DOI: 10.20514/2226-6704-2024-14-6-442-456
УДК 616-003.829.1-06:[616.12-008.64+616.36-004]
EDN: ERQADO

Е.В. Резник[1,2], М.Х. Э. Лауар[1], В.Ю. Воинова[1], Г.Н. Голухов[1,2]

[1]— Федеральное государственное автономное образовательное учреждение Российский национальный исследовательский медицинский университет имени Н.И. Пирогова Министерства здравоохранения РФ, Москва, Россия
[2]— Государственное бюджетное учреждение здравоохранения Городская клиническая больница № 31 им. Акад. Г.М. Савельевой Департамента Здравоохранения Москвы, Москва, Россия

ГЕМОХРОМАТОЗ И ПОРАЖЕНИЕ СЕРДЦА

E.V. Reznik[1,2], M.H. E. Laouar[1], V.Yu. Voinova[1], G.N. Golukhov[1,2]

[1]— Pirogov Russian national research medical University of the Ministry of healthcare of the Russian Federation, Moscow, Russia
[2] — GBUZ «City Clinical Hospital № 31» named after. Academician G.M. Savelyeva of Healthcare Department of Moscow, Moscow, Russia

Hemochromatosis and Heart Involvement

Резюме

Гемохроматоз при отсутствии терапии представляет собой опасное для жизни состояние, связанное с избыточным содержанием железа в организме. Выделяют первичный (наследственный) гемохроматоз, возникающий в результате мутаций генов, и вторичный (приобретенный) в результате чрезмерного потребления или поступления железа с пищей или в составе лекарственных препаратов, заболеваний печени или многократных гемотрансфузий. Отложение избытка железа в паренхиматозных тканях приводит к клеточной дисфункции и клиническим проявлениям заболевания. Чаще всего поражаются печень, поджелудочная железа, суставы, кожа, гипофиз и сердце. Гемохроматоз сердца в ряде случаев приводит к развитию сердечной недостаточности, которую потенциально возможно предотвратить. Первоначально развивается диастолическая дисфункция и нарушения ритма, на более поздних стадиях — картина дилатационной кардиомиопатии. Выявить признаки поражения сердца при гемохроматозе можно с помощью комплексной 2D- и допплеровской эхокардиографии, МРТ сердца с измерением времени релаксации T2* и других диагностических методов. «Золотым стандартом» диагностики первичного гемохроматоза является генетическое тестирование, которое должно проводиться всем пациентам с подозрением на данную патологию после исключения вторичных причин перегрузки железом. Основу терапии гемохроматоза составляют лечебная флеботомия и хелатирование железа. Средняя продолжительность жизни у нелеченых пациентов с гемохроматозом и тяжелой сердечной недостаточностью не превышает одного года. Однако при раннем и агрессивном лечении выживаемость приближается к таковой у пациентов с сердечной недостаточностью другой этиологии.

Ключевые слова: *гемохроматоз, сердце, сердечная недостаточность, аритмия, флеботомия, фиброз печени, цирроз печени, гепатоцеллюлярная карцинома, сахарный диабет, хелатирование железа, эритроцитаферез*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 11.06.2024 г.
Одобрена рецензентом 08.07.2024 г.
Принята к публикации 24.07.2024 г.

Для цитирования: Резник Е.В., Лауар М.Х.Э., Воинова В.Ю. и др. ГЕМОХРОМАТОЗ И ПОРАЖЕНИЕ СЕРДЦА. Архивъ внутренней медицины. 2024; 14(6): 442-456. DOI: 10.20514/2226-6704-2024-14-6-442-456. EDN: ERQADO

Abstract

Hemochromatosis is a life-threatening condition if left untreated, that is caused by excess iron in the body. It can be primary (hereditary) hemochromatosis, resulting from genes mutations, and secondary (acquired) as a result of excessive intake of iron from food or drugs, liver diseases or repeated

blood transfusions. Deposition of excess iron in parenchymal tissues leads to cellular dysfunction and clinical manifestations of the disease. The liver, pancreas, joints, skin, pituitary gland and heart are most often affected. Cardiac hemochromatosis is an important and potentially preventable cause of heart failure. Initially, diastolic dysfunction and arrhythmias develop, at later stages a picture of dilated cardiomyopathy can appear. Signs of heart damage in hemochromatosis can be detected using complex 2D and Doppler echocardiography, cardiac MRI with T2* relaxation time measurement and other diagnostic methods. Genetic testing is the gold standard for diagnosing hemochromatosis and should be performed after secondary causes of iron overload have been excluded. The basis of therapy is therapeutic phlebotomy and iron chelation. Median survival is less than a year in untreated patients with severe heart failure caused by hemochromatosis. However, with early and aggressive treatment, survival approaches that of patients with heart failure of other etiologies.

Key words: *hemochromatosis, heart, heart failure, arrhythmia, phlebotomy, liver fibrosis, liver cirrhosis, hepatocellular carcinoma, diabetes mellitus, iron chelation, erythrocytapheresis*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 11.06.2024
Reviewer approved 08.07.2024
Accepted for publication on 24.07.2024

For citation: Reznik E.V., Laouar M.H.E., Voinova V.Yu. et al. Hemochromatosis and Heart Involvement. The Russian Archives of Internal Medicine. 2024; 14(6): 442-456. DOI: 10.20514/2226-6704-2024-14-6-442-456. EDN: ERQADO

MRI — magnetic resonance imaging, LVEF — left ventricular ejection fraction, ECG — electrocardiogram, NT-proBNP — N-terminal precursor of the brain natriuretic peptide, SAT — transferrin saturation coefficient, SF — serum ferritin, NAFLD — non-alcoholic fatty liver disease, HCC — hepatocellular carcinoma, CT — computed tomography, AFib — atrial fibrillation, DXA — dual-energy X-ray absorptiometry, *HFE* — Human homeostatic iron regulator gene, *HAMP* — Hepcidin anti-microbial peptide gene, *HJV* — Hemojuvelin gene, *TFR2* — Transferrin receptor 2 gene, *SLC40A1* — Ferroportin gene, *DMT1* — Divalent metal transporter 1, T2 — spin echo decay time constant, T2* — gradient echo-induced relaxation time

Introduction

Hemochromatosis is a disease characterized by the systemic iron overload and iron deposition in various organs, including the heart. Two hemochromatosis types exist: primary and secondary disease. Primary hemochromatosis is a hereditary disease, while secondary one results from the prolonged use of iron drugs or frequent hemotransfusion in anemias, liver diseases [1].

