

HYPERFERRITINAMIA: WHAT THE CLINICIAN MUST KNOW

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Abstract: Ferritin is the main intracellular iron storage protein in all organisms. A small proportion of this protein circulates freely in the blood, constituting an indirect marker of iron deposits in the body. Serum ferritin concentrations $> 300 \mu\text{g/L}$ in men and $> 200 \mu\text{g/L}$ in women determine a state of hyperferritinemia, commonly found in routine laboratory tests in asymptomatic individuals. The key to diagnosis is determining its cause and whether it is related to iron overload. Hereditary hemochromatosis (HH) is the most common cause of iron overload, and is often considered the cause of hyperferritinemia, however, between 58% and 70% of cases do not have iron overload. Among the main causes of hyperferritinemia are: alcoholism, inflammatory syndrome, cytotoxicity and metabolic syndrome. If hyperferritinemia is accompanied by transferrin saturation $>50\%$, a diagnosis of HH must be considered. The etiological diagnosis of hyperferritinemia is made through a careful clinical evaluation, including a detailed history of alcohol consumption, as well as metabolic risk factors (obesity, type 2 diabetes mellitus, dyslipidemia and hypertension). In addition to the clinical history, it is essential to perform ferrokinetic studies (serum ferritin and transferrin saturation). If there is still doubt about the association with iron overload, Nuclear Magnetic Resonance (NMR) must be used, as it is a non-invasive method and allows indirect quantification of the iron content in different organs. If major diagnoses are excluded, it is imperative to investigate rarer causes. It must be remembered that 40% of patients with hyperferritinemia have several causes simultaneously. The treatment for reducing excess iron in patients with hyperferritinemia associated with iron overload is phlebotomy. Other therapeutic modalities such as the use of iron binders and erythrocytapheresis may be considered in patients who cannot tolerate

phlebotomy.

Keywords: Hyperferritinemia; iron; hemochromatosis; iron overload; ferritin.

INTRODUCTION

Iron is an essential component that actively participates in multiple vital metabolic processes. With the advancement of molecular medicine, it was possible to identify the main components of the metabolism of this ion, which enabled a better understanding of its pathophysiology and disorders (GROTTO, 2010).

According to Zandman-Goddard and Shoenfeld (2007), the main intracellular iron storage protein in all organisms is ferritin.

A small proportion of ferritin circulates freely in the blood, therefore, the determination of serum ferritin is the main test to detect iron deficiency or overload in the body, since its value is proportional to the iron reserves available in the body (BOEIRA; CUNHA, 2018). However, although low serum ferritin values are absolute evidence of iron deficits, high values predict iron overload with much less reliability (ALTÉS et al., 2014).

Elevated ferritin, hyperferritinemia, may indicate increased iron stores, but is more commonly seen in acute phase reactions and as a result of ferritin release from damaged cells, or as a result of increased cellular synthesis and secretion of ferritin over several stimuli such as cytokines, hypoxia, oncogenes and growth factors (SANDNES et al., 2021).

Iron overload, the most common cause of which is Hereditary Hemochromatosis (HH), is often considered to be the cause of hyperferritinemia. However, between 58% and 70% of cases do not actually have iron overload. Thus, proper investigation of hyperferritinemia is important to aid in the diagnosis and proper management. Several diagnostic tests are available, but their interpretation can be challenging (ONG;

LITERATURE REVIEW: HYPERFERRITINEMIA

IRON METABOLISM

Iron is an essential component for the formation of Heme, part of the hemoglobin molecule, in addition to participating in multiple metabolic processes, including oxygen and electron transport and DNA and protein synthesis (GROTTO, 2008).

It has two main sources: the diet and the recycling of senescent red blood cells. Dietary iron is found in two forms: organic (heme) and inorganic (Fe^{2+} and Fe^{3+}). An average intake of 14 mg/day of iron is estimated, with 1-2 mg of heme iron and 10-15 mg of non-heme iron. However, only 30% of heme iron and 5-10% of non-heme iron are absorbed, totaling an absorption of about 2 mg/day, necessary for iron homeostasis (BEATON; ADAMS, 2012).

The heme form comes from the breakdown of Hemoglobin (Hb) and myoglobin contained in red meat. Inorganic iron comes from vegetables and grains and is found mainly in the ferric form (Fe^{3+}). Fe^{3+} is insoluble and therefore is not absorbed by the organism, however, it is easily reduced in contact with an acidic medium, passing to the form of Fe^{2+} , being able to be absorbed by the cells of the intestine (LORENZI, 2006).

Phagocytosis and degradation of senescent red blood cells represent an important source of iron (from 25 mg to 30 mg/day). This amount of recycled iron together with the absorption of about 2 mg/day through the diet is sufficient to maintain the daily iron requirement (GROTTO, 2010).

The human body cannot excrete all excess iron. At an average of 1 mg/day, it is eliminated through sweat loss, skin cell desquamation and gastrointestinal leakage (BEATON; ADAMS, 2012).

Different cells are involved in iron metabolism and each plays an essential role in its homeostatic cycle. The four main cells are: duodenal enterocytes that act in the absorption of dietary iron, erythroid precursors associated with iron utilization, reticuloendothelial macrophages responsible for storage and recycling, and hepatocytes that act in storage and endocrine regulation (CULLIS et al., 2018).

