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Hyperferritinemia; More than the Metabolic Syndrome, Inflammation and Hereditary Hemochromatosis

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Abstract

Hyperferritinemia is a common reason for referral to a hepatogastroenterologist. The most frequent causes are not associated with iron overload (e.g. inflammatory diseases, alcohol abuse, metabolic syndrome, etc.). However, hyperferritinemia can also be caused by a genetic mutation in one of the iron regulatory genes, called hereditary hemochromatosis, often but not always associated with iron overload. A mutation in the human Hemostatic Iron Regulator protein (*HFE*) gene is the most common genotype, but many other mutations have been described.

In this paper we discuss two cases of rare hyperferritinemia associated disorders, ferroportin disease and hyperferritinemia-cataract syndrome. We also propose an algorithm for evaluating hyperferritinemia, facilitating a correct diagnosis and preventing potentially unnecessary examinations and therapeutic actions.

Keywords: Hyperferritinemia; Hereditary hemochromatosis; Ferroportin disease; Hereditary hyperferritinemia-cataract syndrome

Introduction

Iron plays an essential role in the human body. Deficiency can lead to anemia, impairment of the immune system and cognitive dysfunction [1]. On the other hand, iron overload can be toxic for human cells [2,3]. The regulation involves Iron Regulatory Proteins (IRP), binding to Iron-Responsive Elements (IRE); as well as a delicate balance of iron absorption, recycling and loss [4].

The most relevant proteins to discuss are transferrin, ferroportin, ferritin and hepcidin. Transferrin is a blood plasma iron transporter and is able to bind iron ions, which it acquires from ferroportin [5]. Ferroportin is acellular exporter of iron, predominantly found on the basolateral surface of duodenal enterocytes and on the membrane of macrophages, allowing iron absorption and recycling [6]. Its expression is inhibited by hepcidin [7,8]. Ferritin is a large cellular iron storage protein, preventing the catalyzation of free radical formation [9]. Iron storage primarily happens in the reticuloendothelial cells and hepatocytes [10]. Hyperferritinemia causes the ferritin proteins to aggregate. These aggregates are broken down to hemosiderin, which slowly releases its iron [11,12].

Hyperferritinemia is a common reason for referral to a hepatogastroenterologists. As such, an extensive knowledge of the work-up is of utmost importance.

The most frequent causes of hyperferritinemia are inflammatory diseases (including neoplasia), hepatitis, alcohol abuse, Metabolic Associated Fatty Liver Disease (MAFLD), metabolic syndrome and acquired iron overload. Hyperferritinemia can also be caused by a genetic mutation in one of the iron regulatory genes, called hereditary hemochromatosis. A mutation in the human Hemostatic Iron Regulator protein (*HFE*) gene is the most common genotype, but many other mutations have been described.

When the most common causes have been ruled out, hepatogastroenterologists should include rare causes of hyperferritinemia in the differential diagnosis, since accurate diagnosis can avoid unnecessary examinations, interventions and phlebotomies. For example, a patient presenting with hyperferritinemia and normal transferrin saturation in the absence of inflammation, features of metabolic syndrome or alcohol abuse requires further analysis. The absence of hepatic/splenic iron overload and intolerance of venesection (resulting in anemia) also are red flags of rare conditions.

In this paper we present two cases of rare hyperferritinemia associated disorders in order to

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increase awareness in your gastroenterologist daily practice.

Case Series

Case 1

A forty-five year old male patient presented with hyperferritinemia (1,624 µg/L) and a transferrin saturation of 36% at the outpatient clinic. Additional blood examination revealed normal liver function tests and CRP. Furthermore, no inflammatory disorders, features of metabolic syndrome or alcohol abuse were present. Gene sequencing showed no *C282Y* gene mutation. A Magnetic Resonance Imaging (MRI) scan of the upper abdomen showed clear iron overload in the liver, not in the spleen. A liver biopsy was performed and microscopic examination revealed moderate liver steatosis and iron overload with a clear gradient pattern, favoring the Kupffer cells. Because of the typical iron overload gradient and radiological features specific genetic analysis was performed, confirming a heterozygous p.Arg178Gln mutation of the *SLC40A1* gene, diagnostic for Ferroportin-associated hereditary hemochromatosis. Monthly phlebotomies were started and were well tolerated. First degree relatives were advised to get yearly blood checks.

