

* CHAPTER 23

Diagnosis and treatment of HFE-haemochromatosis

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1. Introduction

Haemochromatosis related to the HFE gene (1), also called HFE-haemochromatosis, p.Cys282Tyr/p.Cys282Tyr (previous nomenclature: C282Y/C282Y) haemochromatosis or type 1 haemochromatosis, is one of the most frequent autosomal recessive diseases in the Caucasian population. Characterised by the development of diffuse iron overload, its prognosis, in the absence of treatment, may be severe, but early diagnosis and effective treatment can prevent the development of any tissue damage. The diagnosis can now be made using a simple bio-clinical approach. Venesection remains the mainstay of treatment but major recent improvements in the knowledge of the pathophysiology of the disease (2-5) are leading to new therapeutic approaches.

2. Diagnosis of HFE-haemochromatosis

2.1 Clinical features

A wide variety of clinical features can be present and the diagnosis is often not immediately apparent. The usual age of presentation is around the age of 40 years in men and 50 years in women.

- Chronic asthenia is frequently present and the general practitioner may suspect this is due to iron deficiency rather than to iron overload.
- Arthropathies, either acute or chronic, may affect various joints and are also frequently misdiagnosed. Involvement of the metacarpophalangeal joints is particularly suggestive, and may cause pain especially on shaking hands. Rarely, fractures occur, due to marked osteoporosis, and this can lead to diagnosis. Radiologically, the appearances are those of subchondral osteoarthropathy, chondrocalcinosis and/or osteoporosis.
- Impotence (6), in males, should suggest the diagnosis, after having ruled out a psychological explanation.
- Diffuse melanodermy (hyperpigmentation) is typical but, surprisingly, rarely leads to diagnosis, often due to the fact that the patient does not draw attention to this symptom since he/she "has always been like that".
- Liver abnormalities, ranging from slight hepatomegaly to a firm cirrhotic liver, can be detected during clinical examination. Sometimes, the only abnormality is moderate hypertransaminasaemia (less than 2-3 times the upper normal limit). Symptoms and signs of liver dysfunction, such as portal hypertension or hepatic failure, are usually not found since, even at the cirrhotic stage, hepatic function remains well preserved. Sometimes, a picture of hepatocellular carcinoma can lead to the discovery of a previously undiagnosed underlying cirrhotic haemochromatosis.

- A diabetic syndrome may be the first sign of haemochromatosis.
- Cardiac symptoms such as arrhythmias or cardiac failure can reveal an hitherto latent haemochromatosis.
- An increase in serum ferritin is a common route leading to suspicion of the diagnosis.

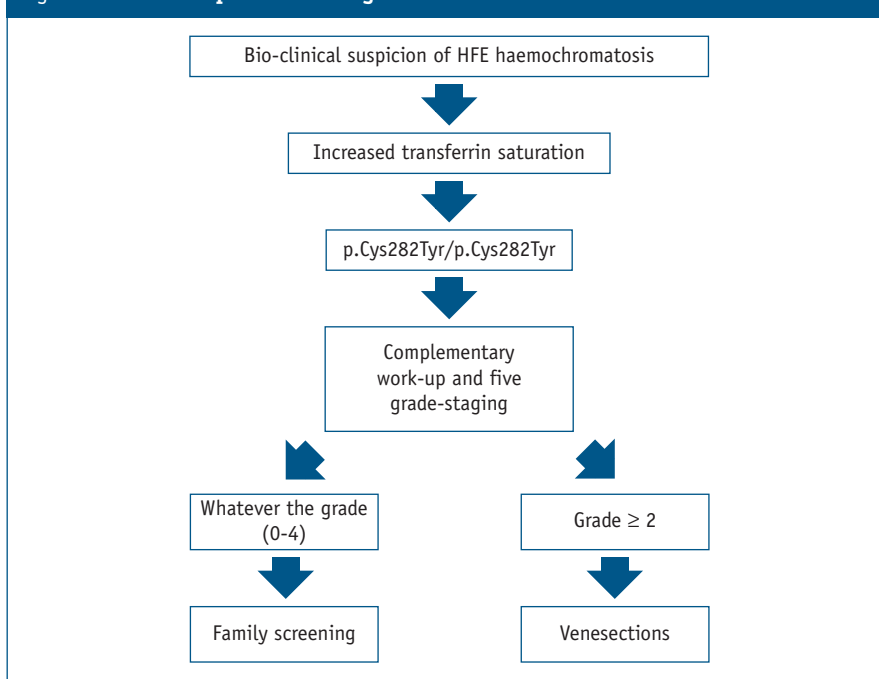
In summary, the symptoms expressing haemochromatosis are very variable.