The beginning of the metabolization process happens from the absorption of dietary iron by duodenal enterocytes. During the absorption of inorganic iron, Fe^{3+} is reduced to Fe^{2+} by the action of iron reductase so that it can pass through the enterocytes. The transporter DMT1 (Divalent Metal Transporter 1), which acts coupled to ferric reductase, allows the passage of the iron molecule to the cytoplasm of the enterocyte. Iron is exported from enterocytes to plasma via the basolateral transporter ferroportin. In plasma, this ion binds to transferrin, which corresponds to the protein responsible for iron transport. Most of the transported Fe^{2+} is transferred both to iron deposits and to bone marrow erythroblasts (ZAGO; FALCÃO; PASQUINI, 2013).

According to Cullis et al. (2018) the reticuloendothelial cells of the liver, spleen and bone marrow store iron in the forms of ferritin and hemosiderin, and the ferritin molecule has a special structure that allows iron to freely enter and leave its interior, according to the needs of the body.

Hepcidin acts as a regulator of iron influx into the plasma. This molecule is produced in the hepatocyte and binds to the iron exporter ferroportin and induces its degradation, thus decreasing the transfer of iron from enterocytes to the circulation. Therefore, hepcidin is considered a negative regulator of iron metabolism (SOUTO; PUGLIESI; LOPES, 2016; PORTO; OLIVEIRA; PINTO, 2012).

Iron reaches the bone marrow, where it is used by erythroid precursors to form hemoglobin. These cells circulate for a period of 80 to 100 days and then are destroyed by tissue macrophages that metabolize Hb, releasing iron that will be reused by the bone marrow in erythropoiesis (LORENZI, 2006).

FERRITIN

The origin and exact pathway of serum ferritin secretion are still not fully understood. Hepatocytes, lymphoid cells and, mainly, macrophages and Kupffer cells, secrete ferritin (PIPERNO; PELUCCHI; MARIANI, 2023).

Serum ferritin is the method for assessing the status of iron storage in the body, replacing other initial laboratory tests. Its great value lies in the finding that serum ferritin values are directly proportional to iron reserve levels (CULLIS et al., 2018).

In addition to storing iron in a biologically available form for vital and critical cellular processes, it protects proteins, lipids and DNA from the potentially toxic effects of this metallic element (ROSÁRIO et al., 2013).

Its main role is iron sequestration, in which it functions as a ferroxidase, converting Fe^{2+} to Fe^{3+} as the iron is internalized and sequestered in the ferritin mineral core. Iron is toxic in cellular systems because of its ability to generate reactive species that can directly damage DNA and proteins. Ferritin captures and buffers the intracellular iron pool and is therefore a key component in the body. It also plays a role in a large number of other conditions, including inflammatory, neurodegenerative and malignant diseases (KNOVICH et al., 2019).

Ferritin is a protein that has an iron core of up to 4500 Fe^{3+} atoms as an inorganic complex. Apoferritin refers to the free iron form of the protein, while the form that contains internalized iron is called holo ferritin or simply ferritin. (YAMANISHI et al., 2007)

Generally, serum ferritin levels between 30-300 $\mu\text{g/L}$ for men and 15-200 $\mu\text{g/L}$ for women are considered normal, but reference values vary according to each laboratory. Age, gender, menopausal status, weight, race (black), factors such as alcohol consumption and smoking can also alter the ferritin value (ONG; NICOLL; DELATYCKI, 2016). As it is an acute-phase protein, its levels will be increased in the presence of systemic inflammation, commonly related to obesity, diabetes and metabolic syndrome. Serum levels are usually high in individuals with daily and chronic consumption of alcoholic beverages and other chronic liver diseases, such as hepatitis caused by viruses B and C, acute or drug-induced hepatitis, or neoplastic and hematological diseases (BARROS et al., 2017; ADAMS; BARTON, 2011).

While values above the upper limit of normality characterize hyperferritinemia, values below the lower limit of normality indicate hypoferritinemia and, according to the result, the health professional will follow different conducts. Serum ferritin is usually part of the panel of several blood tests and is now a valuable tool for the clinician, both in the evaluation of common disease states, such as iron deficiency anemia, and in the evaluation of hereditary and acquired conditions of iron overload. iron, such as hereditary hemochromatosis and chronic transfusion therapy. Thus, it is routinely requested in order to diagnose and manage these pathological conditions, being considered a useful marker for different clinical diagnoses (WANG et al., 2010).

DIAGNOSTIC INVESTIGATION

According to Cullis et al. (2018) the diagnostic evaluation of the laboratory finding of elevated serum ferritin requires a sequence of steps that include a careful anamnesis and clinical history, physical examination

