Hyperferritinaemia

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Key messages:
1. Ferritin is an intracellular protein that stores iron in the liver, and it is also an acute phase protein.
2. The majority of the patients with liver disease, who are discovered to have an elevated serum ferritin in medical routine, does not have hepatic iron overload.
3. In liver diseases, hyperferritinemia is related to increased ferritin release from injured cells in acquired and genetic conditions with or without iron overload.
4. Elevated serum ferritin with normal tranferrin saturation has been associated with alcohol liver diseases, nonalcoholic liver disease, metabolic syndrome, and chronic hepatitis B and C virus.
5. In clinical practice, hyperferritinemia is very common and a careful clinical evaluation is necessary. A history of alcohol consumption, and metabolic risk factors such as obesity, diabetes, dyslipidemia and hypertension should be considered.

Learning objectives:
1. Understand that hyperferritinemia may be associated with acquired and genetic liver diseases with or without iron overload.
2. Identify the most frequent causes and mechanisms of elevated serum ferritin related with liver diseases.
3. Develop an approach to investigate hyperferritinemia in the most frequent genetic and acquired liver diseases.

Abstract:
Introduction
Ferritin is an intracellular protein that stores iron in the liver. It is also an acute phase protein, which is induced in primary and secondary liver disorders, resulting in increased hepatic and circulating elevated serum ferritin (SFE) levels. The mechanism of elevated SFE has been suggested by studies developed in liver cell and tissues. There is evidence that pro-inflammatory cytokine TNFα increases the production of ferritin and that it contributes to iron overload (1-3). Oxidative stress and lipid peroxidation may also induce ferritin release from hepatic endothelial cells, depending on the specific oxidant stimulus (4-6).

In clinical practice, hyperferritinemia (HYF) is common and it may or may not be associated with hepatic iron overload. For patients who present with this finding, a careful clinical evaluation is necessary.

Age, gender and ethnicity are factors that may influence in high levels of ferritin. A multi-ethnic, multi-racial screening study of iron overload was performed in North America (7). Elevated ferritin concentration was defined as >300 ug/l in men and >200 ug/L in women. Transferrin saturation (TS) values >50% in men and >45% in women were considered elevated. An elevated SFE was more frequent in African Americans and lowest in African Americans.

Serum ferritin <1000 lg/L with a normal TS has been reported in the general population in relationship with daily alcohol consumption daily and obesity associated with metabolic syndrome. It also has been observed in anemia due to renal insufficiency, chronic disease, marrow failure and chronic inflammation of different causes (8-10).

Transferrin saturation is also considered a serum marker of iron overload, and it is part of the investigation of HYF. However, reference values of TS vary across laboratories due to differences in analytical techniques and reference populations. In the evaluation of diseases associated with elevated hepatic iron, performing two TS tests (first test random, second test fasting) has been recommended before performing additional diagnostic procedures, including liver biopsy or DNA-based testing. However, it is considered complex to screening program (10, 11).

The most frequent causes and mechanisms of the liver diseases and in other conditions with HYF are presented in tables 1 and 2 respectively. This review discusses the common presentation and approach of most frequent liver diseases that present elevated serum ferritin: hereditary hemochromatosis (HFE C282Y homozygote) and acquired diseases as non-alcoholic fatty liver disease, alcoholic liver disease and chronic hepatitis B and C virus.

Hyperferritinemia and Hemochromatosis
Hereditary hemochromatosis (HH) is a genetic disorder that involves an inappropriate absorption of dietary iron, which leads to the development of severe complications as hepatic cirrhosis and hepatocellular carcinoma (HCC) (11-14).

The principal HFE gene mutation is C282Y, the substitution of tyrosine by cysteine at amino acid position 282 of the protein product. The frequency of C282Y homozygote (C282Y-HH) is estimated in 80%-85% of patients with HH and is associated with hepatic iron overload, HYF and elevated TS (15). Two other mutations have been identified and in general population and are not associated with iron in hepatic cells. They correspond to the substitution of aspartate by histidine at amino acid position 63 (H63D), and the substitution of cysteine for serine at amino acid position 65 (S65C). However, hepatic iron overload can be observed in heterozygote as C282Y/ H63D or C282Y/ S65C. Mutations in other genes coding for iron regulatory proteins (hepcidin, hemojuvelin, transferrin receptor 2, and ferroportin) have been described in inherited iron overload syndromes (11, 14, 16).

Hypferritinemia in HH reflects hepatic iron overload and it should be considered a serologic iron marker in the clinical diagnosis, that also includes, according recent guidelines (8, 14), measurement of ferritin serum and TS; HFE testing (performed only in those with increased TS); evidence of increased iron stores (magnetic resonance imaging (MRI) or liver biopsy). Liver biopsy has been recommended in HH-C282Y homozygous patients with serum ferritin> 1000 lg/L, elevated AST, hepatomegaly, or age over 40 years. In patients with HFE-homozygous and evidence of iron overload, phlebotomy has been recommended; C282Y-HH patients without evidence for iron overload can be monitored annually and treatment instituted when the ferritin rises above normal.
Hyperferritinemia and nonalcoholic fatty liver disease
NAFLD has a large spectrum that includes steatosis, steatohepatitis (NASH), cirrhosis and HCC. It has been considered the most common liver disease in Western countries and is associated with obesity, diabetes, dyslipidemia and elevated cardiovascular risk (17-20).