2.2 Steps in making the diagnosis

Starting from these different initial situations the diagnostic strategy comprises five main successive steps (Figure 1).

- To consider, of course, the possibility of HFE-haemochromatosis.*
- To look for an increased plasma transferrin saturation* (calculated from the ratio of serum iron to transferrin concentration) of > 60% in men and > 50% in women (in fact often > 80%). This is essential since it is the earliest biochemical parameter to be increased in the natural course of the disease. In practice, one

Figure 1: Schematic practical management of HFE-haemochromatosis



can assume that a normal transferrin saturation excludes the diagnosis of HFE-haemochromatosis. The only exception is the fortuitous coexistence of an inflammatory syndrome, which can mask the increase in transferrin saturation. This is why it is essential to check plasma CRP (C Reactive Protein) together with transferrin saturation. Conversely, increased transferrin saturation is not specific for HFE-haemochromatosis. It can be found:

- in other types of iron overload, especially of transfusional origin;
- in non iron overload conditions such as marked cytolysis, especially of hepatic origin (as seen in acute hepatitis) which increases plasma serum iron, and/or hepatic failure which decreases plasma transferrin concentration. These situations can generate very high levels of transferrin saturation.

Any difficulty in interpretation of high transferrin saturation can be easily resolved by the clinical context and by checking haemoglobin (in order to eliminate chronic anaemia) and both transaminases and prothrombin index (to exclude hepatic disease).

- c. *Genetic testing.* This test should be done only after having checked transferrin saturation and found it increased (in the absence of the above-mentioned confounding factors). Typically, the p.Cys282Tyr mutation will be found in the homozygous state (p.Cys282Tyr/p.Cys282Tyr). This confirms the diagnosis of HFE-haemochromatosis and no further investigations are necessary to confirm the diagnosis. Some genetic results may raise diagnostic difficulties:
- Compound heterozygosity (p.Cys282Tyr/p.His63Asp) (ex nomenclature: C282Y/H63D). This profile is generally considered as a possible cause of a mild picture of HFE-haemochromatosis. It should be pointed out however that: a) in the vast majority of cases compound heterozygosity has no significant bio-clinical phenotypic expression, and b) when it has some expression it is usually associated with conditions such as alcoholism or the dysmetabolic syndrome.
 - p.His63Asp homozygosity. This has been reported as exceptionally associated with a phenotypic picture of haemochromatosis but, here again, this is usually in association with co-factors (alcoholism, dysmetabolic syndrome) (7, 8).
 - It must be emphasised that simple p.Cys282Tyr heterozygosity or simple p.His63Asp heterozygosity can in no way be responsible by itself for a bio-clinical picture of haemochromatosis.
 - The clinical relevance of a complementary search for further HFE mutations (especially p.Ser65Cys (9) or p.Gln283Pro (10) –previous names S65C and Q283P, respectively) in case of simple p.Cys282Tyr heterozygosity or for associated non HFE mutations (especially haemojuvelin, ferroportin, transferrin receptor 2, hepcidin) in case of particularly severe phenotypic expression of p.Cys282Tyr homozygosity (11-13) remains to be defined.

- d. Quantification of iron overload and evaluation of visceral damage.** Once the diagnosis of HFE-haemochromatosis has been established based on the conjunction of increased transferrin saturation and p.Cys282Tyr homozygosity, a complementary work-up is needed in order to quantify body iron overload and to evaluate the possible visceral damage created by this iron excess. This work-up should be adapted to the situation as proposed by the French health institution HAS (Haute Autorité de Santé) (14).

Qualification of iron overload. Two non invasive tools are at the disposal of the clinician:

- The “obligatory” one is plasma ferritin level (N < 300 µg/L in men and < 200 µg/L in women). Indeed, a raised ferritin level is, in HFE-haemochromatosis, closely correlated with the degree of body iron excess. Mild iron excess corresponds to values < 500 µg/L, medium to 500-1000 µg/L, and severe iron overload to levels > 1000 µg/L. This threshold of 1000 µg/L must be kept in mind since, beyond this value, severe clinical complications become very likely. The interpretation of increased plasma ferritin values should, however, take into consideration the four main possible confounding situations represented by Cytolysis, Inflammation, Alcoholism and Dysmetabolism (the “CIDA” syndrome).
- The other possible tool is MRI (magnetic resonance imaging) assessment of liver iron concentration (LIC) (15, 16). Its main indication is the presence of confounding factors for the interpretation of plasma ferritin (see above). It can be performed without special equipment, and LIC calculation based on an algorithm available on (15): <http://www.radio.univ-rennes1.fr>.

