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Hereditary hemochromatosis: pathogenesis, symptoms, diagnosis and current treatment - literature review

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ABSTRACT

Introduction:

Hereditary hemochromatosis is the most common genetic disorder in Northern Europe. It involves an overload of iron in the tissues due to a deficiency of the protein hepcidin. 85-90% of cases are associated with homozygous mutations of the C282Y gene in the HFE gene. Symptoms are nonspecific and include cardiac disorders, liver cirrhosis, hepatocellular carcinoma, diabetes, hypogonadism and sexual dysfunction, and arthritis. The diagnosis of the disease is based on demonstrating elevated serum ferritin levels and transferrin saturation, as well as identifying the mutation responsible for hereditary hemochromatosis. Early diagnosis is crucial in preventing permanent organ complications. Treatment methods include phlebotomy, therapeutic erythrocytophoresis, and the use of iron chelating drugs. Early detected and properly treated hemochromatosis allows for a lifespan comparable to the general population.

Aim:

The purpose of this article is to provide a comprehensive summary of the etiology, symptoms, diagnosis and treatment of hereditary hemochromatosis with an emphasis on the importance of early detection and treatment of the disease.

Review methods:

A thorough analysis of several dozen research studies from recent years on hereditary hemochromatosis and its complications was conducted. Studies available in PUBMED were reviewed, the following keywords were used to search for sources: hemochromatosis; iron; hepcidin; phlebotomy; deferoxamine; therapeutic erythrocytapheresis.

Conclusion:

Hereditary hemochromatosis is a disease that in most patients runs a covert course. If unrecognized and untreated, it carries many life-threatening complications.

Our work highlights the consequences of excess iron in the body and demonstrates how early detection and appropriate treatment of hemochromatosis can result in a life expectancy comparable to that of the general population.

Keywords: hemochromatosis; iron; hepcidin; phlebotomy; deferoxamine; therapeutic erythrocytapheresis

Introduction

Hereditary hemochromatosis (HH) is the most common genetic disorder in Northern Europe, affecting even 1:200-1:400 individuals. It occurs significantly more often in men. There are four main types of hereditary hemochromatosis (tab. 2). 85-90% of cases involve homozygous mutations of C282Y and heterozygous mutations of C282Y/H63D in the HFE gene on chromosome 6 (chromosome 6p21.3). (1) Types 1, 2, and 3 of hereditary hemochromatosis are inherited in an autosomal recessive manner, while type 4 is autosomal dominant.

In hereditary hemochromatosis, there is an overload of iron in the tissues due to a deficiency of the protein hepcidin - the primary regulator of iron metabolism. The diagnosis is most often made between the ages of 40-50, earlier in males than in females. In females, a physiological regulator of iron levels is monthly menstruation.

Symptoms of hemochromatosis are nonspecific and occur only in about 10% of patients with a homozygous mutation (2). Symptoms include liver cirrhosis, hepatocellular carcinoma, joint pain, sexual disorders including impotence, cardiomyopathy, cardiac rhythm disorders, endocrinopathies such as diabetes, hypogonadism, and hypopituitarism. The most characteristic finding in laboratory studies is elevated ferritin concentration - the iron store in the body, and increased transferrin saturation (3). Genetic testing is the gold standard for diagnosing HH.

Materials and methods

A thorough analysis of several dozen research studies from recent years on hereditary hemochromatosis and its complications was conducted. Studies available in PUBMED were reviewed, the following keywords were used to search for sources: hemochromatosis; iron; hepcidin; phlebotomy; deferoxamine; therapeutic erythrocytapheresis.