Primary hemochromatosis is a hereditary autosomal-recessive disease caused by decreased levels of the regulatory hormone hepcidin which controls iron levels or decreased hepcidin-ferroportin binding. Hepcidin regulates the activity of ferroportin, which is the only known cellular iron exporter. The most common form of hemochromatosis is caused by homozygous mutations in the *HFE* (Homeostatic Iron Regulator) gene, in particular the C282Y mutation, which occurs in over 80 % of patients with this disease form. Less common hemochromatosis forms are associated with mutations in other genes: hepcidin anti-microbial peptide gene (*HAMP*), or hemojuvelin gene (*HJV*), or transferrin receptor 2 gene 2 (*TFR2*), or ferroportin gene (*SLC40A1*), which prevent hepcidin-ferroportin binding. Increased plasma iron levels may lead to iron accumulation in parenchymatous organs and tissues, especially in hepatocytes, pancreatic cells and cardiomyocytes, pituitary gland, testes, which results in organ fibrosis and failure. The diagnosis of hereditary hemochromatosis includes genetic testing, assessment of serum iron metabolic parameters, imaging data. Hepcidin may become an innovative future approach to the treatment of this disease [2].

The main pathogenetic mechanism of primary hemochromatosis associated with the *HFE* gene mutation is the increased iron absorption in the intestine [3]. When discussing the issue of hemochromatosis, the acquired iron overload (secondary hemochromatosis) is not considered; rare genetic disorders leading to systemic iron excess due to mechanisms different from primary hepcidin deficiency are not excluded. Such disorders include ferroportin loss of function, atransferrinemia, aceruloplasminemia, or iron overload associated with divalent metal transporter 1 (*DMT1*, also known as *NRAMP2*).

Both *HFE*-associated and non-*HFE*-associated hemochromatosis lead to hepcidin deficiency, increased iron influx from the small bowel cells and splenic macrophages into plasma (Fig. 1, 2). Increased plasma iron levels lead to enhanced iron transport into parenchymatous cells (especially hepatocytes, cardiomyocytes, and pancreatic cells), which in turn leads to predominant iron overload of the liver, heart, and pancreas. Despite the role of hepcidin in the pathogenesis of hemochromatosis, its measurement is not necessary

