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# Iron Overload: Diagnosis, Complications, and Management

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Iron overload encompasses a variety of hereditary and acquired diseases and is responsible for significant morbidity and mortality. Major advances in iron overload pathophysiology, diagnostic tools, and pharmacotherapy have permitted significant improvements in the diagnostic and therapeutic management of human chronic iron excess. Four clinical cases illustrate these advances.

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## Case 1: A Classical Form of Hereditary Hemochromatosis

A 45-year-old man presents with chronic fatigue and painful handshake. He is diffusely hyperpigmented and presents moderate and firm hepatomegaly, without clinical signs of liver dysfunction. Blood tests show ferritin 2350 µg/L ( $N < 300$  µg/L), transferrin saturation 100 % ( $N < 45$  %), ALT 70 IU/L ( $N < 45$  IU/L), AST 60 IU/L ( $N < 40$  IU/L), prothrombin test 100 % ( $N: 100$  %), and HFE test homozygosity for the C282Y mutation (now named *p.Cys282Tyr*). The diagnosis of type 1 HFE-related hemochromatosis is made.

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**Question 1. Considering this overall profile, how would you categorize the disease stage?**

- A. Grade 0
- B. Grade 1
- C. Grade 2
- D. Grade 3
- E. Grade 4

**Expert Opinion** The phenotypic expression of C282Y homozygosity can be classified in five grades of increasing severity (HAS 2005). Grade 0 is the absence of clinical or biochemical expression (normal transferrin saturation, normal serum ferritin). Grade 1 corresponds to the absence of clinical signs but to increased transferrin saturation ( $>45$  %) with normal serum ferritin ( $N$  usually  $<300$  µg/L in men and  $<200$  µg/L in women). Grade 2 has no clinical signs but increased serum transferrin saturation and ferritin. Grade 3 corresponds to increased transferrin saturation and ferritin, together with clinical symptoms that alter quality of life (chronic fatigue, impotence, bone and joint symptoms such as osteoporosis and mostly arthritis touching different joints with a very suggestive second and third metacarpophalangeal location which is notably responsible for painful handshake, non-insulin-dependent diabetes, non- or mildly fibrotic liver disease, hyperpigmentation). Grade 4 corresponds to the full-blown disease, with life-threatening organ damage concerning the liver (cirrhosis, hepatocellular carcinoma), pancreas

(insulin-dependent diabetes), and heart (cardiomyopathy).

**Question 2. What are, among the following investigations, those that should be performed in this patient?**

- A. Glycemia and testosteronemia
- B. Serum hepcidin level
- C. Liver biopsy
- D. Hand x-rays
- E. Hepatic iron MRI

**Expert Opinion (Brissot et al. 2011)**

- Glycemia must be checked, given the risk of diabetes. Testosteronemia is also required, together with asking for erectile dysfunction.
- As to hepcidin (or better hepcidin/ferritin) determination, it is not routinely performed. Low values would favor the diagnosis but remain essentially of theoretical interest, by reflecting the underlying mechanism for iron overload. Indeed, hepcidin is the iron hormone (Nicolas et al. 2001). In HFE (or type1)-related hemochromatosis, it is low, leading to both increased duodenal absorption of iron and increased egress of splenic iron. This double mechanism (Ganz 2013) (Fig. 1) leads to chronic hypersideremia and increased transferrin saturation, which, in turn, generates non-transferrin-bound iron (NTBI) (Brissot et al. 2012). NTBI is very avidly taken up by the parenchymas (especially in the liver, pancreas, and heart), in contrast with transferrin-iron whose fate is essentially the bone marrow.
- For the liver. Mild cytolysis, with transaminase levels usually <3 times the upper normal limits, is compatible with an iron overload origin. A key question concerns the liver biopsy indication. In so far as the patient cumulates the three symptoms, which individually would already justify a liver biopsy (namely, hepatomegaly, cytolysis, and ferritin >1000 µg/L) (Guyader et al. 1998), it is here fully indicated. This biopsy will inform on the quantity of iron excess (with possibility of a histological semi-quantitative and/or biochemical quantitative

evaluation) and on its cellular distribution (typically within the hepatocytes); it will also determine the degree of fibrosis, especially if there is cirrhosis (Deugnier and Turlin 2011).