Iron Metabolism

Iron is a chemical element essential to life. The daily iron requirement of the human body is 0.5-3.0 mg. The daily loss of iron is about 1 mg, occurring through the shedding of epithelium and epidermis, and in women, additionally through menstrual bleeding. Iron is primarily absorbed in the duodenum and the initial section of the small intestine. Only 10% of the dietary iron is absorbed, and 90% is excreted with feces. Iron can bind with apoferritin to

form ferritin or be transported with a protein carrier - ferroportin - to the extracellular fluid, where it binds with transferrin and as a complex is distributed to the liver or bone marrow. Iron is involved in many biochemical pathways, including hormone synthesis, deoxyribonucleic acid (DNA) synthesis, and is a component of proteins - including hemoglobin, myoglobin - responsible for oxygen transport. Iron plays a crucial role in erythropoiesis, in immunological reactions, and in DNA replication and repair. The total body pool is 3-4 g - about 70% occurs in the form of hemoglobin, and about 20% is stored as ferritin. (4, 5, 6, 7)

Ferritin is a protein whose main role is to store iron - it can store up to 4,500 atoms of iron. It also serves as an acute-phase protein, with its levels increasing in inflammatory conditions, autoimmune diseases, liver diseases, and malignant tumors. (7, 8, 9, 10)
Ferritin possesses ferroxidase activity - it converts Fe^{2+} to Fe^{3+}, which it stores. The ferritin molecule consists of the protein apoferritin and a core containing iron ions. It is composed of 24 subunits of two types - heavy (FTH) and light (FTL) ferritin chains. Tissues that store iron, such as the liver/spleen, contain ferritin primarily composed of light chains, which have a more stable structure and can store more iron than heavy chains. In contrast, tissues with high iron oxidation activity, such as the heart/brain, contain ferritin primarily composed of heavy chains, which have significant antioxidant activity. Ferritin is synthesized in response to high levels of iron, whereas when the demand for iron increases, ferritin undergoes degradation. (11)

Transferrin is a protein produced by the liver, whose main task is to participate in the transport of iron. Transferrin also serves a protective function - it binds free, toxic forms of iron, thereby limiting its chemical activity and preventing the formation of free radicals. Transferrin saturation (TSAT) determines how much iron is bound to transferrin and is calculated as the ratio of serum iron to total iron-binding capacity (TIBC) x 100%. The normal range for TSAT varies from 20-45% and is elevated in HH. (6, 12, 13)

The concentration of iron is primarily regulated by hepcidin - a system-wide regulator of iron homeostasis. **Hepcidin** is a protein secreted by the liver, encoded by the HAMP gene, whose main task is to maintain iron homeostasis in the body by regulating iron absorption in the small intestine, regulating iron levels in the plasma, and distributing iron in tissues. Hepcidin secretion depends on the level of iron in tissues, inflammatory states, and erythropoiesis. (7, 14)
An increase in iron concentration signals the release of hepcidin. Hepcidin is then secreted into the bloodstream. Hepcidin binds to the cellular iron exporter, ferroportin. Ferroportin binds

divalent iron and transports it across the cell membrane into the circulation, where it is oxidized by iron oxidase - hephaestin (HFE) - to the trivalent iron form (Fe3+) that binds to transferrin. Binding of hepcidin to ferroportin causes internalization and degradation of both proteins. Hence, hepcidin is a direct inhibitor of ferroportin. Hepcidin inhibits iron absorption from the gastrointestinal tract and inhibits its release from macrophages - resulting in reduced serum iron concentration. Under conditions of iron deficiency, there is a decrease in hepcidin secretion by hepatocytes. This prevents degradation of ferroportin and allows the release of iron into the bloodstream, simultaneously increasing iron absorption in the gastrointestinal tract - a process handled by enterocytes of the duodenal villi.