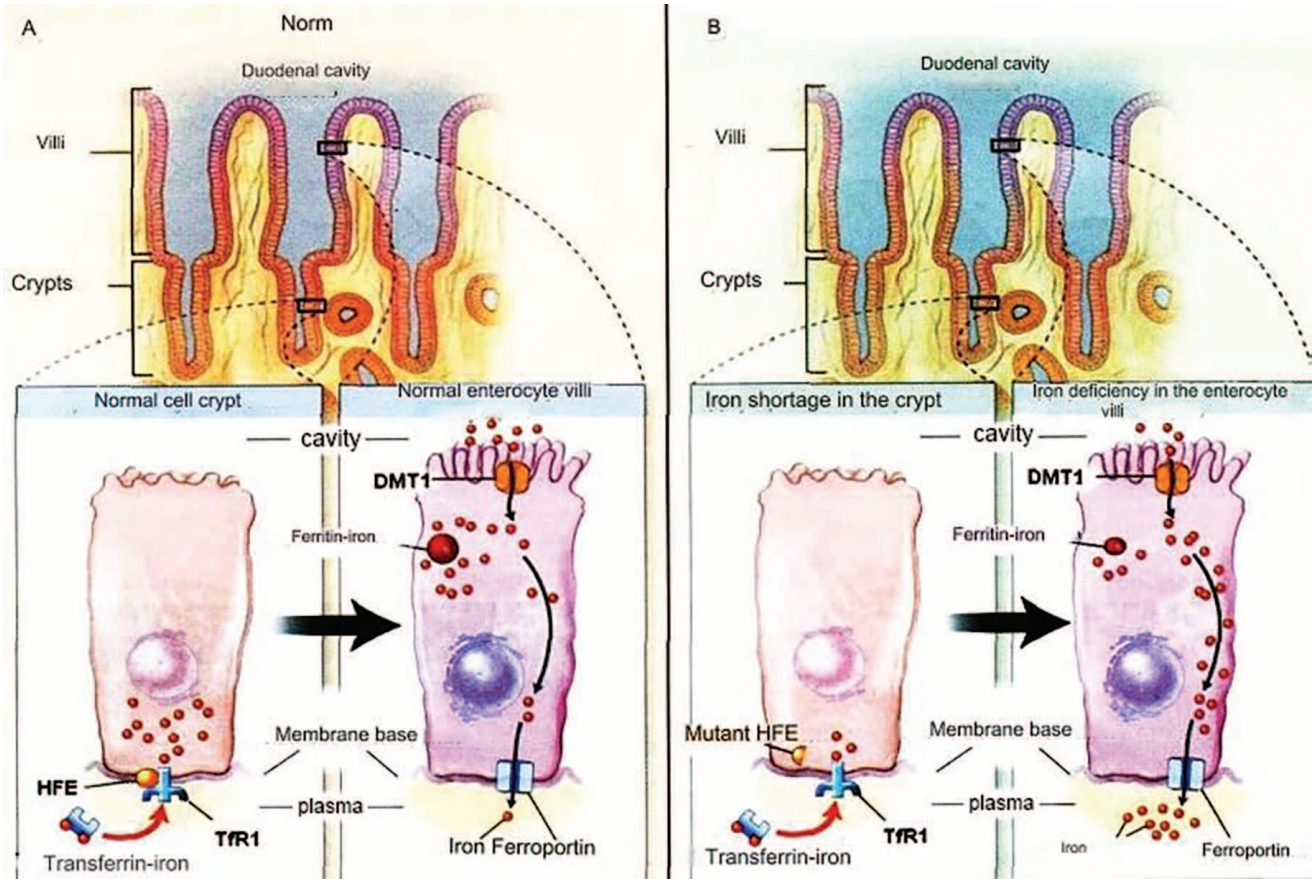

Figure 1. *The mechanism of absorption of iron from food in the duodenum. Arutyunov A.T., Ivanikov I.O., Syutkin V.E. et al. Scientific and practical journal N 9-10, 2008. [Electronic resource]. URL: http://bono-esse.ru/blizzard/img/RPP/Abdomen/Fe3.jpg. (date of the application: 30.04.2024).*

Note. A: Normal, B: With a mutation in the *HFE* gene

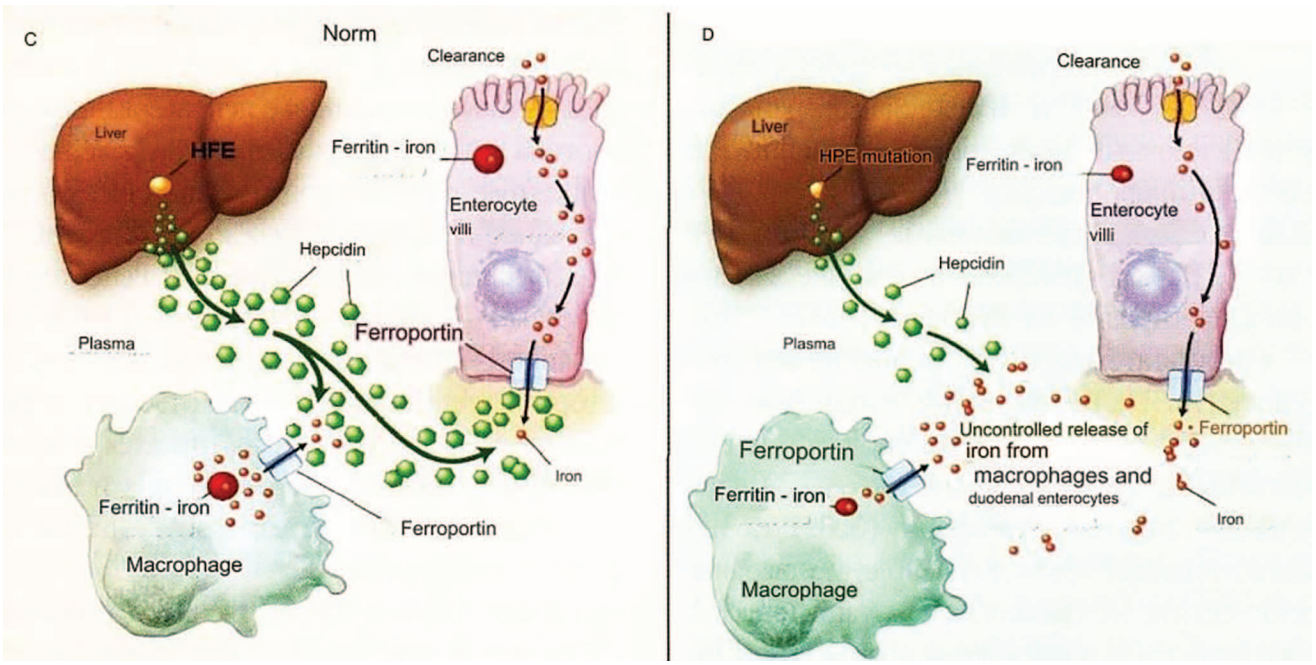

Figure 2. *Model of iron metabolism based on hepcidin. Arutyunov A.T., Ivanikov I.O., Syutkin V.E. et al. Medical advice. Scientific and practical journal N 9-10, 2008. [Electronic resource]. URL: http://bono-esse.ru/blizzard/img/RPP/Abdomen/Fe4.jpg. (date of the application: 30.04.2024).*

Note. C: Normal, D: With a mutation in the *HFE* gene

for diagnosis, as increased transferrin saturation (with iron) or increased plasma ferritin levels are considered sufficiently specific hepcidin deficiency markers. Transferrin saturation is the ratio of the number of occupied iron binding sites to the total number of plasma transferrin iron binding sites. The increase of this parameter is decisive for the diagnosis of hemochromatosis. Besides, strict interpretation of serum ferritin levels (which is the main iron depot protein in the body) should be used for diagnosis.

- **Epidemiology of hemochromatosis**

When *HFE* gene was first identified as a hemochromatosis-associated gene, the most common causes of this disease were identified as homozygous p.Cys282Tyr (C282Y) and p.His63Asp (H63D) mutations.