- For bone and joints: Hand x-rays will search for chondrocalcinosis and subchondral arthropathy. Bone scintigraphy is recommended due to the risk of osteoporosis (Guggenbuhl et al. 2011).
- Hepatic “iron MRI” (magnetic resonance imaging for assessment of liver iron overload) (Gandon et al. 2004) has no real indication since a liver biopsy will be performed.
- This work-up should also include electrocardiogram and echocardiography.

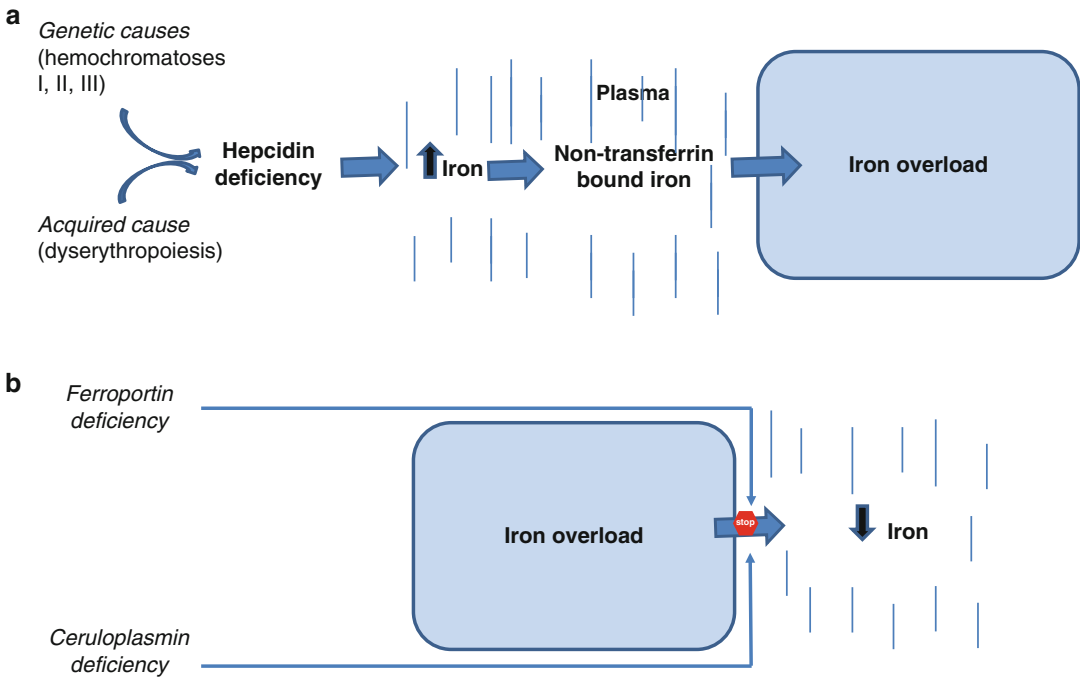
**Question 3.** The patient had no diabetes and no hypotestosteronemia but had massive hepatocyte iron deposition with cirrhosis.

**Indicate the appropriate therapeutic measures to be engaged:**

- A. Iron-poor diet
- B. Venesections every week
- C. Venesections every month
- D. Iron chelation
- E. Liver ultrasound and serum AFP (alpha-fetoprotein) every year

**Expert Opinion**

- Iron-poor diet is not required. However, the patient should of course avoid iron pills and vitamin C tablets (vitamin C increases iron absorption).
- The recommended venesection schedule is a weekly one during the induction phase (= the phase aiming to eliminate iron excess) until the objective of serum ferritin of the order of 50 µg/L is reached. Afterward, during the maintenance phase (= the unlimited period during which iron overload reconstitution must be avoided), venesections will be performed every 1–3 months, with the objective of maintaining serum ferritin close to 50 µg/L.
- Iron chelation has no indication as long as venesections are technically feasible.