Like ferritin, hepcidin is an acute-phase protein - in acute inflammatory states or chronic diseases, its concentration increases. Reduced hepcidin levels occur in conditions of iron overload such as HH, in thalassemias, dyserythropoietic anemias, and in states of iron deficiency. (7, 14)

Maintaining proper iron levels is crucial, as both deficiency and excess of this element are undesirable. Iron deficiency results in anemia, pica eating disorder (consumption of non-edible substances such as chalk), delayed psychological development, and weakened immune system response. Excess iron can also be toxic - unbound divalent iron participates in the Fenton reaction. This results in the formation of highly reactive hydroxyl free radicals, followed by 8-oxo-2'-deoxyguanosine, which causes damage to lipids, proteins, and DNA mutations leading to the process of carcinogenesis. (15)

Diagnosis

The first and very characteristic biochemical indicator of iron tissue overload is an elevated transferrin saturation (TSAT >45%). An increase in TSAT can precede an increase in ferritin by several years. (13) In hereditary hemochromatosis, the TSAT level exceeds 45%, while the ferritin levels in females exceed 200 ng/ml, and in males and postmenopausal women exceed 300 ng/ml. These are not specific markers for hemochromatosis, as their elevated values also occur in many other disease entities. (tab.1)

tab. 1 Laboratory Tests Used in the Diagnosis of Hereditary Hemochromatosis (16, 17)

Diagnostic test	**Criteria for hereditary hemochromatosis**	**Differentiation**
Ferritin	>200 ng/ml in females >300 ng/ml in males	1. Hereditary Hemochromatosis 2. Still's Disease 3. Macrophage Activation Syndrome 4. Hemophagocytic Lymphohistiocytosis (HLH) 5. Acute Phase Reaction 6. Chronic Kidney Disease (CKD) 7. Alcoholic Hepatitis 8. Chronic Viral Hepatitis Type B and C 9. Excessive Iron Supplementation 10. Multiple Blood Transfusions Due to Chronic Anemia
Transferrin Saturation	>45%	1. Hereditary Hemochromatosis 2. Sideroblastic Anemia 3. Excessive Iron Supplementation 4. Chronic Liver Diseases

The gold standard for detecting HH (Hereditary Hemochromatosis) is genetic testing. 80-90% of patients with clinically symptomatic HH are homozygous for the p.C282Y variant in the HFE gene. Detecting homozygous C282Y mutations, along with elevated serum ferritin levels and increased transferrin saturation, is sufficient for diagnosing HH. (18) In patients with symptoms of iron overload and proven iron overload, such as increased iron stores in the liver shown in biopsy or MRI, and a negative test for p.C282Y homozygosity, it is advisable to conduct genetic tests for other genetic variants associated with HH. (tab.2) (18)

Features of iron overload and a negative HFE mutation for a young person, especially before the age of 30, may indicate the presence of juvenile hemochromatosis (JH). This is a very rare form of hemochromatosis - affecting only about 1 in 4.8 million people - females and males equally. Juvenile hemochromatosis, depending on the subtype, is caused by mutations in the HJV gene on chromosome 1q21 (subtype 2A) or in the HAMP gene on chromosome

19q31.1 (subtype 2B). Only a few cases of type 2B HH have been recorded. The most common symptoms of JH are hypogonadism and cardiomyopathy. (19, 20, 21, 22)

Table 2. Types of hereditary hemochromatosis (2)

Type	Gene	Inheritance
1A (homozygous)	HFE - mutation C282Y	**AR**
1B (heterozygote)	HFE - mutation C282Y, H63D	**AR**
1C	HFE - mutation S65C	**AR**
2A (juvenile hemochromatosis)	HJV	**AR**
2B (juvenile hemochromatosis)	HAMP	**AR**
3HH	TFR2 (transferrin receptor 2)	**AR**
4A	SLC40A1	**AD**
4B	SLC40A1	**AD**

Ferritin levels above 1000 ng/ml are associated with higher mortality and a more frequent occurrence of liver cirrhosis and hepatocellular carcinoma (HCC) (23) and are an indication for performing a liver biopsy. (13)

Liver elastography (FibroScan) is a useful tool in the diagnosis and detection of complications of HH. It is a non-invasive test that detects liver fibrosis. (13)

In a study conducted by Legros et al., it was shown that elastography has an 86% sensitivity and 91% specificity in detecting liver fibrosis. Despite this, liver biopsy remains the gold standard for assessing liver fibrosis. (24)