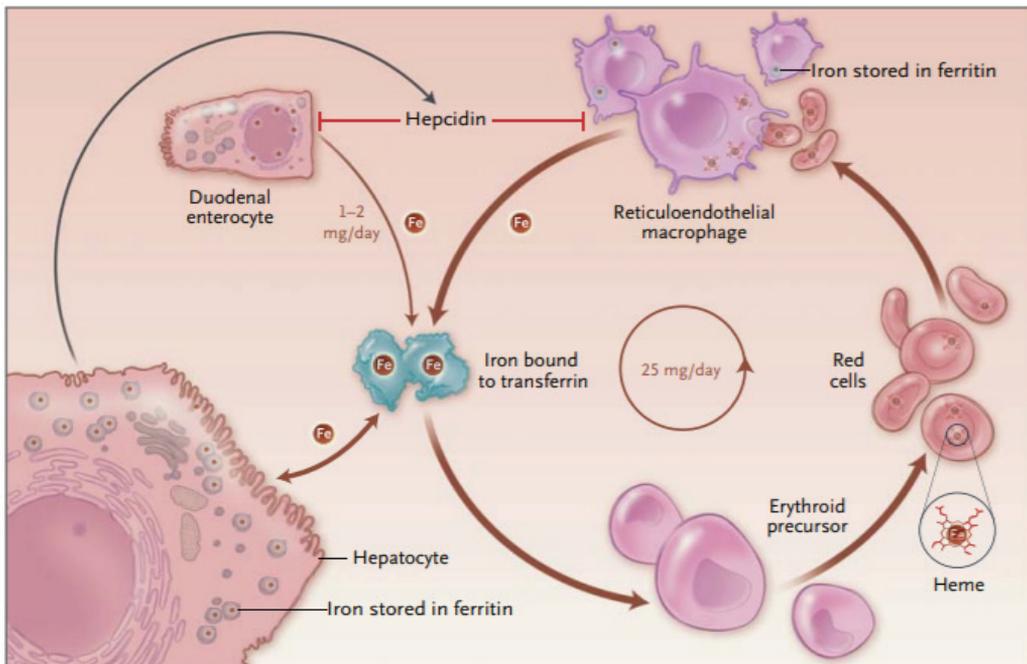


Figure 1. Iron Cycle.

Duodenal enterocytes absorb approximately 1 to 2 mg of iron per day to offset losses. Absorbed iron circulates bound to transferrin and is used primarily by erythroid precursors in the synthesis of heme. Reticuloendothelial macrophages clear senescent erythrocytes and release the iron from heme to export it to the circulation or store it in ferritin. Hepatocytes are another site of iron storage as ferritin and the principal site of production of the peptide hormone hepcidin. Hepcidin blocks the release of iron from enterocytes and reticuloendothelial macrophages by degrading the iron exporter ferroportin.

Figure 1 – Iron cycle. Taken from the article: “Investigation and management of a raised serum ferritin” [12].

Serum Ferritin (300 – 1,000 ug/L) <ul style="list-style-type: none"> <input type="checkbox"/> NAFLD metabolic syndrome <input type="checkbox"/> Daily alcohol consumption <input type="checkbox"/> Systemic inflammation <input type="checkbox"/> Premature hemochromatosis <input type="checkbox"/> Malignancy <input type="checkbox"/> Unknown cause 	Serum Ferritin (300 – 1,000- 5,000 ug/L) <ul style="list-style-type: none"> <input type="checkbox"/> Hemochromatosis <input type="checkbox"/> Aceruloplasminemia <input type="checkbox"/> Mutations in the ferroportin gene <input type="checkbox"/> Hereditary cataract syndrome due to hyperferritinemia <input type="checkbox"/> Alcoholic liver disease <input type="checkbox"/> Viral hepatitis <input type="checkbox"/> Secondary iron overload <input type="checkbox"/> Related to transfusion <input type="checkbox"/> Ineffective erythropoiesis 	Serum Ferritin (300 – 10,000 ug/L) <ul style="list-style-type: none"> >Still's disease >Histiocytosis >Fulminant liver failure
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Table 1 – Associated causes. Adapted from the article: “Treatment of hyperferritinemia” [8].

