Diagnosis of hyperferritinemia in routine clinical practice

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Summary

The discovery of hyperferritinemia is often fortuitous, revealed in results from a laboratory screening or follow-up test. The aim of the diagnostic procedure is therefore to identify its cause and to identify or rule out hepatic iron overload, in a three-stage process. In the first step, clinical findings and several simple laboratory tests are sufficient to detect four of the most frequent causes of high ferritin concentrations: alcoholism, inflammatory syndrome, cytolysis, and metabolic syndrome. None of these causes is associated with substantial hepatic iron overload. If transferrin saturation is high (/> 50%), hereditary hemochromatosis will be considered in priority. In the second phase, rarer diseases will be sought. Among them, only chronic hematologic diseases (acquired or congenital) and excessive iron intake or infusions (patients on chronic dialysis and high-level athletes) are at risk of iron overload. In the third stage, if a doubt persists about the cause or if the ferritin concentration is very high or continues to rise, it is essential to verify the hepatic iron concentration to rule out overload. The principal examination to guide diagnosis and treatment is hepatic MRI to assess its iron concentration. It is essential to remember that more than 40% of patients with hyperferritinemia have several causes simultaneously present.

Introduction and review of ferritin

The discovery of hyperferritinemia can initially disconcert a clinician for at least two reasons:

- serum ferritin assays are most often requested when low ferritin levels are suspected, so that a finding of hyperferritinemia is surprising;
- the physician fears that the responsible cause will not be discovered.

Nonetheless, in the vast majority of cases, a simple, non-invasive diagnostic procedure can determine its cause [1]. There are four principal causes: alcoholism, an inflammatory syndrome, cytolysis, and the metabolic syndrome [1], none of them, interestingly, associated with substantial hepatic iron overload (HIO). If transferrin saturation is high (> 50%), hereditary hemochromatosis will be considered in priority [1]. In the second phase, rarer diseases will be sought. Among them, only chronic hematologic diseases (acquired or congenital) and overload due to excess intake or
infusions (patients on chronic dialysis and high-level athletes) are at risk of HIO [1]. In the third stage, if a doubt persists about the cause or if the ferritin concentration is very high or continues to rise, the hepatic iron concentration must be assessed, to rule out overload. Hepatic MRI to determine its iron concentration is the principal examination used to guide diagnosis and treatment [1].

Before considering the diagnostic procedure, it is important to review several aspects of the pathophysiology of ferritin, which is the form in which the body mainly stores iron. It is a hollow sphere composed of 24 protein subunits capable of storing up to 4500 iron atoms [2,3]. A large portion of serum ferritin is non-glycosylated (60–80%) and comes from macrophages. The non-glycosylated fraction (20–40%) is derived from cell lysis [3]. Ferritin levels increase from childhood to adulthood, reaching a plateau in men of around 120 µg/L, after the age of 32 years. Its values remain low in women, around 30 µg/L until menopause when they increase to around 80 µg/L [4]. Serum ferritin levels are considered normal from 30 to 300 µg/L in men and from 15 to 200 µg/L in women [3,4].

The diagnostic procedure in cases of hyperferritinemia

Hyperferritinemia is frequent, found in 13% of the people in some populations [5]. Once detected, its cause must be ascertained and the existence of an iron overload in the body determined. Hyperferritinemia can accompany numerous diseases [1,6] (table 1). Moreover, it must be stressed that in 40–50% of cases high ferritin concentrations are explained by a combination of two or more diseases [1,6]. These observations, which can initially be disconcerting, require the application of a three-stage diagnostic procedure [1].

The principal causes

Four causes account for more than 90% of cases of hyperferritinemia: alcoholism, inflammation, cytolysis, and metabolic syndrome [1]. A fifth cause must be considered separately: genetic hemochromatosis [1]. The clinical context and several laboratory tests: complete blood count and hemogram, CRP, liver function tests, transferrin saturation, cholesterol, triglycerides, CPK, blood glucose make it possible to identify these five causes easily [1].