Case 2

A thirty-five year old female patient presented with chronic hyperferritinemia (1,600 µg/L) and a transferrin saturation of 46% at the outpatient clinic. Additional blood examination revealed normal liver function tests and CRP. Furthermore, no inflammatory disorders, features of metabolic syndrome or alcohol abuse were present. The patient and her sister had undergone venesections for several years at the general practitioners, resulting in severe iron deficiency anemia. Genetic testing showed no *C282Y* or *H63D* gene mutations. An MRI scan of the upper abdomen showed no signs of iron overload in the liver not in the spleen. Additional anamnesis revealed cataract in several relatives. Our patient did not wish additional genetic analysis to be performed, however her sister did. Specific genetic analysis confirmed a heterozygous c.-160A>G mutation of the *FTL* gene, diagnostic for Hereditary Hyperferritinemia-Cataract Syndrome (HHCS). The patient could be reassured, no more venesections were necessary. There is no need for hepatologic follow-up. Ophthalmological follow-up was provided.

Discussion

Hyperferritinemia is a common reason for referral to hepatogastroenterologists. The most frequent causes are inflammatory diseases, hepatitis, alcohol abuse, MAFLD and metabolic syndrome. It can also be a sign of iron overload, acquired (iron use or blood transfusions) or hereditary. As a result, the first step is to determine whether the elevated ferritin levels truly represent iron overload. A classic work-up consists of a comprehensive patient and family history, a standard blood test including liver function and iron tests; and an ultrasound of the abdomen. When true iron overload is suspected, additional testing is warranted; genetic testing, MRI scans of the upper abdomen and rarely a liver biopsy might be indicated (Figure 1). We suggest doing an MRI scan when ferritin levels are higher than 1000 µg/L.

Hereditary Hemochromatosis type 1 (HH1) is one of the most common genetic disorders in Europe and the most common genetic cause of hyperferritinemia. It is an autosomal recessive disorder with low disease penetrance, caused by a mutation in the *HFE* gene. *C282Y* and *H63D* mutations are the most common. Laboratory findings typically show elevated transferrin saturation and ferritin levels; and sometimes liver function test abnormalities. The diagnosis is confirmed when gene sequencing shows biallelic HFE mutations [13,14]. An MRI scan can be used to quantify liver iron. Liver biopsy is not essential for the diagnosis and should be reserved to evaluate hepatic cirrhosis or fibrosis [14,15].

Genetic analysis excluded this disorder in the two described cases. An important clinical clue pleading against this diagnosis in the second presented case was the development of severe iron deficiency anemia during phlebotomies.

