basis and withdrawing ~7 mL of blood/kg body weight (upper limit 550 mL) at each phlebotomy,²⁸ their follow-up involves both tolerance (blood pressure and hemoglobin levels) and efficacy (clinical improvement and ferritin decrease). The objective is to reach plasma ferritin levels of 50 µg/L and, thereafter, start the maintenance phase that aims at preventing progressive reconstitution of iron overload and theoretically extends throughout the life. Phlebotomies are usually performed every 2–4 months for maintaining ferritinemia ~50 µg/L. Regarding the purpose of checking plasma TfSat levels, the following view can be proposed: 1) during most of the induction phase, evaluating TfSat has no indication because it remains high as long as plasma ferritin has not yet reached the normal range; however, it becomes useful to ascertain correct “de-ironing” at the very end of this induction phase; 2) during maintenance therapy, considering that the “natural” propensity for increasing TfSat remains high in HC patients, it may be interesting to check this parameter, for instance twice a year, in order to detect persistent major elevation of TfSat (>75%) despite appropriate (50 µg/L) ferritin levels. Indeed, it has been shown that such high TfSat levels are

often associated with the appearance of LPI, the potentially toxic form of plasma iron. Globally, phlebotomy therapy is well tolerated, although a large sample size study has shown that significant side effects can be observed, with some impact on the quality of life.²⁹ In terms of efficacy, most syndromes are improved (general health, hyperpigmentation, and hepatic and cardiac symptoms), and a normal life expectancy can be restored. However, arthropathy is largely refractory to this treatment and can even worsen.^{30,31} In an increasing number of countries, the blood originating from HC patients is accepted for subsequent blood transfusions.^{32,33}

Erythrocytapheresis³⁴⁻³⁶

Although more complex and expensive, erythrocytapheresis, which remains rarely applied in HC, is more efficient than phlebotomies and is globally well accepted by the patients.

Chelation therapy

It can be proposed for the exceptional cases of contraindications to phlebotomies or of technical impossibility (poor venous status). Prolonged subcutaneous infusions of desferrioxamine can then be proposed, and, if poorly tolerated, an oral chelator (such as deferasirox^{37,38}) remains an “off-label” possibility (under the responsibility of the medical prescriber and with written informed consent of the patient).

Non-HFE HC

Types 2A and 2B HC

Due to the severity of iron overload, phlebotomies can be used in combination with parenteral (desferrioxamine) or oral (deferasirox³⁹ as an off-label drug) chelation.

Type 3 HC

The phlebotomy schedule for type 3 HC is similar to that for type 1 HC.

Type 4 HC

The phlebotomies for type 4 HC are as follows. 1) Type 4A HC: the impaired capacity for cellular iron export accounts for diminished efficacy and tolerance (risk of anemia) of phlebotomies; therefore, a softer subtraction schedule is advised (usually one phlebotomy every 2 weeks) with careful follow-up of hemoglobin levels.¹⁶ Whether oral chelation could be beneficial requires further studies.⁴⁰ 2) Type 4B HC: the phlebotomy schedule for this type 4B HC is similar to that for type 1 HC.

HA

Phlebotomies are contraindicated due to anemia. Parenteral or oral chelation gives partial results.⁴¹⁻⁴⁴

The therapeutic future for counteracting iron overload

Withdrawing iron by phlebotomies (and/or chelation) is only a symptomatic approach; therefore, hepcidin supplementation (or induction) in all forms of hepcidin deficiency-related HC^{45,46} is an attractive option. It could be used as an adjunct to phlebotomy therapy during the induction phase and as a possible substitute to phlebotomies during the maintenance period, provided a well-tolerated, oral, and affordable compound can be designed.

Therapeutic management of HC must, of course, involve a preventive dimension. As soon as one case of HC has been diagnosed, the proband's family should benefit from HC screening, especially based on appropriate genetic testing and control of plasma iron parameters (ferritin and TfSat).

Conclusion

HC encompasses a variety of genetic iron overload disorders, *HFE*-related HC being by far the most frequent entity. The diagnosis is based on a rigorous noninvasive strategy combining clinical data, plasma ferritin and transferrin saturation determinations, liver (and spleen) iron-MRI profile, and appropriate genetic testing. For most of the HC forms related to hepcidin deficiency, phlebotomies offer a simple and globally well-tolerated method to remove iron overload and improve significantly the quality of life and life expectancy. However, the future therapeutic approach, based on the molecular understanding of these diseases, should consist of hepcidin supplementation (or induction) calibrated so as to restore normal iron homeostasis.

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Disclosure

The authors report no conflicts of interest in this work.

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