Alcohol and serum ferritin

The prevalence of hyperferritinemia among people with chronic alcoholism ranges from 40 to 70% and is not proportional to the quantity of alcohol consumed [7]. It can be explained by the direct action of alcohol, which increases ferritin synthesis and reduces hepcidin production, and by the more or less substantial hepatic lesions that it induces. Despite the diminution of hepcidin synthesis, HIO is nonetheless moderate in these patients. The ferritin concentration is usually less than 1000 µg/L, and transferrin saturation normal. Nonetheless, in around 15% of people with chronic alcoholism, serum ferritin exceeds 1000 µg/L and the transferrin saturation is greater than 60% [8]. Stopping all alcohol consumption significantly reduces ferritin levels, by around 50% in 15 days [9]. The return to normal levels can, however, take more than 6 weeks [8,10].

Inflammatory syndrome and ferritinemia

All inflammation, acute or chronic and regardless of its cause, can raise serum ferritin levels. Transferrin saturation most often decreases in this situation [10]. During inflammatory syndromes, cytokines, IL-6 in particular, stimulate the synthesis of ferritin and hepcidin [11]. The rise in serum hepcidin levels results in the sequestration of iron in the enterocytes and macrophages, which in turn causes ferritin synthesis to increase (see the article by Daher et al. about Iron metabolism and the role of the iron-regulating hormone hepcidin in health and disease published in this issue). Serum ferritin starts to climb 1 to 2 days after an inflammatory reaction starts and peaks in 8 days [2,3]. The ferritin increase is often moderate, from 500 to 700 µg/L [10], and is higher during infections than in autoimmune diseases [12]. In lupus, serum ferritin levels are positively correlated with the SLEDAI score and inversely correlated with the C3 and C4 complement fractions [13]. Nonetheless, ferritin levels exceeding 2000 µg/L, or even than 10,000 µg/L, can occur in septic shock (with cytolysis) and in infectious diseases with macrophage activation but also in some inflammatory diseases, such as Still disease (see Section ‘Is the risk of overload related to the serum ferritin concentration?’) [1,10].

<table>
<thead>
<tr>
<th>Causes of hyperferritinemia</th>
<th>With iron overload</th>
<th>Without iron overload</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemochromatosis</strong> (HFE-1 and the others)</td>
<td>Inflammatory syndrome</td>
<td>Inflammatory syndrome</td>
</tr>
<tr>
<td><strong>Mutation of the gene encoding ferroportin</strong></td>
<td>Cytolysis (liver, muscle)</td>
<td>Cytolysis (liver, muscle)</td>
</tr>
<tr>
<td><strong>Aceruloplasminemia</strong></td>
<td>Cancer and hemopathies</td>
<td>Cancer and hemopathies</td>
</tr>
<tr>
<td><strong>Compensated dyserythropoiesis</strong></td>
<td>Chronic alcoholism</td>
<td>Chronic alcoholism</td>
</tr>
<tr>
<td><strong>Repetitive transfusion</strong></td>
<td>Metabolic syndrome</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td><strong>Chronic liver diseases</strong></td>
<td>Hyperthyroidism, diabetes</td>
<td>Hyperthyroidism, diabetes</td>
</tr>
<tr>
<td><strong>Porphyria cutanea tarda</strong></td>
<td>Gaucher disease</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td><strong>Metabolic syndrome</strong></td>
<td>Macrophage activation syndrome</td>
<td>Macrophage activation syndrome</td>
</tr>
<tr>
<td><strong>Excess iron intake or infusions</strong> (patients with chronic dialysis and high-level athletes)</td>
<td>Still disease l-ferritin, with or without cataracts</td>
<td>Still disease l-ferritin, with or without cataracts</td>
</tr>
</tbody>
</table>
Cytolysis and ferritiniemia
All cytolysis, in either the liver or muscles, can increase serum ferritin concentrations, quite frequently simultaneously with transaminase levels [1].

Hepatic cytolysis and ferritiniemia
Acute or chronic hepatitis can cause ferritin levels to climb, sometimes to levels greater than 10,000 μg/L [2]. Elevated transferrin saturation (especially in cases associated with hepatocellular insufficiency) is often found with it [10]. During chronic hepatitis due to hepatitis virus C (HVC), serum ferritin is elevated in 30–40% of patients, but HIO is rare and generally moderate [14,15]. Associated factors (heterozygosity for the C282Y mutation, H63D, and alcohol intake) increase the risk of iron overload. During antiviral treatment for chronic HVC, ferritin levels rise initially before returning to normal several months after treatment ends. A substantial increase (more than 2.5 times the baseline after 12 weeks of treatment) may be correlated with better treatment response [16].