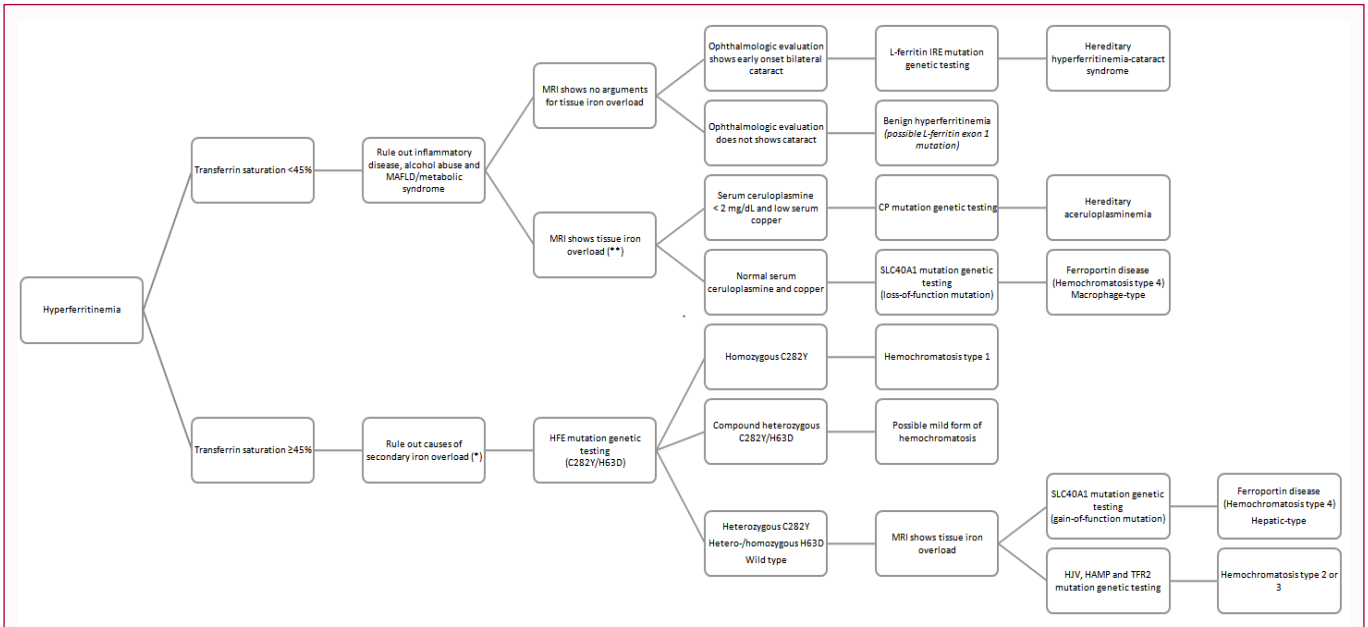

Figure 1: Flowchart differential diagnosis hyperferritinemia. *Iron use, multiple blood transfusions, hematological disorders (e.g. thalassemia, myelodysplasia,…). **Splenic iron overload is very suggestive of ferroportin disease macrophage-type. When in doubt; repeat iron test after 3 to 6 months, consider liver biopsy or specific genetic testing [36].
MAFLD: Metabolic Associated Fatty Liver Disease; MRI: Magnetic Resonance Imaging

Table 1: Summery table, comparing features of HH1, ferroportin disease and HHCS.

	HH1	Ferroportin disease (hepatic-type)	HHCS
Prevalence OMIM	**1/220-250 [14] OMIM #235200**	**<1/1,000,000 [33] OMIM #606069**	**1/200,000 [34] OMIM #600886**
Clinical presentation	Asymptomatic Fatigue, skin hyperpigmentation, arthralgia, impotence Signs of iron overload usually present from the 4th to 5th life decade: diabetes mellitus, liver cirrhosis	Asymptomatic Fatigue, skin hyperpigmentation, arthralgia, impotence, arrhythmias Signs of iron overload usually present from the 3rd to 4th life decade [35]: diabetes mellitus, liver cirrhosis	None Decreased vision/early onset cataract (familial)
Biochemical	Hyperferritinemia Elevated transferrin saturation Liver function abnormalities possible	Hyperferritinemia Elevated transferrin saturation Liver function abnormalities possible	Hyperferritinemia (often ≥ 1000 µmg/L) Normal transferrin saturation
Imaging (MRI)	Signs of hepatic iron overload	Signs of iron overload(no splenic iron deposition)	Normal
Liver biopsy	A degree of iron overload, primarily in the hepatocytes Steatosis, cirrhosis	A degree of iron overload, primarily in the reticulo-endothelial system (Kupffer cells) Steatosis, cirrhosis	Normal
Genetic analysis	HFE gene mutation Autosomal recessive, variable penetrance	SLC40A1gene mutation (gain-of-function) Autosomal dominant, higher penetrance [35]	L-ferritin IRE gene mutation (>25 known mutations) Autosomal dominant [27,29]
Treatment	Therapeutic phlebotomy Avoid iron and vitamin C supplementation	Cautious therapeutic phlebotomy Avoid iron and vitamin C supplementation	No therapeutic phlebotomy Cataract surgery if necessary
Follow-up	Hepatological	Hepatological	Merely ophthalmological
Familial screening	Analysis of iron tests and genetic analysis for all first degree family members	Analysis of iron tests and genetic analysis for all first degree family members	Analysis of iron tests for all first degree family members

The first case described a patient with hepatic-type Ferroportin disease. In this patient presenting with hyperferritinemia, additional genetic testing was performed because of the presence of iron overload. Since this patient presented at our unit eight years ago, a liver biopsy was still performed. Currently we would immediately go for MRI and skip the liver biopsy.