Homozygous p.C282Y variant in the *HFE* gene occurs among over 80 % of Caucasian people with hemochromatosis. Homozygous p.H63D mutations is detected no more frequently among patients with non-p.C282Y homozygous hemochromatosis than in the general population. The total prevalence of p.C282Y/p.H63D compound heterozygotes among patients with clinically overt hemochromatosis is 4.1 % [4]. However, p.C282Y/p.H63D compound heterozygosity itself is not sufficient to cause hemochromatosis. Phenotypic hemochromatosis develops only if this genotype coincides with additional genetic or ecological risk factors of the liver disease [5].

The incidence of hemochromatosis and its genetic cause in various populations were analyzed in multiple studies. They are summarized in Table 1. It has been demonstrated that the prevalence of the most well-known *HFE* mutations (i.e. p.C282Y and p.H63D) which may cause hemochromatosis varies depending on ethnic groups [6]. The most common cause of hemochromatosis is definitely homozygous p.Cys282Tyr substitution. Among patient with the diagnosis of hemochromatosis in Australia, UK, France, this reaches 96 %, while in Italy it is only 62 %, in Greece — 39 %. p.Cys282Tyr/p.His63Asp compound heterozygosity in the *HFE* gene is more common than p.Cys282Tyr homozygosity, though it has a much lower biochemical and clinical penetrance.

The Hemochromatosis and Iron Overload Screening Study (HEIRS) evaluated the prevalence, genetic and ecological determinants among other hemochromatosis factors in the multiethnical primary care sample among 100,000 adults within 5 years in the USA and Canada. Among 99,711 subjects not belonging to the same family, 299 people were *C282Y* homozygotes. Presumed C282Y homozygosity prevalence was 0.44 % among non-Hispanic whites, 0.11 % among Native Americans, 0.027 % among Latinos, 0.014 % among blacks, 0.012 % among Pacific Islanders, 0.000039 % among Asians. C282Y homozygosity prevalence in Ireland was 1.2 %. Besides, the average prevalence of C282Y homozygosity 0.4 % and C282Y heterozygosity 9.2 % was demonstrated in the review of 27 studies including 6302 Caucasians. The same study demonstrated the prevalence of C282Y homozygosity 0.5 % and C282Y heterozygosity 9 % in the North America. In Asia, Africa, Middle East, and among native Australasians (including indigenous persons, Vanuatu Australians, and Papuans), C282Y homozygosity was not detected (n=3752), though the prevalence of C282Y heterozygosity varied from 0 % to 0.5 %. The prevalence of C282Y/H63D heterozygosity and H63D homozygosity was 2 % both in the Caucasian population; in America, the prevalence of compound heterozygosity was 2.5 %, while the prevalence of H63D homozygosity was 2.1 %. Other studies reported the highest rate of C282Y substitution among Europeans of non-Finnish descent (5.14 % allele prevalence) [7].

Table 1. *Separate population studies of homozygous frequencies HFE p.Cys282Tyr*

Country	Studied population	Cohort size	Frequency of *HFE* p.Cys282Tyr
Australia	Workers	11 307	1 of 221
Australia	Voters of Northern European descent	29 676	1 of 146
USA	Primary Health Care Laboratory Clients	99 711	1 of 333
Great Britain	Persons, registered in the National Health Service	451 243	1 of 156
Norway	Hospitalized persons (Europeans only)	1 900	1 of 136
Spain	Blood donors	5 370	1 of 671
France	Visitors of health assessment centers	9 396	1 of 174

In the USA, almost 1 out of 300 white Caucasians suffers from hereditary hemochromatosis; 1 out of 15 persons of North American descent has at least one mutant *HFE* copy, which is the most common gene mutation associated with hereditary hemochromatosis [8]. Hereditary hemochromatosis is not associated with sex, though it is more likely symptomatic in males. In females, symptoms of hemochromatosis may develop at a later age (after menopause) due to regular menstrual blood losses. Almost 75 % of people have hemochromatis diagnosed before clinical signs develop (mainly due to genetic testing). Despite the high prevalence of *C282Y* homozygosity, only a small amount of people accumulate enough iron to cause organ damage. Accounting for *C282Y* autosomal-recessive inheritance, the prevalence of *C282Y* homozygosity in males and females is the same, though the prevalence of clinical signs differs. One study demonstrated that clinical signs of hemochromatosis were detected only in 28.4 % of males and 1.2 % of females with *C282Y* homozygosity. However, in the beginning of the study, 81.8 % of males and 55.4 % of females had increased serum ferritin levels, i.e. the biochemical penetrance should be higher than the clinical one. Other studies revealed that clinical signs of hemochromatosis developed in 25–60 % of *C282Y* homozygotes. Various factors (i.e. genetic modifiers, environmental or lifestyle factors) probably determine the phenotype in *C282Y* homozygotes [9].

The cohort study that included 22 sites from England, Scotland, Wales (British biobank; in total 451,243 Caucasians) detected 2890 (0.6 %) people with the homozygous *p.C282Y phenotype.* With that, the diagnosis of hemochromatosis was established in 21.7 % of males and 9.8 % of females. This confirms the hypothesis that *p.C282Y*-associated iron overload may be prevented and cured with the early intervention. The study of Brazilian blood donors detected the 2.1 % prevalence of *HFE p.C282Y* alleles.

- **Hemochromatosis classification**

4 hereditary hemochromatosis subtypes have been described — these result from increased iron absorption into the bloodstream from the gastrointestinal tract. Decreased hepcidin activity or synthesis cause the majority of hemochromatosis cases. Type 1 is associated with mutations in the *HFE*gene — this causes over 80 % of hemochromatosis cases, type 2A is caused by mutations in the *HJV* (or *HFE2*) gene, type 2B is caused by mutations in the *HAMP* gene, type 3 is caused by mutations in the *TFR2* gene, type 4 is caused by mutations in the *SLC40A1* gene — these lead to increased ferroportin activity (this disease was initially classified as type 4B, and it differs from the ferroportin disease which is caused by the ferroportin loss of activity and classified as type 4A) [10].