Muscle cytolysis and ferritiniemia
All muscle lysis can raise serum ferritin concentrations [1]. Nonetheless, the literature is sparse. It has recently been suggested that ferritin assays may be useful in cases of myositis associated with interstitial lung disease. These types of myositis have a poor prognosis. The presence of either anti-MDA-5 antibodies or hyperferritinemia aggravates the prognosis still further (50% survival at 1 year) and requires aggressive treatment (corticosteroids plus immunosuppressants) [17]. Both the intensity of hypoxia secondary to the lung damage and the macrophage activation that is frequently observed may explain the rapid rise in ferritin levels [18].

Metabolic syndrome and hyperferritiniemia
This syndrome combines 4 elements: chronic hypertension, dyslipidemia, glucose intolerance, and android obesity [1]. Nonetheless, the first difficulty is defining the syndrome. During the last 15 years, numerous experts have offered different definitions of metabolic syndrome. Depending on the definition chosen, its prevalence in France ranges between 10% and 23% [19]. To attempt to unify these different definitions, a consensus definition was proposed in 2006 (table II).

<table>
<thead>
<tr>
<th>Metabolic Syndrome</th>
<th>Waist measurement differs according to ethnicity in Europe: ≥ 94 cm for men; ≥ 80 cm for women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>≥ 1.7 mmol/L (1.50 g/L)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&lt; 1.03 mmol/L (0.40 g/L) in men; &lt; 1.29 mmol/L (0.40 g/L) in women (or lipid-lowering therapy)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Systolic blood pressure ≥ 130 mmHg, Diastolic blood pressure ≥ 85 mmHg (or blood pressure treatment)</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>≥ 5.6 mmol/L (1.0 g/L) (or previous diagnosis of type 2 diabetes)</td>
</tr>
</tbody>
</table>

Serum ferritin is moderately elevated in metabolic syndrome, to approximately 500 μg/L but can sometimes exceed 1000 μg/L [20,21]. Serum iron and transferrin saturation are most often normal [21]. Nonetheless, transferrin saturation can be elevated in up to 35% of cases [22]. Serum concentrations of hepcidin are also high in metabolic syndrome [23].

Hyperferritinemia in metabolic syndrome is not synonymous with HIO. Nonetheless, two points must be underlined:
• around 15% of patients with metabolic syndrome have HIO (specifically, hemochromatosis) [24]. Hepatic MRI measuring the iron burden (N < 36 μmol/g) is a non-invasive method able to quantify iron overload at ranges from 50 to 350 μmol/g. The methodological details of this technique developed by the team at Rennes University Hospital Center are available at the following URL: http://www.radio.univ-rennes1.fr [25]. In metabolic syndrome, the HIO is most often moderate, less than 150 μmol/g [21]. When, however, serum ferritin exceeds 450 μg/L, however, HIO must be considered [21]. A ferritin level > 450 μg/L is significantly associated with elevated transaminases, especially ALAT, and with more severe histologic liver damage (hepatic fibrosis) [26];
• hepatic iron overload is not visible on ultrasound. The “liver overload” described during hepatic ultrasound in metabolic syndrome involves an overload of fat rather than iron [1].

Metabolic syndrome is associated with an increased cardiovascular risk because of the risks inherent in each of its components [27] but also with an increased risk of cancer. This augmentation is moderate and varies with ethnicity and sex. In men, metabolic syndrome is associated with an increased risk of liver and colorectal cancers (relative risks (RR) respectively of 1.43 and 1.25) [28]. Women with this condition appear to be at higher risk of endometrial, pancreatic, breast, rectal, and colon cancer (RR respectively ranging from 1.61 to 1.34) [28]. Different contributing factors, including excess iron, may be involved [20,29]. Nonetheless, neither the management of each component of metabolic syndrome nor weight loss lead to any notable reduction in iron overload [20,21,30]. For this reason, some authors have proposed phlebotomy in the treatment of metabolic syndrome, although for the moment, the benefits of this treatment have not been assessed [21,31].