**Fig. 1** The two main mechanisms accounting for iron overload: (a) increased cellular entry; (b) decreased cellular egress

- Due to the presence of cirrhosis, liver ultrasound examination and serum AFP control must be performed every 6 months in order to detect the emergence of a hepatocellular carcinoma (Bruix et al. 2005).

**Question 4. The patient (= the proband) has two sisters, aged 42 and 40, and two children, aged 10 and 20. You start a family study. Among the following proposals, indicate the correct one:**

- To check only iron blood parameters (transferrin saturation and ferritin) in all relatives
- To check only the *C282Y* mutation in all relatives
- To check the *C282Y* mutation and iron blood parameters in all relatives
- To check the *C282Y* mutation in both sisters and in the 20 years old child, without controlling iron blood parameters
- To check the *C282* mutation in both sisters and in the 20 years old child, together with control of iron blood parameters

**Expert Opinion (HAS 2005)**

- Searching for the *C282Y* mutation is essential in all individuals  $\geq 18$  years (with their written consent). Therefore, here, it has not to be checked in the 10 years old child. The information provided by this genetic study is critical: in the absence of *C282Y* mutation, there is no risk of hemochromatosis; *C282Y* heterozygosity does not expose to the risk of hemochromatosis (only risk of mutated gene transmission to the offspring); *C282Y* homozygotes (*C282Y/C282Y*) are at risk for developing the disease, but it should be noticed that it is not an obligatory evolution since only 30% of men and 1% of women may develop the clinically expressed disease.
- Assessing iron blood parameters is recommended in all genetically tested relatives, since they permit, in those family members who happen to be *C282Y* homozygotes, to be, at the same time, informed on their degree of biochemical expression.
- Checking transferrin saturation and ferritin to the age of 15 (after puberty) can be proposed.

## Case 2: A Case of Juvenile Hemochromatosis

A 23-year-old sporty woman, whose past history was represented by secondary amenorrhea since the age of 16, experienced increasing dyspnea with palpitations, painful hepatomegaly, and leg edema. Clinical examination, joined to electrocardiogram and echocardiography, rapidly concluded to global cardiac failure due to severe dilated cardiomyopathy with an ejection fraction of 15%. She was hyperpigmented, with plasma transferrin saturation of 100% and serum ferritin of 7000 µg/L ( $N < 200$  µg/L). The diagnosis of juvenile hemochromatosis was therefore highly suspected.

**Question 5. Among the following items, indicate those who are highly suggestive of juvenile hemochromatosis:**

- A. Age
- B. Endocrine background
- C. Cardiac picture
- D. The level of transferrin saturation
- E. The level of serum ferritin

**Expert Opinion (Brissot et al. 2011; Camaschella and Poggiali 2011)**

- Juvenile hemochromatosis should be evoked whenever major iron overload is suspected in a young person, aged less than 30.
- Clinical expression is dominated by cardiac and endocrine symptoms.
- A highly elevated transferrin saturation is not, by itself, indicative of juvenile hemochromatosis since it can be present at an early stage in type 1 hemochromatosis.
- The very high level of serum ferritin also favors the diagnosis.

**Question 6. Among the following investigations, indicate those that, today, would be preferred to confirm the diagnosis:**

- A. Cardiac biopsy
- B. Liver biopsy

- C. Liver MRI
- D. Cardiac MRI
- E. Genetic testing

**Expert Opinion**

- Although endomyocardial biopsy is a key procedure to prove cardiac iron overload, it would be replaced today by noninvasive cardiac MRI.
- For the same reason (especially considering cardiac failure), liver biopsy would be replaced, for iron overload assessment, by hepatic MRI.
- Genetic testing provides the definitive diagnostic proof. In this patient, the *C282Y* mutation was absent, and compound heterozygosity for hemojuvelin gene mutations was present. Three main entities of juvenile hemochromatosis have been identified: mostly juvenile hemochromatosis type 2A related to *HFE2* (or *HJV*) mutations (Papanikolaou et al. 2004) and juvenile hemochromatosis type 2B related to hepcidin gene (*HAMP*) (Roetto et al. 2003) mutations, but also type 3 hemochromatosis related to transferrin receptor 2 (*TFR2*) mutations (this latter disease can also affect adults) (Camaschella et al. 2000).