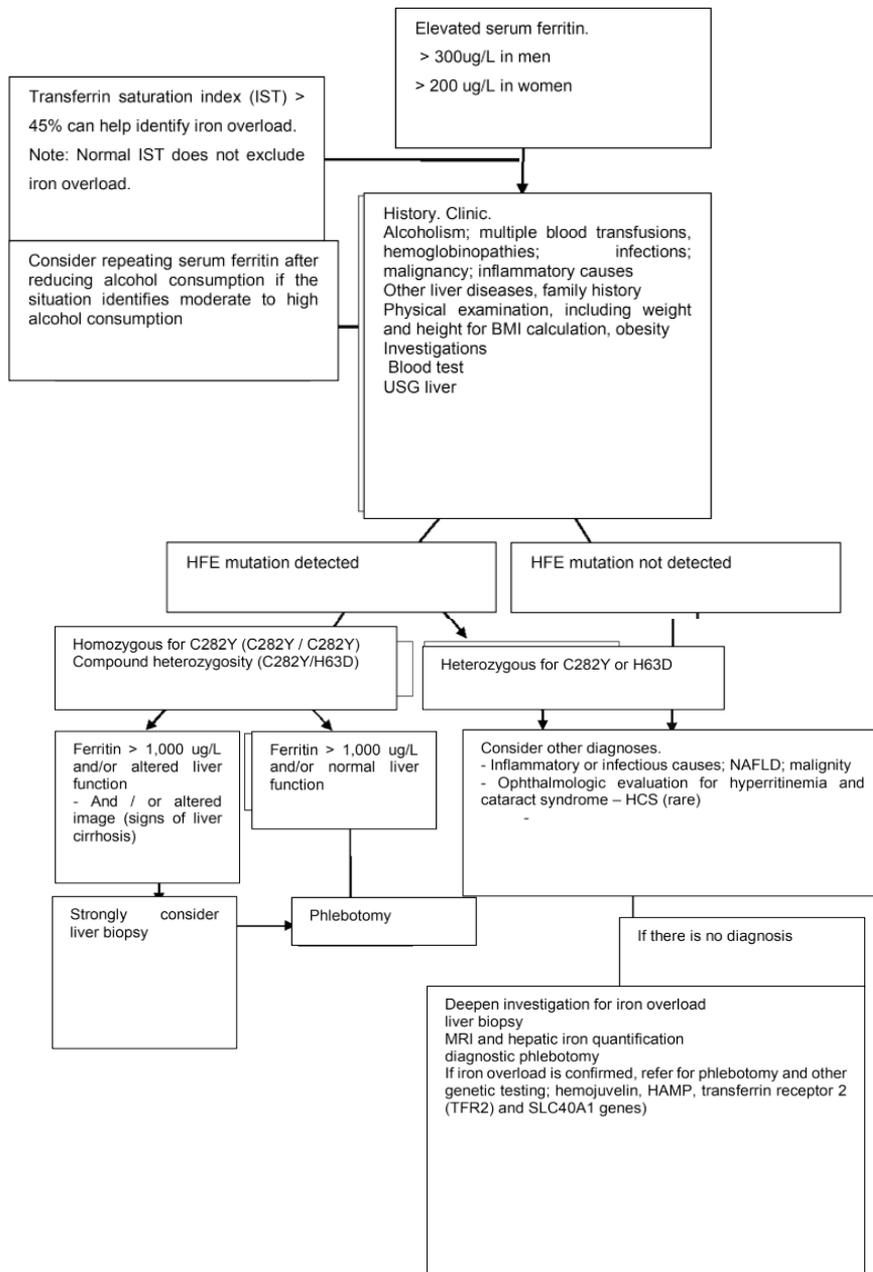


Figure 2 – Investigation algorithm. Adapted from the article: “How must hyperferritinaemia be investigated and managed” [7].

and complementary tests, and must initially question whether this elevation is secondary to a clinical condition or if it is due to iron overload, to institute treatment.

Figure 2, below, shows the algorithm adapted for the investigation of the diagnosis of the patient with hyperferritinemia.

The first step for the diagnostic evaluation in view of the finding of hyperferritinemia is to confirm the serum ferritin values with a new test and request other laboratory tests, such as: serum iron, total iron binding capacity (TIBC), transferrin saturation index, blood count complete, C-reactive protein (CRP), liver function, TSH, blood glucose, cholesterol, triglycerides, creatine kinase, reticulocytes and haptoglobin. Along with the exams, the patient's clinical history must be analyzed (ALTÉS et al., 2014; CAMPUZANO-MAYA, 2017; CULLIS et al., 2018).

In the anamnesis, questions must be asked about alcohol intake and other risk factors for liver disease, history of transfusions or oral iron supplementation, family history of iron overload to delineate hereditary causes, presence or absence of diabetes mellitus, obesity, syndrome metabolism and hypertension, history of early cataracts, as well as symptoms and signs that may point to an underlying chronic or malignant inflammatory process (CAMPUZANO-MAYA, 2017; CULLIS et al., 2018).

According to Sandnes et al. (2021) an important guide in the diagnostic evaluation process for differentiating iron overload and other causes of hyperferritinemia is the transferrin saturation index (IST) analysis. Two consecutive high STI levels, with values above 45% for women and 50% for men, indicate the possibility of a diagnosis of hereditary hemochromatosis (HH).

The IST is one of the tests used to complement the diagnosis of HH. Its result is obtained from the relationship between the

amount of circulating serum iron and the total iron-binding capacity (TIBC), multiplied by 100. Its normal value is between 30% and 40% (SOUZA; CARVALHO FILHO; CHEBLI, 2001). The most accepted cut-off point for the diagnosis of HH is 45% or higher. When the STI value is greater than 50% for women and 60% for men, it has a sensitivity of 92%, specificity of 93% and positive predictive value of 86% for the diagnosis of HH (AYMONE et al., 2013). The quality of the test is due to IST being more stable than serum iron and changing earlier than other markers. With an IST dosage above 45%, together with increased serum ferritin, it is possible to have more than a 90% chance that the diagnosis is HH (SOUTO; PUGLIESI; LOPES, 2016).

However, STI-associated hyperferritinemia greater than 50% can occur in other diseases that are rarely accompanied by hepatic iron overload, such as: alcoholic liver disease, some metabolic syndromes, hepatitis B and C. Conversely, some patients have hyperferritinemia with STI normal associated with hepatic iron overload proven by liver biopsy. Thus, neither serum ferritin concentration nor transferrin saturation values provide definitive evidence of the presence or absence of iron overload (LORCERIE, 2017; WALKER et al., 2010). Therefore, a normal STI must not exclude the diagnosis of hemochromatosis, but both it and serum ferritin must be used together to guide further investigations in the future, such as: HFE genetic testing and/or liver biopsy. The confirmatory HH test is only possible with molecular biology techniques and liver biopsy (BEATON et al., 2012; SOUTO; PUGLIESI; LOPES, 2016).

When obtaining an STI result in two determinations greater than 45%, the next step will be the genetic study for mutation of the HFE gene (C282Y and H63D), as this result will indicate possible iron overload.

If the individual has no detected HFE mutations, or only carries a single p.C282Y or p.H63D mutation, the hyperferritinemia is unlikely to be due to HH. Other common causes of hyperferritinemia (without iron overload) such as non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, inflammatory and infectious causes need to be considered. SOUZA; CARVALHO FILHO; CHEBLI, 2001).