The “fifth element”: hemochromatosis
When hyperferritinemia is associated with high transferrin saturation (> 50%), hemochromatosis is the first diagnosis to rule out [1]. Type I hemochromatosis (HFE-T) is a genetic disease with autosomal recessive transmission, and its diagnosis is...
based on the presence of the homozygous C282Y mutation in the HFE gene. It is frequent in Western Europe, with a prevalence ranging from 2 to 5% in France to as much as 1% in Ireland [32]. In a given population, the homozygous C282Y mutation is found in 3% of people with hyperferritinemia [5].

**Hereditary hemochromatosis (HH) and ferritinemia**

Serum ferritin assays are sometimes requested when clinical signs suggest HH. These signs include melanoderma, diabetes, cardiomyopathy, and rheumatic damage (for example, painful handshakes due to lesions of the second and third metacarpophalangeal joints, and chondrocalcinosis) [33]. In a population of patients with the homozygous C282Y mutation, serum ferritin concentrations were found to be distributed fairly uniformly from 300 to more than 1000 μg/L [34]. Transferrin saturation always exceeded 50% in men and is most often greater than 80% [10].

Nonetheless, many patients with this homozygous mutation do not have and will not develop clinical signs. Penetration varies highly, estimated at 20–50% [35,36]. Similarly, some patients homozygous for the C282Y mutation do not have elevated ferritin levels [35]. In view of the variability of both penetrance and ferritin levels, it is clear that although the C282Y mutation is necessary for diagnosis, it is not sufficient for HH expression. When iron overload is present in these patients, they often have a combination of environmental (e.g., alcohol or HVC) and genetic (HAMP or HJV, see Section 'Genetic diseases and iron overload') factors [32].

The presence of clinical signs and serum ferritin concentrations are correlated with iron overload [37].

**HH and iron overload**

In HH, the ferritin concentration is a good reflection of iron overload [10]. Hepatic MRI assesses the iron burden but cannot determine whether substantial hepatic fibrosis is present. If the ferritin level is less than 1000 μg/L, hepatomegaly is not present, and transaminase levels are not elevated, there is no risk of severe fibrosis [38]. On the other hand, if serum ferritin reaches or exceeds 1000 μg/L, transaminases are above normal, and the platelet count is less than or equal to 200,000/mm³, the risk of cirrhosis is above 80% [39]. In these circumstances, a hepatic biopsy is useful to determine the extent of liver damage and, if cirrhosis is present, to allow closer monitoring of these patients given their higher risk of hepatocarcinoma.

The treatment of HH relies on repeated phlebotomy that aims to reduce the ferritin concentration below 50 μg/L [10]. It is important to underline that phlebotomy very rarely if ever improves any arthropathy that may be present [33]. Patients homozygous for C282Y who have no clinical signs have a life expectancy identical to that of the general population [40]. Those who also have diabetes or cirrhosis due to the iron overload have a reduced life expectancy, which is nonetheless improved by regular phlebotomy [40]. The principal causes of death are diabetes, cardiomyopathy, liver failure due to cirrhosis, and hepatocarcinoma [37,40].

**The H63D mutation is more frequent than the C282Y mutation**

The incidence of this homozygous mutation is about 2%, and the incidence of the heterozygous form 23% [41]. Even though transferrin saturation can sometimes be high, this mutation is not associated with a significant iron overload [41]. The composite heterozygous C282Y/H63D genotype is rarely accompanied by clinical signs suggesting iron overload (0.5–2%) [37]. Serum ferritin is most often relatively low, below than 500 μg/L, as is transferrin saturation (less than 65%) [10]. If higher values are observed, additional, supplementary risk factors must be considered (such as metabolic syndrome or hepatitis C) [37].

**Rarer causes**

If the five principal causes described above are ruled out, it is necessary to continue both questioning the patient and the clinical examination to search for causes that are necessarily rarer or have a still more “discreet” clinical expression: ask about a history of bullous skin lesions on the back of the hand (porphyria), about a family history of early cataracts (L-ferritin mutation), and weight loss, even moderate (hyperthyroidism, malignant disease); look for hepatosplenomegaly (Gaucher disease) or pallor (or anemia) [1]. Finally, for patients on chronic dialysis and for high-level athletes, excessive iron intake must be considered.