Symptoms and Complications of Hereditary Hemochromatosis

The classic triad of HH symptoms - diabetes, liver cirrhosis, and skin hyperpigmentation - currently occurs in only 10% of patients. (25)

Most cases of HH are diagnosed due to abnormal laboratory results (elevated ferritin levels) or the occurrence of hemochromatosis in family members. (26)

Symptoms of hereditary hemochromatosis include skin hyperpigmentation, hepatomegaly, liver cirrhosis, hepatocellular carcinoma, cardiac complications such as restrictive and dilated cardiomyopathy, cardiac arrhythmias, endocrinological complications including pituitary hypofunction, hypogonadism, diabetes, and arthritis. (13, 27)

1. Heart:

In 10-15% of patients with hereditary hemochromatosis, the main symptoms of the disease are cardiac. The most common cardiac complications are restrictive cardiomyopathy and dilated cardiomyopathy. These complications have a progressive course, and in severe cases, they can lead to death. The risk of developing cardiomyopathy is 306 times greater in patients with HH than in the general population. (28)

Restrictive cardiomyopathy (RCM) is characterized by increased stiffness of the heart muscle, resulting in abnormal filling of the chambers and progressive diastolic heart failure. Systolic function is usually preserved in the early stages. As the disease progresses, systolic dysfunction of both ventricles occurs, sometimes with rapid progression to acute heart failure. RCM can cause symptoms of failure of both the left and right ventricles. (29) In echocardiographic examination, characteristic features include enlargement of the walls of both atria with relatively small ventricles and diastolic dysfunction of the left ventricle and high filling pressures. Chronically elevated LV diastolic pressure induces pulmonary hypertension, which tends to exacerbate right ventricular failure. Atrial enlargement and remodeling can lead to atrial fibrillation. (30)

For dilated cardiomyopathy (DCM), characteristic features include enlargement of the heart chambers - particularly significant is the dilation of the left ventricle with a reduction in ejection fraction and a decrease in the thickness of the heart chamber walls. (31) Symptoms of DCM result from progressive systolic heart failure. Detection of DCM is possible through an echocardiogram, with the diagnostic criteria being LV end-diastolic volumes or diameters >2 standard deviations from normal and an ejection fraction <50%. (32) The definitive diagnosis of cardiomyopathy is made based on a heart muscle biopsy. (6)

A common cardiac symptom in HH is arrhythmias caused by the deposition of iron in the sinoatrial node, atrioventricular node, and the cardiac conduction system, as well as oxidative stress. (33)

Early recognition of cardiac disorders is crucial and allows for the avoidance of permanent complications. Screening for DCM and RCM is performed using transthoracic echocardiography, while cardiac rhythm disorders are detected with Holter ECG monitoring.

2. Liver

The liver is the main iron storage site in the body, which makes it the organ most susceptible to iron overload. (34) The most common hepatic complications of hereditary hemochromatosis (HH) are liver cirrhosis and hepatocellular carcinoma (HCC). Iron accumulation in hepatocytes leads to their damage and the development of fibrosis, which then progresses to cirrhosis and HCC. (35) The risk of liver cirrhosis in patients with HH is 13 times higher than in the general population. (6)

Hepatocellular carcinoma is the most common primary malignant tumor of the liver. It originates from hepatocytes and most often develops on the basis of liver cirrhosis. HCC occurs in 8-10% of patients with HH and is the cause of 45% of deaths in HH. (35) Patients with HH have a 20-fold higher risk of developing HCC over their lifetime compared to the general population. (2, 36) The risk of developing HCC in patients with HH is further increased by chronic HBV infection and alcoholism. (35) Alcohol increases iron absorption and accelerates liver damage. (6) Hepatocellular carcinoma, if detected early enough, can be effectively treated. The treatment of choice is radical resection or liver transplantation - possible for patients who meet the Milan criteria, i.e., a single tumor $\leq$ 5 cm or up to three separate tumors, none larger than 3 cm. (37) Resection is performed for tumors localized within one lobe, without vascular invasion, metastasis, and with preserved liver function. (38) In advanced-stage HCC, sorafenib - a multi-kinase inhibitor with both antiproliferative and antiangiogenic activity - has proven effectiveness. (39) In palliative treatment, ablative therapy and transarterial chemoembolization (TACE) are used, which involves direct administration of appropriately large doses of cytostatics to the arteries supplying the tumor.