- **Clinical signs of hemochromatosis**

Clinical signs of homozygous *HFE*-associated hemochromatosis (*p.C282Y)* were initially described by A. Trousseau and F.D. von Reclinghausen. Early clinical cohort studies detected significant morbidity and mortality in this disease [11], [12].

After the *HFE* gene discovery, population studies demonstrated various biochemical and clinical signs of hemochromatosis. Crossover cohort studies demonstrated that hemochromatosis was not associated with increased mortality. Later population studies demonstrated that *p.C282Y*-homozygous males (but not females) had a significantly higher risk of death to the age of 75 years (19.5 % vs. 15.1 % in the control group). It was also detected that complex or simple *p.C282Y* and/or *p.H63D* heterozygosity was not associated with the increased risk of premature death [13, 14]. *p.C282Y* homozygosity was associated with significant dementia, delirious disorders, sarcopenia, weakness, and chronic pain in males over 60 years of age [15, 16].

HFE-associated hemochromatosis may be asymptomatic for over 30 years (even over 40 years in males and over 50 in females). In non-*HFE*-associated hemochromatosis, symptoms may emerge at the age of about 20–30 years. In general, symptoms are variable, which explains late diagnosis [17].

In hemochromatosis, iron location in different tissues is determined by several factors, including the disease stage, total iron overload value, and genetic predisposition of specific organs to iron overload. Excess tissue iron may be stored in the reticuloendothelial system until the threshold is exceeded. When this occurs, other organs (including the liver, heart, pancreas, spleen, pituitary gland) may also serve as excess iron depots. Animal studies demonstrate that the source of excess iron may partially determine the iron deposition degree in the heart.

Fatigue and arthralgia are among the most common symptoms. Skin signs mainly include melanodermia (skin pigmentation), sometimes — dry skin and nail changed (even paradoxical koilonychia, a classic sign of iron deficiency anemia). Main hepatic symptoms include hepatomegaly and mild transaminitis with the preserved liver function. Hemochromatosis may cause diabetes mellitus, hypogonadism, or hypopituitarism. It is very important to remember that *HFE*-associated

hemochromatosis occurs in Caucasian people, while non-*HFE*-associated hemochromatosis may be detected in many ethnic groups, although it is much less common [18].

The most common and significant clinical signs include liver diseases and arthritis [19]. *p.C282Y*-homozygous males (but not females) have a more than 4-fold risk of hepatic diseases compared to persons without *HFE* mutations. Male *p.C282Y* homozygotes also have an increased risk of arthritis, colorectal cancer, and diabetes mellitus. Female *p.C282Y* homozygotes also have an increased risk of arthritis, colorectal cancer, and breast cancer compared to females without *HFE* gene mutations [13].

• **Liver pathology:** Progressive liver fibrosis or cirrhosis in non-*HFE*-associated hemochromatosis is rare before the age of 45 years in the absence of other concomitant liver diseases [20]. The risk factors for liver fibrosis or cirrhosis include excessive alcohol consumption, diabetes mellitus, arthritis, serum ferritin levels over 1000 μg/L, and hepatic iron levels over 200 μmol/g [21].

In *HFE p.C282Y*-homozygous males, the lifetime risk of primary hepatic carcinoma is 12-fold compared to males without *HFE* gene mutations. *HFE p.C282Y*-homozygous females do not have increased hepatic carcinoma risks [13]. The largest risk of primary hepatic carcinoma is present in patients with liver cirrhosis [22]; liver ultrasound every 6 months is recommended for timely diagnosis [23].

• **Arthritis:** Joint lesions are detected in at least 24 % of patients with hemochromatosis. Classic arthropathy involves metacarpophalangeal joints, followed by the hip, ankle, wrist, elbow, shoulder, and knee joints, as well as the lumbar spine. It can be hard to differentiate the hemochromatosis-associated arthropathy from osteoarthritis. It is unknown why arthropathy affects only some patients with hemochromatosis. Arthritis may develop at various disease stages and even after successful phlebotomies. Risk factors for arthritis include older age, progressive liver fibrosis, prolonged periods of serum ferritin levels over 1000 μg/L and serum iron transferrin saturation ≥50 % [24].

Hepatic diseases and arthritis usually manifest simultaneously. The probability of arthritis is higher with larger iron loads or during the later stage of liver lesions [17]. The recent study demonstrated that arthritis was closely associated with significant liver fibrosis, i.e. arthritis was diagnosed in 84 % of *HFE p.C282Y* homozygotes with significant liver fibrosis, while 34 % of *p.C282Y* homozygotes with arthritis had significant liver fibrosis. It is important to note that late-stage liver fibrosis was observed only in 5 % of patients without arthritis. Thus, the absence of arthritis had a 95 % negative prognostic value for progressive liver fibrosis [25].

• **Other clinical signs:** Other conditions typical for *HFE p.C282Y* homozygous hemochromatosis include diabetes mellitus, hyperpigmentation, hypogonadotropic hypogonadism, and cardiomyopathy. Such conditions are usually treated in accordance with general clinical guidelines in combination with the iron overload treatment. Cardiomyopathy is a rare complication, which is potentially reversible with iron overload treatment [14].

• **Diagnosis of hemochromatosis**

The modern diagnostic approach to hemochromatosis is non-invasive, i.e. liver biopsy is no longer required. Hemochromatosis may be diagnosed only based on the combination of clinical, laboratory, and imaging data.