**Porphyria cutanea tarda**

This is the most frequent of the porphyrias. Its prevalence varies between countries from 1/5000 to 1/70,000. Cutaneous signs with the appearance of bullae on the back of the hand, promoted by minimal injuries or sun exposure, can suggest this diagnosis [1]. Porphyria cutanea tarda is acquired in 80% of cases and hereditary in the other 20% [42]. In either case, other factors must also be present (alcohol, hepatitis C, etc.) to induce HIC, which will most often remain moderate. The principal treatment is phlebotomy, until the ferritin concentration falls below 25 μg/L [42].

**L-ferritin**

Hereditary hyperferritinemia-cataract syndrome (HCS) is a rare condition transmitted as an autosomal dominant trait [43,44]. This syndrome is secondary to diverse mutations (31 described since 1995) of the L-ferritin gene. Bilateral cataracts appear early, often in childhood, and lead to progressive diminution of vision due to deposition of L-ferritin crystals [45]. The serum ferritin concentration is high, ranging from 600 to more than 3000 μg/L [45,46]. Serum iron is normal, as is transferrin saturation. The high ferritin concentration and the familial character may result in an erroneous diagnosis of hemochromatosis and treatment by repeated phlebotomy. Tolerance of this therapy is poor, because it rapidly causes anemia; it is also futile because no hepatic iron overload exists [45].
Diagnosis of hyperferritinemia in routine clinical practice

**Hyperthyroidism**
In a given population, mean serum ferritin concentrations do not differ significantly between subjects with normal, low, or high thyroid activity, because of the wide interindividual variety in ferritin levels [47]. Hyperferritinemia secondary to hyperthyroidism is therefore very moderate. Treatment of the hyperthyroidism progressively decreases the ferritin concentration (reduction by 50% in a month), which then returns to normal levels [48].

**Malignancies**
Local cancers do not raise serum ferritin levels (< 500 μg/L), but metastatic cancer can cause them to rise, often to more than 1000 μg/L, probably because of factors associated with it (inflammation, cytosis, etc.) [12].

**Gaucher disease**
Gaucher disease, a genetic disorder with autosomal recessive transmission, is a lysosomal storage disorder due to a glucocerebrosidase deficiency; its most frequent signs are hepatosplenomegaly, bone pain, thrombocytopenia, and anemia [1]. In a series of 54 patients, ferritinaemia exceeded 300 μg/L in 87% of the patients, with a mean concentration of 739 μg/L (range: 46–2371 μg/L). Transferrin saturation was normal [49]. Ferritin concentrations are much higher in patients who have had splenectomies than in those who have not [50]. Gaucher disease does not usually lead to more than slight, if any, HIO [50]. Nonetheless, it must be checked in patients with splenectomies when the serum ferritin level exceeds 1000 μg/L. Regular hepatic monitoring is advised for them, because of the possibility of hepatocarcinoma [51]. Enzyme replacement therapy slowly improves the serum ferritin concentration. One study reported that after a mean treatment time of 90 months, the number of subjects with ferritinemia greater than 300 μg/L fell to 33% (vs. 87% before any treatment) [49]. The low levels of glycosylated ferritin in untreated patients also rise after treatment [52].

**Dyserythropoiesis, ferritinemia, and iron overload**
Chronic hematologic diseases, acquired or congenital, can induce iron overload. This overload is variable, depending on the intensity of the dyserythropoiesis, anemia, or hypoxia, and the frequency of blood transfusions necessary (one unit of concentrated red cells provides 200 mg iron) [1]. Iron overload appears after transfusion of more than 20 units [53]. Transferrin saturation is often very high, especially in patients with multiple transfusions [53]. Dyserythropoiesis thus leads to a reduction in hepatic synthesis, which in turn increases intestinal absorption of this excess iron. This is very marked in Blackfan-Diamond anemia and the different forms of congenital dyserythropoiesis. It is more variable in sickle-cell anemia, myelodysplastic syndromes, and hemolytic anemias [53]. In a series of 33 patients with a pyruvate kinase (PK) deficiency, hyperferritinemia was found in 60% of those who had not had transfusions (range: 58–3160 μg/L). Of the 9 patients who had undergone a liver biopsy, fibrosis was found in 8, and 2 died before the age of 45 years from HIO-induced cirrhosis [54]. During these chronic hematologic diseases, the principal cause of death was cardiac damage, induced by iron overload [55].