**Question 7. Indicate the appropriate therapeutic management:**

- A. Symptomatic treatment of cardiac failure
- B. No venesections
- C. Weekly venesections alone
- D. Weekly venesections + iron chelator
- E. Vitamin C to be avoided

**Expert Opinion**

- It is critical to adopt a powerful strategy for decreasing the iron burden. Weekly venesections may, therefore, be associated to chelation therapy.
- Vitamin C must be avoided, not only because it facilitates iron absorption but, mostly, because it can promote the release of stored iron into the blood, which may worsen the cardiac status.

### Case 3: A Case of Hereditary Aceruloplasminemia

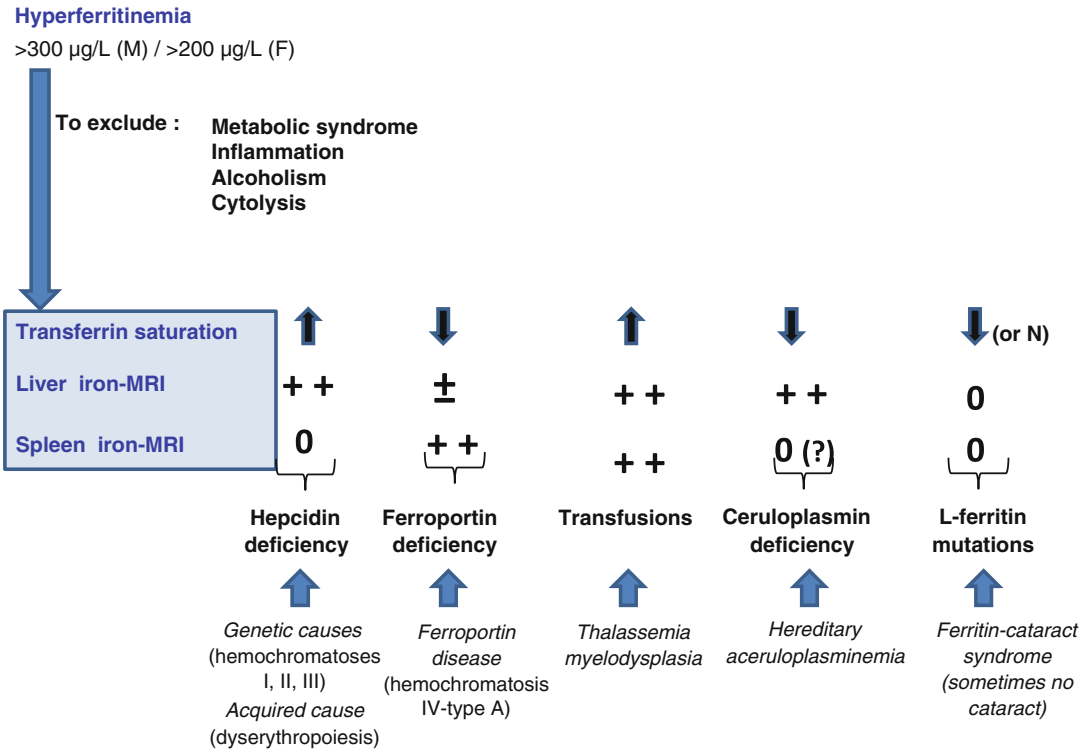
A 63-year-old woman was explored for chronic microcytic anemia. Hemoglobin was 10.7 g/L. Serum iron and transferrin saturation were low (5.6  $\mu\text{mol/L}$ ,  $N$  12–22 and 10%  $N$ , 20–45%, respectively). Reticulocyte, leukocyte, and platelet counts were normal. She was first investigated for possible gynecological or digestive blood losses, but all explorations were negative. In fact, serum ferritin was found markedly elevated, 1450  $\mu\text{g/L}$  ( $N$ <200  $\mu\text{g/L}$ ), which led to the modification of etiological orientations.