Search for visceral damage. The work-up should be both a general one and also guided by the presenting symptoms. The main target organs should be explored according to good clinical practice (i.e. comprising first clinical examination and non-invasive investigations). For instance, for the liver: transaminases and ultrasound (followed by liver biopsy if there is suspicion of cirrhosis), for joints and bone: bone densitometry, for the pancreas: blood glucose level, for the heart: ECG and echocardiography, for the endocrine glands, testosterone levels. Besides the already mentioned threshold ferritin value of 1000 µg/L, the detection of plasma non-transferrin bound iron and especially of the labile plasma iron (17) may become valuable in order to evaluate the circulating levels of these potentially toxic iron species.

- e. To stage the phenotypic expression of HFE-haemochromatosis.** This is important in order to define the most appropriate measures for both treatment and follow-up. A five grade scale has been recently proposed (2) and adopted by HAS as a basis for its clinical recommendations on the management of HFE-haemochromatosis (14).

- Stage 0 = p.Cys282Tyr homozygosity without biochemical (normal plasma transferrin saturation and ferritin) or clinical symptoms.
- Stage 1 = p.Cys282Tyr. homozygosity with increased transferrin saturation (> 45%) but normal serum ferritin values and no clinical symptoms.
- Stage 2 = p.Cys282Tyr homozygosity with both increased transferrin saturation and increased ferritin level (> 300 µg/L in men; > 200 µg/L in women) but no clinical symptoms.
- Stage 3 = p.Cys282Tyr homozygosity with increased transferrin saturation, increased ferritin level, and clinical symptoms affecting the quality of life (asthenia, impotence, arthropathies).
- Stage 4 = p.Cys282Tyr homozygosity with increased transferrin saturation, increased ferritin, and evidence of organ damage leading to reduced life expectancy (cirrhosis with the risk of hepatocellular carcinoma, insulin-dependent diabetes, cardiomyopathy).

3. Treatment of HFE-haemochromatosis

We will only consider here the management of iron overload since there is nothing specific to haemochromatosis in the management of the various visceral complications which can be observed in this disease (the only exception concerns the symptomatic treatment of cardiomyopathy for which it is essential to include venesection therapy).

Venesection (phlebotomy) constitutes the basis for obtaining iron depletion. Nutritional advice has very little place, except to avoid taking vitamin C tablets supplementation. Vitamin C can increase iron intestinal absorption and can also facilitate the release of iron from storage sites, which can be responsible for lethal cardiac failure.

3.1 Venesection

3.1.1 Induction phase

Indication. Venesection therapy should be started at stage 2 of the phenotypic classification of HFE-haemochromatosis, corresponding to increased plasma ferritin levels.

Schedule. The venesections must be performed on a weekly basis. The volume should be adapted to body weight, as proposed by HAS: 7 mL/kg body weight, not exceeding 550 mL per phlebotomy.

Aim. The goal is to obtain a serum ferritin level ≤ 50 µg/L.

Monitoring. Efficiency is based on serum ferritin level, 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, ferritin should be measured every two venesections. Tolerance is based clinically on general assessment (with blood pressure surveillance) at each withdrawal. Venesections must be stopped whenever haemoglobin values become < 11 g/dL.

3.1.2 Maintenance therapy

Following the induction phase, maintenance treatment is based on venesection every 1-4 months, according to the patient's needs, with the aim of maintaining serum ferritin level ≤ 50 µg/L. It should be explained to the patient that the main goal concerns ferritin values rather than transferrin saturation because ferritin reflects the amount of stored iron while transferrin saturation levels can fluctuate and are (probably) acceptable as long as values remain < 75%. Ferritin levels should be checked at least every two venesections and haemoglobin checked within the 8 days preceding each venesection. Venesections can be performed in the hospital, in a blood transfusion centre, by the general practitioner, or at home by a nurse provided a good network with written guidelines has been set up between the various medical and non-medical partners.

3.1.3 Results

The results are generally excellent provided the treatment has been started sufficiently early, i.e. prior to the development of stage 4 complications. General health is markedly improved after several weeks of venesections, transaminases return to normal, and hyperpigmentation lessens. Arthralgias may disappear but the patient should be informed that this is not always the case and that the symptoms may even worsen during the venesection induction phase. In most patients the quality of life is restored and life expectancy returns to normal. In case of stage 4 complications, diabetes will remain insulin-dependent and there remains a risk of hepatocellular carcinoma if cirrhosis was present prior to venesection therapy, despite elimination of the iron burden. Whether the regression of cirrhosis, sometimes observed under venesection therapy in this disease, means disappearance of the risk of developing hepatocellular carcinoma requires further studies.