**Excess intake or infusions of therapeutic iron**
In dialysis patients
Before the advent of erythropoietin (EPO), patients undergoing chronic dialysis underwent repeated blood transfusions to correct anemia, with the risk of iron overload correlated with the number of transfusions. Since the advent of wide EPO use, the need for blood transfusions in these patients has clearly fallen. Nonetheless, the substantial blood loss in patients on dialysis as renal replacement therapy (because of the dialysis itself, as well as intestinal loss due to uremic enteropathy and repeated blood samples) and the use of their iron reserves induced by EPO reduce these stores and require intravenous (IV) iron, according to the criteria of various learned societies [56,57].

In 2012, Rostoker et al. followed up 119 unselected hemodialysis patients receiving EPO and regular IV iron supplementation in accordance with the international guidelines in effect. They prospectively performed MRI (according to the method described by the Rennes group) to look for iron overload in the liver [58]. Overloads ranging from mild to severe were observed in 100 patients (84%); 36 (30%) had a severe overload: > 200 μmol/g dry weight (N: < 36 μmol/g); their transferrin saturation remained normal [58]. After cessation or substantial reduction of iron infusions, the HIO observed on MRI fell sharply, from 220 μmol/g (range: 60–340) to 50 μmol/g (range: 5–210) [58]. This iron overload might be the source of a variety of complications, in particular an increase in cardiovascular events and death, through increased hepcidin levels causing macrophage activation on atheromatous plaques and destabilizing them [59].

These observations have stimulated other work to attempt to reduce the risk of HIO by closer patient monitoring and modifying the form of iron supplementation [57,60]. Serum ferritin is the iron marker best correlated with HIO; one study has shown that for ferritinemia > 290 μg/L, the liver iron concentration exceeds 200 μmol/g in hemodialysis patients [61]. From a treatment perspective, iron supplementation should be used only to compensate for blood loss and not to economize on EPO [57,58,60]. To minimize the risk of HIO in hemodialysis patients, the IV iron dose should not exceed 250 mg/month [62].

**In high-level athletes**
As part of the battle against doping in sports, blood tests were taken of professional cyclists in the 1998 Tour de France; these showed that 30% had serum ferritin concentrations > 300 μg/L (range: 306–1671) [63]. Of the 83 subjects examined, 37% had elevated transferrin saturation. All were asymptomatic and had normal clinical examinations; 7 admitted having used EPO [63].
All had had oral, and sometimes IV, iron supplementation, either as self-medication or prescribed for low serum iron [63]. Over a 3.9-year period, the (total oral and IV) iron supplementation was estimated at 25.5 g (range: 1.4–336) and was correlated to ferritin concentrations [63]. The liver iron concentration measured by MRI was elevated in 24 of the 27 subjects who underwent this examination, with concentrations reaching 187 µmol/g [63]. Serum ferritin levels remained elevated after cessation of iron intake, which may suggest the need to propose treatment by phlebotomy to avoid potential complications [63]. The utility of iron supplementation in high-level athletes has not been scientifically demonstrated. Moreover, serum iron concentration is not a marker of iron reserves: only ferritinemia levels should be considered [63].

**Identifying iron overload**

If the diagnosis remains uncertain after these first two steps, the remaining essential question is whether or not there is an undetected hepatic iron overload [1]. How should clinicians proceed if they suspect HIO? Does the risk of iron overload depend on the genetic nature of the hyperferritinemia? On its cause? Its level? Or on the level of transferrin saturation?