Ferroportin disease, also known as Hereditary Hemochromatosis type 4 (HH4), is a rare genetic condition. Two phenotypes have been described [16]. The macrophage-type or classical disease is caused by loss-of-function mutations, resulting in a ferroportin molecule that is not exporting iron properly. Aside from hyperferritinemia, these patients have normal to reduced transferrin saturation and mild anemia [17-19]. The hepatic-type or non-classical disease is caused by gain-of-function mutations, resulting in a ferroportin molecule that is resistant to hepcidin, in turn resulting in excess iron exportation. These patients have an elevated transferrin saturation and hepatic iron overload, presenting similar to HH1. Anatomopathological examination of liver tissue primarily shows iron overload in the reticuloendothelial system (e.g. Kupffer cells) as opposed to in the hepatocytes, like seen in HH1 [20-26]. Patients are at risk for the same organ complications as patients suffering from HH1, though usually the disease is milder than classical hemochromatosis as iron overload is better tolerated and less fibrogenic than parenchymal cell iron overload. Therapeutic phlebotomy is indicated, however because of poor tolerance a lower frequency should be applied [16].

The second patient was diagnosed with HHCS, first described by Girelli et al. [27] and Bonneau et al. [28] in 1995. In contrast to the previous case, this patient did not present with hepatic/splenic iron overload. Because of the typical family anamnesis of cataract and absolute intolerance of phlebotomies additional genetic testing was performed.

HHCS is characterized by hyperferritinemia (often ≥ 1000 µg/L), with normal transferrin saturation and no arguments for tissue iron overload, in association with early onset bilateral cataract [27].

The responsible gene mutations for HHCS are point mutations and deletions in the highly conserved IRE structure (mRNA), a 5' untranslated region of the light chain or *L-ferritin* gene on chromosome 19. These mutations reduce IRE-IRP binding, resulting in *L-ferritin* upregulation [27,29]. L-ferritin is an isoferritin. It is responsible for stabilizing the ferritin shell and acts as a catalyst promoting iron oxidation. However, it is not involved in iron uptake [9]. Ferritin measured in serum samples mainly contains L subunits. This explains the existence of hyperferritinemia without tissue iron overload. The only organ that is affected by this L-hyperferritinemia is the eye. Lenzhofer et al. [30] described a HHCS patient with a 23 to 25-fold increase in aqueous humor ferritin levels versus a control group, resulting in early onset bilateral cataract. A long-term observational study showed a slowly progressive opacification of the lens over the years [31].

There is no need for any form of treatment, besides management of ophthalmological symptoms. Therapeutic phlebotomy is not indicated, and can even be hazardous since it can cause severe symptomatic anemia.

As a result of the increased availability of MRI, the necessity for liver biopsy to determine tissue iron deposition has diminished. As mentioned, a liver biopsy is not required for the diagnosis of HH1. Specific histological abnormalities can help differentiate in cases of non-HFE hemochromatosis and guide specific genetic testing, however liver biopsy is not required for the diagnosis of ferroportin

disease or HHCS either. The only absolute indication is to stage hepatic fibrosis and rule out concurrent liver disease [14,15].

We acknowledge this article does not cover all hereditary hemochromatosis syndromes, like hereditary aceruloplasminemia, a rare genetic disorder causing iron overload in the brain. Also, juvenile hemochromatosis due to variants in the genes for hemojuvelin (HH2), hepcidin or transferrin receptor 2 (HH3). The latter being an extremely rare autosomal recessive disorder with an early age of onset and a more severe clinical course compared to HH1 and HH4 [32].

Conclusion

In this article we describe two patients presenting with hyperferritinemia. We confirm ferroportin disease in patient number one and HHCS in patient number two. Except for HH1, these two primary iron storage diseases are most prevalent, however often unfamiliar. We discuss (differential) diagnosis and treatment. We propose a flowchart, facilitating a correct diagnosis and preventing potentially unnecessary examinations and therapeutic actions.

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