Cançado and Chiattonne (2010) emphasize that complementary tests must also be performed to investigate the diagnosis of iron overload. This can be confirmed by means of a liver biopsy, but currently the Nuclear Magnetic Resonance Imaging (NMR) test, as it is a non-invasive method and allows the indirect quantification of the iron content in different organs, has become an important imaging test for this investigation.

Liver biopsy, considered the gold standard for diagnosis, in addition to assessing liver injury, can be used to measure the Hepatic Iron Index (IHF = micromoles per gram divided by the patient's age) to confirm iron overload (SOUTO; PUGLIESI; LOPES, 2016). The IHF is calculated from the division between the hepatic iron concentration ($\mu\text{g/g}$ dry tissue) by the patient's age (in years), multiplied by 55.8. The final value is expressed in $\mu\text{mol/g}$. For patients with HH, the value found is $> 1.9 \mu\text{mol/g}$. In patients with alcoholic liver disease it is less than 1.5 and in normal individuals it is between 0.7 and 1.1. For individuals with values between 1.5 and 1.8 there is a need for a more rigorous evaluation, since many young people who have HH or who are female have rates within these limits. It is noteworthy that 10% to 20% of C282Y homozygous patients with clinical HH have IHF less than 1.9. IHF is an important marker that can be used to assess iron overload, especially for homozygous patients with the C282Y mutation, since in these patient's tissue deposition increases

proportionally to the patient's age, which does not occur with heterozygotes and in diseases accompanied by some secondary iron overload (SOUTO; PUGLIESI; LOPES, 2016; SOUZA; CARVALHO FILHO; CHEBLI, 2001).

According to Souto, Pugliesi and Lopes (2016), the qualitative analysis of the biopsy is performed using specific stains for iron, such as the Perls stain ("Prussian blue"), observed in Figure 3, below. In patients with HH, grades III and IV are usually found, but lower grades may be present in the early stages of the disease.

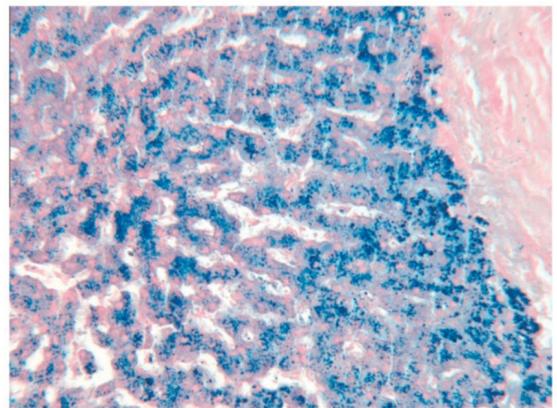


Figure 3 – Liver biopsy and Perls stain.
Retrieved from Article: "A diagnostic approach to hyperferritinemia with a non-elevated transferrin saturation" [25].

Biopsy is essential to: 1. confirm iron overload; 2. identify the characteristic pattern of periportal and hepatocytic distribution of iron deposits; 3. promote semi-quantitative assessment of excess iron; 4. identify the presence of fibrosis or cirrhosis; and 5. detect potential premalignant lesions, such as, for example, free foci of iron deposits (SOUZA; CARVALHO FILHO; CHEBLI, 2001; AYMONE et al., 2013).

Aymone et al. (2013) also says that, although liver biopsy is a generally safe procedure, it is invasive and carries a risk of adverse events, including bleeding and pain, in addition to presenting a mortality risk of 0.01% to 0.1%.

In addition, the biopsy may present inaccurate results depending on the heterogeneity of the sample, with potential diagnostic error, since a single biopsy represents only 1/50,000 of the sample. Thus, routine liver biopsy is no longer used for diagnostic purposes unless the etiology is unclear or it is necessary to assess and document liver damage (fibrosis and cirrhosis) (BEATON et al., 2012; ONG; NICOLL; DELATYCKI, 2016). However, when serum ferritin values are greater than 1,000 ng/ml or in the presence of increased transaminases or hepatomegaly, histological examination is necessary to assess the extent of liver disease (AYMONE et al., 2013).

An indirect way of measuring liver iron content is MRI, which depends on the paramagnetic properties of storage iron (ferritin and hemosiderin). It is a method that helps in the detection of liver fibrosis, but has low sensitivity for diagnosis when the concentrations of this metal are not very high. MRI has shown promise for the accurate, non-invasive measurement of liver iron and as a means of assessing response to therapy for iron overload. Currently, this diagnostic technique is being used as the method of choice to estimate iron overload (BEATON et al., 2012; AYMONE et al., 2013).

Beaton (2012) also describes that abdominal ultrasonography is another exam that can help in the differential diagnosis. This exam is capable of revealing hepatomegaly, infiltration of fat in the liver, biliary disease, liver cirrhosis and the presence of portal hypertension.

DIFFERENTIAL DIAGNOSES

The discovery of hyperferritinemia is often revealed on routine laboratory tests in asymptomatic patients. Iron overload, whose main cause is hereditary hemochromatosis, is often the clinician's first hypothesis.

However, between 58% - 70% of the causes of hyperferritinemia do not occur due to iron overload (ONG; NICOLL; DELATYCKI, 2016).

According to Lorcerie et al. (2017) there are 4 main causes: alcoholism, inflammatory syndrome, cytotoxicity and metabolic syndrome that correspond to 90% of cases. None of these are associated with substantial iron overload in the body. A fifth cause can be considered separately: Hemochromatosis.