3. Hypogonadism, Infertility

Approximately 50% of men with hereditary hemochromatosis experience sexual dysfunctions such as erectile problems, ejaculation issues, reduced libido, decreased body hair, impotence, less commonly gynecomastia, and infertility. Hypogonadotropic hypogonadism is

the second most common endocrinological complication in HH after diabetes, occurring in about 10% of cases. (40) The mechanism of hypogonadism in HH includes damage to the pituitary gland as well as dysfunctions in the gonadotropic axis - reduced production of Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH), but also direct damage to the testicles and reproductive cells. In some cases, the testicles atrophy due to insufficient secretion of gonadotropins, secondary to iron accumulation in the pituitary gland. (41) A decrease in LH levels results in reduced testosterone production by Leydig cells, leading to decreased sexual drive and ejaculation problems. Physiologically, FSH acting on Sertoli cells stimulates spermatogenesis and ensures the proper development of the seminiferous tubules. (42) Histological examination of the testicles in patients with HH showed arrest of sperm maturation at the spermatocyte stage, associated with iron deposition in endothelial cells and perivascular spaces. In females, symptoms of hypogonadism include secondary amenorrhea, loss of libido, abnormal menstrual cycles with lack of ovulation, infertility, premature menopause, and loss of body hair.

Hypogonadism in HH is more frequent and severe in males. In females, physiological regulators of iron concentration include regular iron loss during menstruation, lactation, pregnancy, and childbirth.

The treatment for hypogonadism focuses on addressing the underlying condition, HH. Normal pituitary function can be restored within a few months. During this time, replacement therapy is recommended - testosterone for men and estrogens and progesterone for women. (41)

4. Diabetes

Diabetes occurs in approximately 20% of patients with HH (Hereditary Hemochromatosis). The pathogenesis of diabetes development in the course of HH is multifactorial. Most likely, the primary factor is the loss of insulin secretion ability caused by the deposition of iron in the pancreas. Secondary roles are played by insulin resistance, liver cirrhosis, and metabolic syndrome. (43) The effectiveness of phlebotomy in treating diabetes is dubious, with scientific research results being contradictory. It is certain, however, that phlebotomy improves insulin secretion in the early stages of the disease. (44) The frequency of occurrence of microvascular and macrovascular complications is similar to that in the general diabetic population. (45)

5. Arthritis

Arthritis symptoms are common in patients with symptomatic hereditary hemochromatosis and can significantly impair their quality of life. The mechanism underlying the development of arthritis associated with excess iron levels remains not fully understood. The most commonly affected joints are the metacarpophalangeal joints, wrist joints, knee joints, hip joints, and shoulder joints. Radiological examinations of hand joints often reveal the presence of osteophytes, joint space narrowing, bone sclerosis, and subchondral cysts. In the differential diagnosis of arthritis in the course of hemochromatosis, it is important to consider diseases associated with CPPD deposition (calcium pyrophosphate dihydrate deposits), which can be challenging as both conditions may present similar radiographic appearances. Iron is known to impede the removal of CPPD crystals from the joint, which can exacerbate inflammation symptoms. The symptoms of arthritis in HH can also resemble those of osteoarthritis or rheumatoid arthritis. (46, 47)

According to current research, there is a strong correlation between arthritis in the course of hemochromatosis and advanced liver fibrosis. The absence of arthritis indicates a low probability of advanced liver fibrosis. The presence of arthritis in the course of the disease might serve as a marker for advanced liver fibrosis. (48)

Treatment of arthritis includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), rehabilitation, and surgical interventions, including joint arthroplasty. (49)