1. Laboratory tests

The most common diagnostic biochemistry tests include the following plasma parameters: iron, transferrin saturation coefficient (SAT), and serum ferritin (SF). Increased SAT is the earliest biochemical disorder in hemochromatosis, reflecting increased iron absorption. It is >45 % (often >60 % in males and >50 % in females) and should be confirmed by the repeated test. Increased SF (>300 μg/L in males and postmenopausal females, >200 μg/L in premenopausal females) is typical for hemochromatosis, but this may also occur in inflammatory processes, metabolic syndrome (especially in diabetes mellitus), alcohol consumption, and hepatic lesions [26].

2. Genetic testing

Genetic testing is arranged in patients with high SAT provided that other mechanisms are excluded, except for iron excess in the body (especially hypotransferrinemia due to hepatocellular failure, nephrotic syndrome, or malnutrition). Hemochromatosis should be considered not as a simple monogenic disease, but rather as a complex result of interactions between the environment, lifestyle, and genetic factors that have not been yet identified. It is widely thought that homozygous p.C282Y mutations in the *HFE* gene form the necessary basis for iron excess in the body. Regarding p.C282Y/p.H63D compound heterozygosity, it may predispose only to mild iron overload, and the physician should be cautious when informing the patient, as mentioning

hemochromatosis may lead to unnecessary anxiety of the patient and his/her family.

If the genetic testing for *HFE* gene mutations is negative, further genetic tests may be arranged with other genes participating in iron metabolism and hepcidin synthesis. Non-*HFE*-associated hemochromatosis is less prone to the effects of cofactors and is characterized by a more severe and uniform clinical condition manifesting at a younger age. Modern approaches based on the next-generation sequencing (NGS) expand the diagnostic possibilities of rare lesions; however, at the same time they create issues for the interpretation of results. Tertiary centers (both state and private ones) are required for the NGS technology, its costs remain high, though they tend to decrease with time [26].

It should be noted that the direct sequencing tests for *HJV*, *HAMP*, *TFR2*, *SLC40A1,* and even *HFE* genes in most hospitals is not widely available globally. Treatment usually does not depend on molecular diagnosis. Thus, it is important to remember that patients with the clinical diagnosis of hemochromatosis should not wait for the DNA test results in cases of difficult access to genetic identification to start the treatment [27]. Nevertheless, results of genetic tests are important for the prognosis of the disease course and the assessment of risk of giving birth to sick children in the family.

3. Tissue biopsy

Liver biopsy is the best method for the quantifying assessment of iron overload. However, there's no correlation between iron deposition in the liver and myocardium. Liver deposition in the myocardium progresses slower than iron absorption by the liver. Endomyocardial biopsy may be required for patients with cardiac manifestations. Increased iron levels are always detected during endomyocardial biopsy in patients with the left ventricular dysfunction associated with the cardiac hemochromatosis.

4. Imaging methods

Magnetic resonance imaging (MRI) may be useful for the detection and quantification of iron overload in the body, especially in the liver and spleen (the contrast between significant iron overload in the liver and no iron overload in the spleen is common for hemochromatosis). Laboratory tests in combination with MRI have currently replaced liver biopsy in many situations.

Liver ultrasound is often the first diagnostic step when the patient demonstrates increased liver enzyme levels, or the liver disease is suspected. Ultrasound cannot detect iron in the liver tissue, and, thus, it cannot be used to diagnose iron overload in hemochromatosis, though it may be useful in the differential diagnosis to exclude other causes of elevated liver enzymes and non-alcoholic fatty liver disease (NAFLD). Ultrasound may also be used in the diagnosis of liver cirrhosis and hepatocellular carcinoma (HCC).

Ultrasound elastography (Fibroscan®) of the liver was used to evaluate fibrosis in patients with hemochromatosis only in several studies. The issue of whether this method can be used for *HFE*-associated liver fibrosis diagnosis and follow-up should be analyzed additionally [28].

Computed tomography (CT) of the liver can detect iron in the liver parenchyma, however this method requires special scanner programming, is semi-quantitative, and has several sources of errors. After MRI implementation, CT is rarely used to detect iron concentration in the liver, though it may help to visualize focal liver lesions [29].

X-ray of joints is used to evaluate the degree of arthritis. The rheumatological evaluation system based on X-rays of hands, wrists, knees, and ankles was checked in the group of patients with hemochromatosis and arthritis.

Dual-energy X-ray absorptiometry (DXA) is used to determine the bone tissue density in the diagnosis of osteopenia and osteoporosis [30].

- **Treatment of hemochromatosis**

1. Diet therapy

Patients with hemochromatosis should not take oral iron drugs. Consumption of large vitamin C amounts quickly mobilizes iron from the heart, increases the production of free radicals, and causes lethal arrhythmias. Due to this, synthetic vitamin C should not be used in hemochromatosis, though vegetables and fruit rich in vitamin C may be consumed. Alcohol increases iron absorption, while some red wines contain large amount of iron, so they should not be consumed. The low-sodium diet is indicated for patients with cardiomyopathy and heart failure [31].

2. Iron removal

Phlebotomy. Bloodletting remains the main method of *HFE*-associated hemochromatosis treatment. Phlebotomy is also the preferable treatment method in non-*HFE*-associated hemochromatosis; however, additional oral chelation can be used in the most severe cases (e.g., in patients with juvenile hemochromatosis). Bloodletting is also efficient in the treatment of patients with ferroportin disease, though it should be less frequent, accounting for the risk of anemia due to poor iron recirculation in these patients. Many physicians and patients insist that high serum ferritin levels corresponds to iron

overload, and it should be treated with phlebotomy. However, as mentioned earlier, patients without *C282Y* homozygosity may not always have iron overload.