If the 5 main causes above are excluded, it is important to proceed with the investigation and remember to ask the patient about factors that lead us to rarer causes. Questions such as: history of pemphigoid lesions on the back of the hand (porphyria), family history of early cataracts (mutation of L-ferritin), blood transfusions, among others. It is important to emphasize that 40% of patients with hyperferritinemia have a combination of one or more diseases simultaneously (LORCERIE et al., 2017).

HEREDITARY HEMOCHROMATOSIS (HH)

HH is the most common genetic disorder, affecting 1 in every 200-400 individuals in populations of Caucasian origin. It is related to several iron metabolism disorders, causing its tissue overload (CANÇADO; CHIATTONE, 2010).

HH is associated with mutations of the HFE gene (located on chromosome 6) which can appear by H63D (homozygous and heterozygous), C282Y / H63D (compound heterozygous), C282Y (heterozygous and homozygous) and S65C. Homozygosity for C282Y affects 1 in 190 individuals while compound heterozygosity for C282Y/H63D affects 1 in 45 individuals in northern European populations. In Brazil, however, the most frequent mutation, which affects about 80% of people with the disease, is H63D. Other

genes involved in iron metabolism in addition to HFE may be related to HH (RIBEIRO, 2013; LORCERIE, 2017).

It is known that the greatest risk of iron overload is associated with homozygosity for the C282Y mutation, but it is estimated that less than 50% of individuals homozygous for this mutation will develop laboratory or clinical evidence of iron overload. Although the C282Y mutation is necessary for diagnosis, it is not sufficient for the appearance of HH symptoms. When there is clinical evidence of iron overload in these patients, they usually have a combination of environmental, genetic and clinical factors (CANÇADO; CHIATTONE, 2010; LORCERIE, 2017). The disease occurs more frequently in people between 40 and 60 years of age, and children are rarely affected. Women are less affected, since they have the protection of menstruation, pregnancy and childbirth (RIBEIRO, 2013).

The pathophysiology of hemochromatosis is characterized by an inappropriate increase in intestinal iron absorption, with consequent progressive accumulation of this ion in different organs and tissues, especially the liver, heart, pancreas, skin and joints (RIBEIRO, 2013).

The mechanism of iron toxicity is related to free iron, which acts as a catalyst for oxidative reactions and, consequently, for the synthesis of superoxide and hydroxyl radicals capable of causing great cellular damage, reactive fibrosis, sclerosis and functional insufficiency (CANÇADO; CHIATTONE, 2010; RIBEIRO, 2013).

The sites typically affected by HH are: liver (which is the most frequently affected), in addition to the pancreas, heart, joints and endocrine glands, often the damage caused to these organs is irreversible. Signs such as hepatomegaly, skin hyperpigmentation, hypogonadism, arthropathy, splenomegaly, diabetes mellitus, liver cirrhosis,

cardiomyopathy and/or arrhythmia are more frequently related to HH, in addition, the most referred symptoms are: fatigue (from 70% to 80%), arthralgia/arthritis (from 40% to 50%), abdominal pain (from 20% to 60%), decreased libido or sexual impotence (from 20% to 50%) and weight loss (from 10% to 50%) (ALTÉS et al., 2014; CANÇADO; CHIATTONE, 2010).

The clinical picture of HH is quite variable, insidious, evolving slowly and progressively. Patients often do not develop symptoms or take decades to become symptomatic, such as women, who generally present symptoms five to ten years later than men (CANÇADO; CHIATTONE, 2010).

The diagnosis of HH includes both clinical evaluation and laboratory confirmation of iron overload and research for mutations in the HFE gene. In the laboratory context, persistently elevated STI is the most important and early parameter for the diagnosis of HH, as it generally appears before the symptoms. Serum ferritin, if constantly elevated, is associated with the presence of symptoms and clinical signs related to iron overload. (CANÇADO; CHIATTONE, 2010; RIBEIRO, 2013).

In HH, iron overload is treated by bleeding. In the rare cases in which the patient does not tolerate phlebotomy due to anemia or hypotension, the use of binders is a therapeutic option in the opinion of specialists (MINISTÉRIO DA SAÚDE, 2013).

ALCOHOL

According to Altés et al. (2014) alcohol consumption increases oxidative stress and intestinal iron stores, due to reduced synthesis of Hcpidin. The prevalence of hyperferritinemia among alcoholics varies between 40 - 70%, however, it is still not possible to correlate the amount, frequency and pattern of alcohol intake with elevated ferritin.

Ferritin concentration is normally less than 1000 µg/L and transferrin saturation is normal. Stopping alcohol consumption significantly reduces ferritin levels by approximately 50% in 15 days. However, the return to normal values may take more than 6 weeks (ONG; NICOLL; DELATYCKI, 2016; LORCERIE et al., 2017).

INFLAMMATORY SYNDROME

Serum ferritin, being an acute phase protein, is often elevated in systemic inflammation caused by autoimmune, rheumatological, infectious and neoplastic diseases (ONG; NICOLL; DELATYCKI, 2016). According to Altés et al. (2014) some inflammatory cytokines, especially cytokine 6, have the ability to stimulate the synthesis of ferritin and hepcidin. Increased hepcidin results in iron sequestration by enterocytes and macrophages with bone marrow depletion. This phenomenon is the basis of the anemia of chronic disease that manifests itself in these patients. Serum ferritin levels begin to rise 1 to 2 days after an inflammatory reaction and peak at 8 days.