3.2 New treatment approaches

Three main approaches will be explored in the near future:

- a. *Oral chelation*. So far, this approach has not been used due to the fact that the only available compound (deferiprone or CP20) was found to be associated with a rare but unpredictable risk of agranulocytosis, which was of course unacceptable when compared to the safety of venesection. Provided that the new

emerging compound (deferasirox or Exjade®) (18) proves to have no problematic side-effects in HFE related haemochromatosis, using this oral chelator could be interesting as an adjunct to venesections during the induction phase and as a possible substitute for venesections in case of poor psychological or venous tolerance.

- b. *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.
- c. *Correction of the systemic iron regulating defect.* This approach is based on the understanding of the pathogenesis the disease (5, 19-24). Knowing that iron excess in HFE-haemochromatosis is mainly due to insufficient circulating hepcidin levels, the therapeutic challenge is now to find pharmacological ways of counteracting this hepcidin deficiency.

4. Prevention

The potential severity of visceral complications and the efficacy and simplicity of the therapeutic approach are powerful incentives to adopt high standards of prevention policy. These standards can be applied at three main levels.

4.1 Individual prevention

The determination of plasma transferrin saturation is relevant in all situations (see section 2.2) which could indicate a haemochromatosis phenotype (25).

4.2 Family prevention

Family screening is of the utmost importance (26). After having diagnosed the disease in a given individual, his (her) first-degree family members must be tested by both evaluating their serum iron parameters (iron, transferrin saturation, and ferritin) and testing their HFE profile. In France, this procedure must be initiated by the proband him/herself who is the sole person legally allowed to inform the family members, and offspring younger than 18 years (the age of legal majority) are not eligible for genetic testing since no therapeutic consequences are expected at this age. This policy, i.e. to delay genetic testing until late teenage years, is shared by others (27).

4.3 Mass population screening

The frequency of p.Cys282Tyr homozygosity, the potential severity of the disease, the availability of non-invasive diagnostic tests 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 (28, 29). However, this policy has not yet been adopted because i) penetrance of p.Cys282Tyr homozygosity is lower than previously thought (30), especially in women (31), and ii) cost-effectiveness of such mass screening is much inferior to that of family screening (32). Pilot regional protocols need to be set up in order to document the degree of validity of mass screening procedures.

5. Conclusion

In conclusion, HFE-haemochromatosis is an outstanding example of a genetic disease in which basic molecular, genetic and biochemical studies of its pathogenesis have rapidly led to major advances in clinical management, and can be expected to lead to further advances in the future.

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Multiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/iron-handbook2009answers.htm>

1. The diagnosis of HFE-haemochromatosis should be considered in which one of the following situations:

- a) Anaemia
- b) Extrapyrarnidal syndrome
- c) Cirrhosis in a 20 years old man
- d) Insulin-dependent diabetes in a 45 years old man

2. Which of the following is the earliest biochemical abnormality to be found in HFE-haemochromatosis?

- a) Hyperferritinaemia
- b) Hypersideraemia (raised serum iron)
- c) Elevated plasma transferrin saturation
- d) Elevated serum transaminases

3. Which one of the following does not lead to difficulty in using ferritin values to assess iron overload in HFE-haemochromatosis?

- a) Renal failure
- b) Cytolysis
- c) Alcoholism
- d) Dysmetabolism

4. The recommended diagnostic sequence for diagnosing HFE-haemochromatosis is which one of the following:

- a) Hyperferritinaemia → Elevated transferrin saturation →

- p.Cys282Tyr/ p.Cys282Tyr (= C282Y/C282Y) →
MRI (magnetic resonance imaging)
- b) Elevated transferrin saturation → hyperferritinaemia →
MRI → p.Cys282Tyr/ p.Cys282Tyr
- c) Hyperferritinaemia → MRI → Elevated transferrin saturation →
p.Cys282Tyr/ p.Cys282Tyr
- d) Elevated transferrin saturation → p.Cys282Tyr/ p.Cys282Tyr →
hyperferritinaemia → MRI

5. Which of the following symptoms may not be favourably influenced by venesection therapy in HFE-haemochromatosis:

- a) Hyperpigmentation
- b) Chronic asthenia
- c) Hypertransaminaemia
- d) Joint symptoms