**Question 8. Indicate, among the following situations, the one(s) that can lead to hyperferritinemia without increased transferrin saturation:**

- A. Metabolic syndrome
- B. Inflammatory syndrome
- C. Ferroportin disease
- D. Ferritin-cataract syndrome
- E. Hereditary aceruloplasminemia

#### Expert Opinion (Fig. 2)

- Dysmetabolic hyperferritinemia corresponds today to the most frequent cause of hyperferritinemia, still too often misdiagnosed as hemochromatosis. Its diagnosis rests on (i) clinical background associating more or less overweight, increased blood pressure, non-insulin-dependent diabetes, hyperlipidemia, and hyperuricemia; (ii) increased serum ferritin, usually less than 1000  $\mu\text{g/L}$ ; (iii) normal transferrin saturation (<45%); and (iv) hepatic iron overload (as assessed by MRI) either absent or only moderate (corresponding then to the dysmetabolic iron overload syndrome (Mendler et al. 1999)).
- The inflammatory syndrome involves (i) decreased serum iron due to hyperhepcidinemia which sequesters iron within the macrophages and impairs cellular iron release into the plasma (Nemeth et al. 2004) and (ii) increased serum ferritin because it is an acute phase-reactant protein.
- The ferroportin disease (FD) (Montosi et al. 2001; Njajou et al. 2001), also named hemochromatosis type 4, is, in its usual form (type A), expressed by elevated serum ferritin (at levels often above 1000  $\mu\text{g/L}$ ) contrasting with normal or low transferrin saturation. The underlying mechanism is the impairment of cellular iron export due to mutations of the ferroportin gene (*SLC40A1*) affecting the export properties of ferroportin. Iron overload, in contrast to types 1, 2, and 3 hemochromatoses which involve excessive cellular iron entry due to hepcidin deficiency, is related to intracellular iron retention. Since ferroportin activity is especially important in macrophages, iron overload targets essentially the spleen. FD provides little visceral damage, probably due to the fact that, in the absence of increased transferrin saturation, there is neither circulating non-transferrin-bound iron (NTBI), and therefore no propensity to hepatocyte iron excess, nor formation of labile plasma iron (LPI), and therefore no potentially toxic form of blood iron (Brissot et al. 2012). Treatment still consists in venesections, but, due to the iron recycling difficulties which may lead to anemia, the iron depletion schedule should be less drastic than in hepcidin-deficient-related hemochromatosis. It should be noticed that another form of ferroportin disease, named type B, exists, characterized by a hepcidin resistance status which provides a phenotype similar to hepcidin-deficient hemochromatosis (Drakesmith et al. 2005).
- The ferritin-cataract syndrome is due to mutations of the L-ferritin gene, located in the IRE loop of L-ferritin mRNA (Yin et al. 2014). Serum ferritin is high, transferrin saturation is not elevated, and there is neither hepatic nor splenic iron excess. It is a dominant disease. Some mutations (located in exon1) are only expressed by hyperferritinemia (no cataract) (Kannengiesser et al. 2009).
- Hereditary aceruloplasminemia (HA) is also characterized by a marked contrast between strong elevation of serum ferritin concentration and low transferrin saturation. Like in ferroportin disease, tissue iron overload is due to cellular iron release impairment, probably related to the defect of ceruloplasmin oxidase activity.



**Fig. 2** Diagnostic approach of hyperferritinemia

**Question 9.** What are, among the following features, the one(s) that should be looked for in order to support the diagnosis of HA:

- A. Diabetes
- B. Neurological symptoms
- C. Ophthalmological symptoms
- D. Prevailing hepatic iron overload
- E. Prevailing splenic iron overload

**Expert Opinion (Kono 2013)**

- Diabetes is related to pancreatic iron deposition.
- Neurological expression is a key feature of the disease. HA is the sole form of adult genetic iron overload in which excessive iron deposition occurs in the brain. Movement disorders can be present as well as psychiatric symptoms.
- Retinal degeneration is one of the consequences of the disease.
- Iron overload seems to target preferentially the hepatocytes, sparing the spleen. The

precise mechanism accounting for this organ iron distribution, which mimics that observed in hepcidin-deficient-related hemochromatoses, remains to be elucidated.