According to Lorcerie et al. (2017) the increase in ferritin is usually moderate, around 500 – 700 µg/L, and is higher in infections than in autoimmune diseases. However, serum ferritin levels that exceed 2000 µg/L or even more than 10,000 µg/L can occur in septic shock, in infectious diseases with macrophage activation, and in some inflammatory diseases such as Still's Disease.

METABOLIC SYNDROME

According to Lorcerie et al. (2017), approximately 15% of patients with metabolic syndrome have excess iron in the liver. Elevated serum ferritin levels are increasingly being found in patients with features of the metabolic syndrome and insulin resistance. This fact is particularly relevant in the configuration of

non-alcoholic steatohepatitis (NASH), which represents the hepatic manifestation of the Metabolic Syndrome (BEATON et al. (2012).

NASH can progress to cirrhosis of the liver and even to hepatocellular carcinoma without the presence of cirrhosis necessarily. The finding of fatty infiltration in the liver on abdominal ultrasound may suggest the presence of alcohol consumption related or not to non-alcoholic fatty liver disease (NAFLD). Some studies have sought to relate serum ferritin values as a marker for the development of NASH (ONG; NICOLL; DELATYCKI, 2016). Chronic or excessive alcohol consumption usually causes elevation of liver enzymes, especially gamma-glutamyl transferase (GGT). Hepatitis B and C are also related to elevated levels of serum ferritin, with a normal value of transferrin saturation (CULLIS et al., 2018).

TRANSFUSIONAL HYPERFERRITINEMIA

For individuals without iron deficiency, transfusion of >15 to 20 units of RBCs (>10 units in younger children) can cause clinically significant iron overload, as each unit of RBCs contains approximately 250 mg of iron. This iron gradually accumulates in tissues such as the heart and liver. Transferrin saturation is also quite high in these patients (CAMPUZANO-MAYA, 2017; LORCERIE et al., 2017).

HEMOPHAGOCYTIC SYNDROME (HFS)

Reactive HPS is an uncommon condition, associated with several diseases, such as Cytomegalovirus (CMV) and Epstein-Barr (EBV) infections, the latter being the most common, and malignant hematological neoplasms, especially non-Hodgkin's lymphoma. The etiology of HPS is little known, and is related to an alteration in the immune system, involving activation

of lymphocytes and macrophages. It must always be considered in patients with fever of unknown origin, who have pancytopenia associated with the deterioration of other organs (RONCHI JUNIOR et al., 2011).

It is clinically manifested by persistent fever with peaks $>38.5^{\circ}\text{C}$, anorexia, fatigue, weight loss, pancytopenia, hepatosplenomegaly, liver failure and, in several cases, disseminated intravascular coagulation (DIC). It is associated with very high levels of ferritin exceeding 10,000 or even 100,000 $\mu\text{g/L}$. Screening for EBV, CMV, herpes virus, adenovirus, and varicella zoster is important (PCR is preferred over serology). In all patients a bone marrow aspirate must be analyzed (LORCERIE et al., 2017).

Treatment must always be individualized and directed at the underlying disease process. The course of the disease is generally extremely poor, with a rapid course and high morbidity and mortality. The patient evolves to death in approximately 40 to 50% of cases due to multiple organ failure (RONCHI JUNIOR et al., 2011).

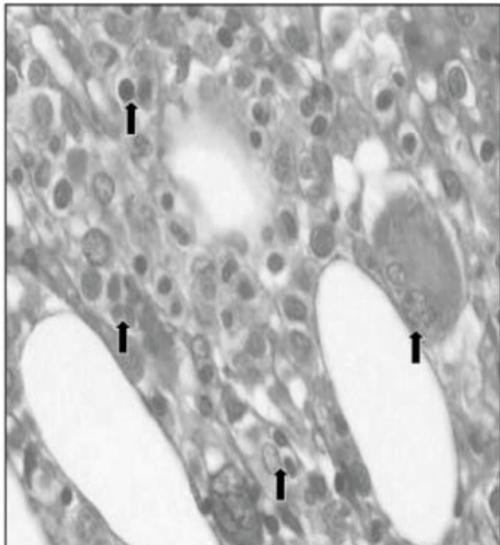


Figure 4 – Macrophages in bone marrow biopsy. Article withdrawal: “Hemophagocytic syndrome. Case report” [27].

COVID-19

According to Zhou et al. (2020) the coronavirus disease 2019 (COVID-19) emerged as a pandemic in 2020 and is associated with a hyperactive immune response in severe disease, related to a high degree of morbidity and mortality. All patients with severe COVID-19 must be screened for hyperinflammation using laboratory parameters such as ferritin, which has proven to be a prognostic marker and an indicator of inflammation in these patients.

Extreme hyperferritinemia with a cytokine profile similar to that seen in secondary HPS is reported in a subgroup of patients with worse outcomes. Serial ferritin measurements can help monitor this hyperinflammatory state and response to treatment, as well as predict worsening and mortality in patients hospitalized with COVID-19 (CHENG et al., 2020). In addition, patients with COVID-19 who had one or more comorbidities had a significantly higher level of ferritin, inferring a worse prognosis in these patients (CHENG et al., 2020).