In NAFLD patients, HYF is considered a marker of histological injury, with or without hepatic iron stores. Several mechanisms for high levels of ferritin have been proposed: genetic background, inflammation, oxidative and endoplasmic reticulum stress, and insulin resistance (IR). Several studies have been demonstrated, that hyperferritinemia in NAFLD may be related with hepatic inflammation, increased iron overload, or a combination of these factors (20-22).

Our group evaluated the relevance of serum ferritin and hepatic iron overload in patients with histological NASH diagnosis and observed that hyperferritinemia was related with iron over load. However, the correlation between liver fibrosis and iron overload was not observed (20). Bugianesi et al (21) observed that HYF in NAFLD patients was a marker of severe histological damage, but not of iron overload. In this case insulin resistance was a major independent risk factor for advanced fibrosis. Kowdley et al (22) in a multicenter study, that includes 628 patients with NAFLD, have demonstrated that HYF (defined as ~1.5 times normal) is an independent predictor of liver damage and a marker to identify patients at risk for NASH and advanced fibrosis. They observed that HYF was associated with hepatic iron deposition and increased inflammation, and it was an independent predictor of advanced hepatic fibrosis among patients with NAFLD.

The relationship of HFE gene mutation and elevated SFE in patients with NASH also has been discussed. Yoneda et al (23) in Japanese patients observed that HYF was significantly higher in NASH patients when compared with those with steatosis, although they didn’t observe a significant difference between the groups with HFE gene mutations C282Y or H63D and S65C. Hepatic iron overload and HFE C282Y and H63D mutations also were investigated in Brazilian patients with NASH. No evidence of hepatic iron overload and HFE mutations were observed in these patients (24). The investigation of HYF in patients with NAFLD should include clinical evaluation, laboratories studies (TS, liver function, enzymes), and depending on the initial results, an MRI or liver biopsy may be considered (Fig 1). The treatment with phlebotomy is controversial. HYF in the majority of the cases is related with liver inflammation. However, it is interesting consider that, in patients who present moderate or severe hepatic iron overload, phlebotomy may decrease insulin resistance, oxidative stress, and levels of TGF-B1, a known stimulant of fibrogenesis (10).

Hyperferritinemia, alcoholic liver disease and chronic hepatitis B and C
These chronic liver diseases are frequently associated with elevated ferritin, although hepatic iron overload is uncommon. Hyperferritinemia in these patients, in general, can be explained by cellular necrosis and inflammation.

In patients with alcoholic liver diseases (ALD), liver iron is increased and it is deposited in both parenchyma cells and Kupffer cells. This excess iron in liver may be an important factor of ethanol injury and toxicity due to the production of reactive oxygen species (9, 25, 26).

In chronic hepatitis C (CHC), it has been suggested that iron overload influences the prognosis of this disease (27, 28). Valentini L et al (28) analyzed the prevalence of altered iron parameters, and the relative contribution of viral, metabolic and genetic factors in Italian patients with CHC. They observed that elevated ferritin was independently correlated with iron stores and host metabolic parameters, whereas hepatic iron deposition was correlated with ferritin and histological severity of hepatitis. The prevalence of HFE mutations and ferritin values increased according to the severity of steatosis. The authors suggest that iron genes influence iron overload and steatosis development, but the major burden is related to HCV itself and host metabolic factors.

In patients with ALD and chronic hepatitis it is important to determine the degree of alcohol consumption, and epidemiology and risk factors of hepatitis B and C. It is necessary to obtain serum hepatic enzymes (AST, ALT, GGT), markers for HBV (HBSAg) and HCV (anti-HCV) infection, and an abdominal ultrasound, and use this initial data to evaluate the need for MRI and liver biopsy. In conclusion, although hyperferritinemia is common in liver diseases, in the majority of cases it does not represent hepatic iron overload. Several mechanisms have been proposed to explain ferritin alteration and its impact on disease severity. An MRI or liver biopsy in patients with HYF can demonstrate elevated hepatic iron and determine the need for phlebotomy. An algorithm is proposed to evaluate patients with hiperferritinemia in liver diseases (Fig 1).

References:

Policy of full disclosure:
None declared

Table 1. Causes of hyperferritinemia in liver diseases

<table>
<thead>
<tr>
<th>Increased ferritin release from liver cells injured</th>
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<tbody>
<tr>
<td>Nonalcoholic liver disease</td>
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<td>Alcoholic liver disease</td>
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<tr>
<td>Chronic viral hepatitis B and C</td>
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<td>Massive liver necrosis due to sepsis</td>
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<td>Acute hepatitis</td>
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<td>Toxic liver injury</td>
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Table 2: Causes of hyperferritinemia in other diseases

| Carcinomas of lung, breast, ovary and kidney |
| Lymphoma and liposarcoma                     |
| Hereditary HYF-cataract syndrome             |
| Autoimmune disorders                         |
| Acute and chronic infections                 |
| Acute myocardial infarction                  |
| Heritable and acquired anemias associated with ineffective erythropoiesis |
| Increased iron absorption from supplementary iron |
| Transfusion iron overload                    |
| Parenteral iron overload                     |
| Aceruloplasminemia                            |
Fig 1: Proposed algorithm to evaluate patients with hyperferritinemia in liver diseases