**Question 10.** Indicate, among the following items, the one(s) who look(s) appropriate:

- A. To perform abdominal and brain iron MRI
- B. To determine serum ceruloplasmin concentration
- C. To search for mutations in the ceruloplasmin gene
- D. To start venesection therapy
- E. To start chelation therapy

**Expert Opinion**

- Iron MRI will show hepatic iron excess, no splenic iron overload, and brain iron overload, especially in the basal ganglia.

- Very low, and often undetectable, ceruloplasmin concentration is a key phenotypic diagnostic feature (and, therefore, should not only suggest Wilson disease).
  - Finding mutations of the ceruloplasmin gene (*CP*) will provide the definitive proof of the disease.
  - Due to anemia, venesections are contraindicated in HA. The only option is chelation therapy. Desferrioxamine is efficient on hepatic iron overload but does not seem active on brain iron (Loreal et al. 2002). Deferasirox is an oral iron chelator, taken once daily, globally well tolerated (side effects concern mainly renal function, gastrointestinal discomfort, and rashes). In HA, it is effective in mobilizing hepatic iron (Finkenstedt et al. 2010; Suzuki et al. 2013), but provided contrasting results for brain iron (Finkenstedt et al. 2010; Suzuki et al. 2013).
- D. In thalassemia, the degree of serum ferritin increase depends on iron cellular distribution.
- E. Abdominal iron MRI can provide information on the pathophysiology of iron overload.

### Expert Opinion

- Each transfusion provides 200–250 mg of iron which are stored in the macrophages (therefore mainly in the spleen) (Porter and Garbowski 2014). The human body having only very limited capacities for regulating iron excretion, tissue iron excess develops rapidly (after a few transfusions) and is globally maintained over time.
- Dyserythropoiesis is another important factor contributing to iron overload. It may explain iron excess in thalassemia in the absence of (or before) any transfusion. Dyserythropoiesis leads to an increased production of the medullary hormone erythroferrone, which, in turn, decreases hepatic production of hepcidin (Kautz et al. 2014). Therefore, the iron overload phenotype related to dyserythropoiesis is close to that of hepcidin-deficient-related hemochromatosis.
- The interpretation of elevated serum ferritin should always consider the possibility of confounding factors which can elevate ferritinemia independently of cellular iron excess. This is the case for the dysmetabolic syndrome, inflammation (see Case 3, Question 1), alcoholism, and cytolysis.
- The interpretation of elevated serum ferritin should also consider iron organ distribution. It has been shown that, for equivalent amounts of stored iron, the corresponding serum ferritin levels are, in macrophagic (posttransfusional) iron deposition, approximately twice those found in parenchymal (dyserythropoiesis-related) iron excess (Taher et al. 2008).
- The interest of abdominal iron MRI goes beyond the mere assertion and quantification of liver iron excess (St Pierre et al. 2005; Wood 2011). Indeed, when the spleen is still present, it is important to assess by IRM its iron content. Two types of liver-spleen

### Case 4: A Case of Thalassemia Intermedia

The medical history of this 31 years old black woman is the following: 9 years old, diagnosis of  $\beta$ -thalassemia intermedia; 10–21 years old, transfused every 4 weeks; 15 years old, splenectomy; 21–31 years old, desferrioxamine (2 g/day, 5 days a week; stopped 2 years, with monthly transfusions, during pregnancies). Her present checkup shows Hb 9 g/dL, MCV 80  $\mu^3$ , leucocytes 14G/L, platelets 610G/L, serum iron 45  $\mu\text{mol/L}$  ( $N < 22 \mu\text{mol/L}$ ), transferrin saturation 95% ( $N < 45\%$ ), serum ferritin 1500  $\mu\text{g/L}$  ( $N < 200 \mu\text{g/L}$ ), and iron MRI, marked hepatic iron overload.