PORPHYRIA CUTANEA TARDA (PCT)

It is the most common form of porphyria, with a prevalence ranging from 1/5000 to 1/70000 across countries (ONG; NICOLL; DELATYCKI, 2016; CAMPUZANO-MAYA, 2017). This condition can be acquired in 80% of cases or hereditary in 20%. In the past, the disease predominated in men, but currently there is an increased incidence in women, due to estrogen intake and increased alcohol consumption. Its acquired form is associated with hepatitis B and C, chronic alcoholism, HIV, DM, among others (VIEIRA; MARTINS, 2006; OLIVEIRA JUNIOR et al., 2010). PCT results from inhibition of the activity of the enzyme uroporphyrinogen decarboxylase (UROD) in the liver. The hereditary form

also corresponds to a deficit in the activity of the decarboxylase enzyme and results in the accumulation of highly carboxylated porphyrins in the liver, plasma and urine (ONG; NICOLL; DELATYCKI, 2016; CAMPUZANO-MAYA, 2017; LORCERIE et al., 2017).

Both the acquired and hereditary forms are clinically characterized by the onset of blisters, vesicles, crusts and hyperpigmentation of the skin, especially in areas exposed to the sun, such as the face and upper limbs. It can also occur with hypertrichosis, alopecia, photosensitivity and skin fragility. The diagnosis of PCT can be made by determining porphyrins in urine, stool, and blood. These patients must be investigated to rule out iron overload and, if confirmed, an approach through repeated phlebotomies and/or administration of oral chloroquine is indicated in most patients (VIEIRA; MARTINS, 2006; OLIVEIRA JUNIOR et al., 2010; BERTGES et al., 2016).

SERUM FERRITIN LEVELS AND DIFFERENTIAL DIAGNOSES

Ferritin levels may suggest the differential diagnoses to be researched, being one more piece of data to guide the diagnostic investigation. Excess iron, as already mentioned, may be related to malignancy, as a result of both inflammation and cytolysis, specifically hematologic malignancies and hepatocellular carcinoma (HCC). The increased risk of HCC is well recognized in patients with HH and even in the absence of HH, individuals with excess iron in the liver are at increased risk for this cancer (BEATON et al., 2012).

Other rarer diagnoses of hyperferritinemia must be investigated when the cause is not well understood. Some cases such as muscle cytolysis, hereditary hyperferritinemia and cataract syndrome (HCHS), aceruloplasminemia and gaucher disease must

be remembered as causes of hyperferritinemia associated with other specific manifestations of each disease (ALTÉS et al., 2014; ONG; NICOLL; DELATYCKI, 2016; CAMPUZANO-MAYA, 2017; WALKER et al., 2010).

Table 1 correlates ferritin levels with possible differential diagnoses.

TREATMENT

In most cases of hyperferritinemia secondary to inflammatory or other conditions, management of the underlying condition will lead to a reduction in serum ferritin levels. For example, alcohol withdrawal usually leads to improvement in serum ferritin within weeks to months; weight loss and better control of diabetes and blood pressure often lead to reduced ferritin levels in patients with metabolic syndrome (CULLIS et al., 2018).

In cases where there is iron overload due to HH, phlebotomy or therapeutic bleeding is the most effective, economical and safe procedure for the treatment, which includes the removal of excess iron from the body (SOUTO; PUGLIESI; LOPES, 2016; CANÇADO; CHIATTONE, 2010).

Therapy must be started soon after the diagnosis of iron overload, preferably still in the asymptomatic phase of the disease, especially before the development of fibrosis, liver cirrhosis or other irreversible organ damage, which means a significant reduction in morbidity and mortality (AYMONE et al., 2013; CANÇADO; CHIATTONE, 2010).

Souto, Pugliesi and Lopes (2016) describe that phlebotomy consists of removing 450 to 500 mL of blood, which means removing 200 to 250 mg of iron. It is suggested that the procedure be performed weekly, although the interval may vary according to the patient. Treatment can last for weeks or months, depending on the amount of iron and the

person's tolerance for this type of treatment.

Problems that may be associated with this therapy include anemia, severe heart failure, hypoproteinemia, vasovagal reactions, difficulty with venous access, and bruising.

Despite the accumulation of iron, patients with aceruloplasminemia and those with ferroportin disease (HH type 4A) usually have anemia and do not respond satisfactorily, or even cannot tolerate, repeated phlebotomy (CANÇADO; CHIATTONE, 2010).

According to Aymone et al. (2013) when phlebotomy is not feasible (such as, for example, in cases of anemia, advanced cardiac dysfunction or liver cirrhosis), treatment with iron chelators can be performed. Iron chelation is indicated in the following situations: patients with anemia of non-iron deficiency etiology, with hemoglobin below 11 g/L; patients with symptomatic hypotension intolerant of phlebotomy; or patients with no possibility of venous access to perform phlebotomy.

CONCLUSION

Understanding iron metabolism and knowing how to assess the causes of hyperferritinemia are extremely important for the general practitioner, since during the investigation of hyperferritinemia, hereditary hemochromatosis is usually considered the main diagnosis. However, it is necessary to exclude other more common etiologies that correspond to approximately 70% of the causes of hyperferritinemia, such as alcohol intake, non-alcoholic fatty liver disease and inflammatory syndromes. None of these are substantially related to hepatic iron overload. Through a good anamnesis, physical examination and simple laboratory tests, it is possible to determine the most frequent causes. If the etiology of the hyperferritinemia is not identified, it is necessary to refer the patient to a specialist for the investigation of rarer causes.

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