Treatment

The cornerstone of treatment for hereditary hemochromatosis is phlebotomy, a procedure involving blood removal to eliminate excess iron from the body. The treatment protocol includes an induction phase, a maintenance phase, and a monitoring phase. During the induction phase, 350-500 ml of blood containing approximately 250 mg of iron is drawn every 1-2 weeks. Hemoglobin levels must be checked prior to each blood draw - if the hemoglobin concentration is <11-12 g/dl, the phlebotomy should be postponed. Ferritin levels should be monitored approximately every four sessions. Phlebotomy is repeated until ferritin serum levels are reduced to <50 ng/ml and transferrin saturation falls below 50%. The maintenance phase consists of 2-4 blood draws per year, aiming to keep ferritin levels within the range of approximately 50-100 mg/l. Ferritin levels should subsequently be monitored approximately every 6 months. A potential complication of HH that may not respond to phlebotomy treatment

is arthritis. Patients with cardiovascular or hepatic complications may not tolerate this treatment well. (6, 29, 50)

An alternative to phlebotomy is therapeutic erythrocytapheresis (TEA), which involves the extraction of erythrocytes from whole blood. This method is specifically recommended for patients with advanced complications of the cardiovascular system and liver, who exhibit poor tolerance to the hypovolemia induced by traditional phlebotomy. Erythrocytapheresis is a modern, efficient method (it removes iron from the body faster than phlebotomy) and is better tolerated by patients than phlebotomy, although it is associated with higher costs. TEA can be used in conjunction with deferoxamine therapy, an iron-chelating agent. (26, 50, 51, 52)

Iron chelation therapy is used in severe cases of hereditary hemochromatosis (HH), particularly in patients who have poor tolerance to blood removal, such as those with advanced heart failure. (29, 53) The most commonly used iron chelating agent is deferoxamine. Deferoxamine has low oral bioavailability, therefore it is administered intravenously or subcutaneously, and it has a short half-life, requiring frequent applications. Deferoxamine is particularly beneficial in cardiac hemochromatosis – it reduces iron load in the heart muscle, improves left ventricular function, and prolongs survival. (21) Side effects of deferoxamine include: hypotension and shock, visual and auditory disturbances (ophthalmic and audiologic evaluations are recommended before initiating therapy), allergic reactions, skin reactions, acute respiratory distress, and infections caused by Yersinia enterocolitica and Yersinia pseudotuberculosi.

Alternatives to deferoxamine include orally administered iron chelators - deferiprone and deferasirox. Side effects of these agents can include agranulocytosis, liver fibrosis, renal damage, and neurological disorders. The use of iron chelating drugs can cause a reddish-brown discoloration of the urine. (54)

Hereditary hemochromatosis is not a contraindication to blood donation. (26)

Patients with hereditary hemochromatosis (HH) should maintain a normal, well-balanced diet; there is no need to exclude iron-containing foods. It is advisable to avoid alcohol consumption due to its hepatotoxic properties and raw seafood because of the increased risk of septicemia caused by the gram-negative bacterium Vibrio vulnificus. (6, 29, 44)

Conclusions

Hereditary hemochromatosis (HH) is a disease entity that is asymptomatic in most patients. The occurrence of the classic triad of HH symptoms - diabetes, skin hyperpigmentation,

and liver cirrhosis - is now rare. (47) It is extremely important to measure ferritin levels (iron storage) and transferrin saturation, particularly in patients with unexplained hypogonadism, cardiac disorders, diabetes, or arthritis. Diagnosis is based on genetic testing - identifying mutations in genes, most commonly in the HFE gene. The average time from the appearance of the first symptoms of the disease to diagnosis ranges from 5 to 8 years. (6) Early diagnosis is crucial in preventing organ damage, including hepatocellular carcinoma, which is the cause of death in 45% of HH patients. Available treatment methods - phlebotomy, therapeutic erythrocytapheresis, and iron chelating drugs - are simple, inexpensive, and widespread. (13) Early detection and treatment of HH can result in a lifespan comparable to the general population. (55)

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