#### Question 11. Indicate the correct proposal(s):

- A. Iron overload is, at least partly, of transfusional origin.
- B. Iron overload is, at least partly, due to dyserythropoiesis.
- C. Before relating serum ferritin increase to body iron overload, some confounding factors must be ruled out.

imaging profiles can then be identified: (i) non-iron overloaded spleen + iron overloaded liver, corresponding to the usual features of dyserythropoiesis overload, as typically seen in non-transfusion-dependent thalassemia (NTDT); and (ii) iron overloaded spleen + iron overloaded liver, corresponding to the usual profile of thalassemia major (or transfusion-dependent thalassemia – TDT), where iron overload is due to both dyserythropoiesis and transfusions.

**Question 12. Indicate, among the following diagnostic and therapeutic proposals, the one(s) that is (are) appropriate:**

- A. To check cardiac status
- B. To check liver status
- C. To check bone status
- D. To start again desferrioxamine
- E. To start oral chelation

### Expert Opinion

- It is important to assess cardiac status. Besides clinical examination, electrocardiogram, and echocardiogram for evaluating cardiac function, cardiac MRI is essential for assessing iron load (Wood and Noetzli 2010). If excessive cardiac iron is expected in case of massive hepatic iron overload, it may still be so in a chelated patient despite moderate residual hepatic iron overload, because kinetics of iron removal is lower in the heart than in the liver.
- The liver and biliary tract should also be explored. For the liver, several harmful factors may cumulate such as iron overload, C and B viral hepatitis (considering the transfusion history), and, more rarely, portal or hepatic vein thrombosis related to the hypercoagulability status. The global consequence may be the development of hepatic fibrosis with the risks of cirrhosis and hepatocellular carcinoma. The latter two complications can now be observed since life expectancy of thalassemia has markedly improved due to the chelation therapy advances. As to the biliary tract, ultrasound examination is recommended since

30–60% of patients develop gallbladder lithiasis, with choledocolithiasis in approximately 20%.

- Osteoporosis is a common feature in thalassemia and should be diagnosed, especially by osteodensitometry.
- Desferrioxamine, despite its powerful chelating properties, is not orally absorbed and has a very short half-life, obliging to use a parenteral (subcutaneous) administration route, 12 h a day and 5 days a week, which represents an important constraint especially for children. This is why it has been replaced by oral chelation, usually resorting now more to deferasirox than to deferiprone (due to the need to be taken three times a day and mostly to the exceptional, but unpredictable, occurrence of agranulocytosis which requires a weekly control of blood cell count) (Deugnier et al. 2011; Hoffbrand et al. 2012; Cassinerio et al. 2015). Deferiprone, however, is efficient in case of severe cardiac iron overload. Whenever, after dose escalation of a single chelator, efficacy remains insufficient, it should be considered to switch to the other oral chelator, to combine the oral chelator to desferrioxamine (Aydinok et al. 2015), or even to combine the two oral chelators (Totadri et al. 2015).

### Key Points

- A thorough clinical examination should remain a prerequisite of iron overload management.
- C282Y/C282Y hemochromatosis is, by far, the most frequent disease in Caucasians.
- Non-HFE-related hemochromatoses are rare diseases but not confined to Caucasians.
- In thalassemia, iron overload is due not only to transfusions but also to dyserythropoiesis.
- The diagnostic approach of iron overload has become a noninvasive one, based – besides clinical data – on serum ferritin and transferrin saturation



concentrations, on hepatic and splenic MRI data, and on genetic testing whenever indicated.

- Low plasma serum iron and transferrin concentration levels can be observed despite major tissue iron overload in some forms of non-HFE-related genetic iron overload (ferroportin disease and hereditary aceruloplasminemia).
- The therapeutic approach of iron overload rests mainly on venesections in hepcidin-deficient-related hemochromatosis.
- The therapeutic future of hepcidin-deficient-related hemochromatosis is hepcidin supplementation.

## Answers

- Question 1. E
- Question 2. A, C, D
- Question 3. B, E
- Question 4. E
- Question 5. A, B, C, E
- Question 6. C, D, E
- Question 7. A, D, E
- Question 8. A, B, C, D, E
- Question 9. A, B, C, D
- Question 10. A, B, C, E
- Question 11. A, B, C, D, E
- Question 12. A, B, C, E

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