The aim of phlebotomy is to remove excess iron and prevent further tissue damage. Due to ethical issues, phlebotomy was not analyzed in randomized clinical trials, which makes understanding the natural course of non-treated diseases difficult. Although some persons (rarely) believe that phlebotomy use is not evidence-based, the majority of experts think that this iron store depletion form may improve chronic fatigue and cardiac function, stabilize the liver function, reverse liver fibrosis, and decrease skin pigmentation in patients with hemochromatosis. However, joint symptoms are poorly controlled by phlebotomy and may worsen. The efficacy of bloodletting is good if it was started before the development of liver cirrhosis. Adverse phlebotomy effects emerge in 37–50 % of patients and include phlebitis, malaise, fatigue. If adverse effects emerge, increased intervals between procedures are possible [32].

Phlebotomy is usually arranged in the outpatient setting by nurses. The blood volume of 400–500 mL is usually removed within 15–30 min with the patient in the supine position. This process is repeated weekly until the serum ferritin level reaches ~50 μg/L. Hemoglobin level is also assessed, and the phlebotomy regimen is altered if hemoglobin level drops below 11 g/dL (e.g., 400–500 mL during one session once every two weeks). Simultaneous oral fluid administration (e.g., a salty sports drink) in the volume equivalent to that of blood removed during phlebotomy is important to maintain the plasma volume during the procedure. The duration of induction therapy depends on the iron overload severity, spanning from several months to several years. After the induction phase, supportive phlebotomies are conducted to maintain serum ferritin at the levels of ~50 μg/L. If bloodletting is continued after serum ferritin levels reach <20 μg/L, iron deficiency may occur. Serum hepcidin levels may decrease during bloodletting [33]. Supportive phlebotomies are conducted 2–4 times per year, while this depends on the rate of iron reaccumulation, which varies in different patients. Serum ferritin levels are checked 3–6 months after the completion of induction therapy may be useful to evaluate the rate of iron reaccumulation. Serum ferritin levels may be assessed monthly during induction phlebotomy and weekly when serum ferritin levels drop below 100 μg/L. As soon as serum ferritin reaches 50 μg/L, serum ferritin levels may be assessed annually or during each supportive phlebotomy. Although evidence confirming supportive treatment use is lacking, many patients appreciate it, especially if they can become voluntary blood donors [34].

Despite successful iron depot depletion, transferrin saturation remains increased in some patients. It is proposed that normal transferrin saturation maintenance may improve symptoms greater than ferritin decrease. However, transferrin saturation may not decrease until the patient almost reaches iron deficiency; thus, maintenance of corresponding ferritin and transferrin saturation levels may be difficult [35].

Red blood cell exchange in hemochromatosis. Red blood cell exchange is the method of selective red blood cell removal with or without erythropoietin administration. This process removes iron excess from tissues twice faster than whole blood phlebotomy. When analyzing patients with hereditary hemochromatosis, therapeutic red blood cell exchange demonstrated almost 70 % decrease in the total amount and duration of treatment vs. phlebotomy. Terminal cardiomyopathy associated with hereditary hemochromatosis was successfully treated with red blood cell exchange in combination with the left ventricular assist device [36].

Chelating agents. Bloodletting is not a treatment option for patients with anemia (secondary disorders associated with iron overload) and patients with severe heart failure. Iron chelating agents are considered the treatment of choice in these patients. Iron chelating agents increase the rate of iron elimination due to binding iron in plasma and tissues, removing iron excess. Serum ferritin levels should be checked periodically. If serum ferritin levels drop below 1000 ng/mL, iron chelating agents should not be started. Deferoxamine, deferiprone and deferasirox are three iron chelating agents approved by the US Food and Drug administration for the treatment of secondary chronic iron overload.

Deferoxamine is a hexadentate molecule which directly binds to labile iron in plasma and tissues, including the heart. Deferoxamine has low bioavailability with oral administration and a short half-life. This product is administered as subcutaneous or intravenous infusions. The recommended dose for adults is 40–50 mg/kg/day, which is administered within 8–12 hours 5–7 times a week. Deferoxamine treatment decreased myocardial iron levels almost by 24 %, delays the onset of clinical cardiac hemochromatosis manifestations, reverses cardiac hemochromatosis in early stages, improves the left ventricular function, and increases survival in transfusion-dependent patients with thalassemia. However, prolonged compliance with deferoxamine treatment regimen leaves much to be desired [37].

Deferiprone is an orally active bidentate iron chelating agent approved for the treatment of iron overload in patients with transfusion-dependent thalassemia, in whom the current chelating treatment is inadequate. The starting deferiprone dose is 75 mg/kg/day, divided into 3 administrations. The maximum deferiprone dose is 99 mg/kg/day. Several studies demonstrated that deferiprone decreased myocardium levels better than deferoxamine. It was detected that combined deferiprone and deferoxamine treatment quickly decreases iron overload and improves cardiac function in patients with iron overload, heart failure, and unstable hemodynamics [37].

Deferasirox is a tridentate iron chelating agent with good oral bioavailability approved for the treatment of iron overload related to repeated blood transfusions. The starting oral deferasirox dose is 20 μg/day once daily (with the maximum dose of 40 mg/kg/day). Deferasirox decreases serum ferritin levels, decreases iron overload in the heart and liver. New iron chelating agents studied in the treatment of iron overload-associated diseases include silibine, deferitrine, and starch-conjugated deferoxamine. The transcutaneous iron and ferritin excretion using the Al-Hijama method (specific transcutaneous blood volume removal using special pots) is a new method of iron overload method in hemochromatosis, β-thalassemia, and sideroblastic anemia [38].