**Genetic diseases and iron overload**

Some genetic mutations much rarer than HFE-1 are accompanied by iron overload (table III). The genes for hemojuelin, hepcidin, and the transferrin receptor are all directly involved in hepcidin synthesis [64,65]. Their mutations result in reducing its production and can thus lead to iron overload:

- in HFE-2, mutations of the HJV (hemojuelin) and the HAMP (hepcidin antimicrobial peptide) genes induce juvenile hemochromatosis. Iron overload in individuals with these mutations is expressed before the age of 30 years and can cause diabetes as well as damage to the liver, the pituitary gland (hypogonadism), and especially the heart (which governs the prognosis) [1,65];
- HFE-3, which is due to a mutation of transferrin receptor 2, is expressed especially in hepatocytes, and the clinical picture is close to that of HFE-1 [1,65];
- HFE-4 is due to a mutation of the gene encoding ferroportin, a protein that enables iron to exit enterocytes and macrophages. In HFE-4, the location of the iron overload within the macrophages explains the hypointense signal observed on MRI of the liver and spleen. Clinical expression is often late and affects black subjects especially [1,65];
- ceruloplasmin, the principal transport protein for copper, is necessary for transferring ferrous iron to ferric iron. This stage is essential for enabling iron, released from cells, to bind to transferrin. The ceruloplasmin mutation leads to diffuse iron overload and is accompanied by cerebral damage causing neurological disorders (cerebellar ataxia, extrapyramidal signs, and progressive dementia) as well as retinal degeneration. Microcytic anemia is frequent, as is paradoxical hyposideremia [64,65].

While some of these genetic diseases result in iron overload, others, such as Gaucher disease and the e-ferritin mutation, do not (table I). The genetic cause of a disease does not always mean that iron overload will develop.

**Is the risk of overload related to the serum ferritin concentration?**

The diseases that cause major elevation of ferritinemia – to concentrations greater than 5000 or even 50,000 μg/L – are macrophage activation syndrome (MAS), Still disease, and malignant blood diseases [1].

**Macrophage activation syndrome**

Some have suggested a new designation for lymphohistiocytic activation syndrome (MAS) [66]. It is often associated with extremely high ferritin concentrations, exceeding 10,000 or even 100,000 μg/L – are macrophage activation syndrome (MAS), Still disease, and malignant blood diseases [1].

<table>
<thead>
<tr>
<th>Gene Transmission</th>
<th>Transferrin saturation</th>
<th>Age at clinical expression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemochromatosis HFE-1</strong></td>
<td>A-R</td>
<td>&gt; 30 years</td>
</tr>
<tr>
<td><strong>Juvenile hemochromatosis HFE-2</strong></td>
<td>A-R</td>
<td>&lt; 30 years</td>
</tr>
<tr>
<td><strong>Hemejuvelin (HJV)</strong></td>
<td>A-R</td>
<td>&lt; 30 years</td>
</tr>
<tr>
<td><strong>Hamp antimicrobial peptide (HAMP)</strong></td>
<td>A-R</td>
<td>&gt; 30 years</td>
</tr>
<tr>
<td><strong>Hemochromatosis HFE-3</strong></td>
<td>A-R</td>
<td>≥ 30 years</td>
</tr>
<tr>
<td><strong>Hemochromatosis HFE-4</strong></td>
<td>A-D</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Acerculoplasminemia</strong></td>
<td>A-R</td>
<td>Normal</td>
</tr>
</tbody>
</table>

A-R: autosomal recessive; A-D: autosomal dominant.
In the autoimmune diseases, MAS is observed either at the beginning of the disorder, which it can reveal, or at any later time when induced by an additional infectious disease [67]. Etoposide is the treatment of choice for severe forms [66].

Still disease

It is an inflammatory disease affecting, in particular, young women; it combines fever with daytime peaks, one or more forms of arthritis, and rash. Hyperferritinemia is present in 90% of cases [13,36]. The absence of hyperferritinemia does not, however, automatically rule out this diagnosis, which is always a diagnosis of exclusion [68]. In a series of 14 patients with Still disease, the mean serum ferritin concentration was 6350 μg/L (94–49,910) and glycosylated ferritin had collapsed to less than 20% in 12 of these 14 cases; under treatment, ferritinemia returned to normal, but glycosylated ferritin remained very low (<20% after a mean follow-up of 37 months in 10 of the 14 patients) [69]. An initial ferritin concentration more than 5 times normal is correlated with the condition becoming chronic [36].

Hyperferritinemic syndrome

It has recently been suggested that the following four diseases should be classified together as “hyperferritinemic syndrome”: MAS, Still disease, catastrophic antiphospholipid syndrome (CAPS), and septic shock [70]. In patients with hyperferritinemia and APS, ferritin levels were significantly higher in patients with CAPS compared with those without this catastrophic complication (816 ± 847 versus 120 ± 230 μg/L) [71]. In a study of septic shock in children, hyperferritinemia greater than 500 μg/L was associated with a relative risk of death of 3.2 (1.3–7.9) [72]. We consider that these four diseases share clinical and laboratory signs as well as some of the same treatments (corticosteroids, IV immunoglobulins, and plasma exchange). It is hypothesized that the extremely high ferritin concentrations not only reflect inflammation and cytolysis, but may also have a direct pathogenic role in the development of the cytokine storm [70]. Despite the extent of the increase in serum ferritin levels, HIO is not a risk in any of these conditions.

**Does the risk of iron overload depend on transferrin saturation?**

Transferrin saturation can be an important guide in the diagnostic procedure (figure 1) [10]. It is generally considered that the higher the transferrin saturation coefficient, the greater the risk of HIO. Nonetheless, two points must be stressed:

- this observation is especially true for HFE-1, for which the intensity of HIO is associated with the strength of transferrin saturation. But hyperferritinemia associated with transferrin saturation greater than 50% can occur in other diseases (alcoholic liver disease, some metabolic syndromes, hepatitis B and C) which are rarely if ever accompanied by HIO [9];
- inversely, some patients have hyperferritinemia with normal saturation (table III), and biopsy-proven liver iron overload [9].

Accordingly, neither the serum ferritin concentration nor transferrin saturation values provide definitive evidence of either the presence or absence of HIO [1]. For this reason, if the result of the work-up is uncertain, or if there are several causes associated with the ferritin concentration, or if it is increasing over
time, it becomes essential to evaluate the iron burden by hepatic MRI [1]. Liver iron concentration can be assessed to measure this HIO, with the MRI method described by the University of Rennes, for values ranging from 50 to 350 μmol/g (N < 36 μmol/g) [25]. This non-invasive method has made it possible to slash the number of liver biopsies for work-ups for unelucidated hyperferritinemia [73].

The MRI result produces two alternative situations (figure 2): • it may show no or moderate iron overload: the principal causes remain the four most already considered (inflammatory syndrome, alcohol, cytolysis, and metabolic syndrome). If none of them is identified, possible diagnoses to be considered next include hyperthyroidism, porphyria cutanea tarda, Gaucher disease, the hyperferritinemia-cataract syndrome, or excess iron intake or infusions (for dialysis patients and athletes). • alternatively, it may show a substantial HIO: • if transferrin saturation is normal, the next step is to consider: hereditary aceruloplasminemia, a ferroportin disease (especially if the MRI shows splenic iron overload) and excessive therapeutic iron intake or infusions in dialysis patients and high-level athletes,

if transferrin saturation is high, the following should be considered: first of all, HFE1 hemochromatosis, then HFE2 or HFE3 as a function of age, dyserythropoiesis, acquired or congenital hemolytic anemia, or excess iron intake or infusions in elite athletes.

**Conclusion**

In addition to a clinical examination, a simple work-up can be proposed for all patients with hyperferritinemia: complete blood count and hemogram, CRP, liver function tests, transferrin saturation, TSH, blood glucose, cholesterol, triglycerides, CPK, reticulocytes, and haptoglobin. This work-up enables detection of the most frequent causes of high ferritin concentrations. Numerous diseases can induce hyperferritinemia. In more than 90% of cases, it is not associated with HIO. The discovery of a cause does not mean that it is the cause of the hyperferritinemia. Very often, several causes are associated. If the serum ferritin concentration is very high (> 5000 μg/L), the priority turns towards testing for MAS, Still disease, or a malignant blood disease.

Finally, to prevent any failure to identify iron overload, MRI should be envisioned in the following situations: in cases with serum ferritin concentrations greater than 500 μg/L, the priority turns towards testing for MAS, Still disease, or a malignant blood disease.

To prevent any failure to identify iron overload, MRI should be envisioned in the following situations: in cases with serum ferritin concentrations greater than 500 μg/L, the priority turns towards testing for MAS, Still disease, or a malignant blood disease.

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