Investigated methods of hemochromatosis treatment

Hepcidin treatment. Murine models demonstrated that hepcidin analogues decreased iron overload and iron-induced tissue hypertoxicity. Minihepcidins represent smaller hepcidin-like peptides which decreased iron concentration in the myocardium of mice with knocked out hepcidin. Minihepcidins prevented iron overload in the model of severe hemochromatosis in mice with hepcidin deficiency. Minihepcidins may be probably beneficial in iron overload-associated disorders or when used separately for prophylaxis, or as concomitant therapy with phlebotomy or chelation. Natural hepcidin and its analogues are investigated in the treatment of iron overload with hemochromatosis.

Apotransferrin treatment. Several studies demonstrated decreased *Fam132b* (erythroferrone) erythroid gene expression, increased hepcidin gene expression in the liver, increased plasma hepcidin-25 levels, and decreased intestinal ferroportin-1 in mice with thalassemia administered apotransferrin. Apotransferrin treatment requires further analysis regarding the normalization of iron levels in the myocardium and other organs [39].

Gene therapy. Gene therapy of such diseases as β-thalassemia and sickle-cell anemia may prevent the need in blood transfusions and iron overload in tissues. *DMT1* and enterocyte ferroportin gene expression inhibition were recommended as gene therapy targets for patients with hereditary hemochromatosis. Other therapeutic approaches to be investigated include wild-type *HFE* gene overexpression in enterocytes and hepcidin (regulatory iron peptide) overexpression in the liver. Mutations in the *HFE* gene may affect the survival of patients with myelodysplastic syndrome; studies are required to determine whether such patients should be treated with powerful iron chelating agents [40].

- **Cardiac hemochromatosis**

Cardiac hemochromatosis, or primary cardiomyopathy with iron overload, is an important and potentially preventable cause of heart failure. Iron overload-associated cardiomyopathy is defined as systolic or diastolic cardiac dysfunction [41] caused by enhanced iron deposition; it is an important cause of chronic heart failure due to the increased incidence of this pathology observed in patients with thalassemia and in patients with hereditary hemochromatosis. Cardiomyocyte ferroportin regulates cellular iron homeostasis, while the location of iron deposition in the myocardium determines the severity of cardiac dysfunction [42]. Due to intensive metabolism, cardiomyocytes are especially sensitive to toxic iron effects. Consequently, iron deposition in the myocardium may lead to cardiomyopathy and heart failure, which is a relatively later, but potentially fatal manifestation of hemochromatosis [43]. Myocardium is especially sensitive to iron-induced oxidative stress due to a large amount of mitochrondria and low antioxidant levels.

The iron from transfusion sources is more likely to accumulate in the heart than the orally taken one. During cardiac iron accumulation, iron predominantly deposits in epicardial myocytes, while affecting the whole wall thickness only later. Cardiac iron overload initially leads to increased perinuclear iron deposition with subsequent deposition in the whole cell. Iron deposition is more widespread in ventricles than in atria. The cardiac conductive system is often involved. Myocardial dysfunction severity correlates with the amount of iron deposition in the myocardium. As iron deposits enhance in the myocardium, this leads to increased left ventricular wall thickness. This may lead to decreased

left ventricular compliance, decreased systolic function, and dilation [44].

Factors affecting the penetrance include sex, age, physiological and pathological blood losses, blood donation, dietary iron and alcohol consumption, hepatitis B and C, obesity, administration of dietary supplements (with iron and vitamin C) [45].

Mechanical alterations associated with myocardial hemochromatosis are aggravated by cytotoxic iron effects inside myocytes. Iron in these cells abruptly accelerates the production of hydroxyl ions, extremely reactive free oxygen radicals which may destroy the cellular lipid bilayer, lysosomes, membranes of other organelles, leading to cellular dysfunction and death.

- **Clinical features of cardiac hemochromatosis**

Clinical signs of cardiac hemochromatosis may be divided into three categories, including arrhythmias, congestive failure due to systolic dysfunction, and congestive failure due to diastolic dysfunction [43].

Hemochromatosis and arrhythmias. Patients with cardiac hemochromatosis often develop atrial and ventricular arrhythmias and blocks due to myocardial dysfunction and iron deposition in the atrioventricular node and the conductive system. Symptoms may include simple palpitations or overt syncope. Palpitations are routine and detected in 37 % of patients. Irregular palpitations may be associated with atrial fibrillation, premature atrial or ventricular contractions, or sinus arrhythmia. Regular, fast palpitations may be related to paroxysmal supraventricular tachycardia, sustained or non-sustained ventricular tachycardia, or atrial flutter. Palpitations may be accompanied by dizziness, chest discomfort, diaphoresis, and dyspnea. Several patients may develop symptoms of pre-syncope or overt syncope associated with bradyarrhythmias, including inadequate sinus bradycardia, 2nd degree (Mobitz II) or even 3rd degree atrioventricular block. Some patients may experience dizziness before losing consciousness, but in other situations no preliminary signs develop before Adams-Stokes attacks. Patients with sick sinus syndrome may manifest with palpitations due to tachycardia alternating with dizziness due to bradycardia. This tachy-brady syndrome may be the result of alternating atrial fibrillation with quick conductivity and subsequent spontaneous conversion to sinus rhythm with significant sinus bradycardia. The diagnostic evaluation in a patient with arrhythmia does not differ depending on whether arrhythmias are caused by hemochromatosis or any other disease. This includes electrocardiography with subsequent Holter monitoring or even longer cardiac event monitoring. If these test results are not decisive, cardiac catheterization and electrophysiological study may be required [43].

Chronic heart failure. By the time chronic heart failure develops due to cardiac hemochromatosis, the diagnosis of this disease has already been verified in the majority of cases based on other existing symptoms. If chronic heart failure is the main manifestation of hemochromatosis, dyspnea on physical exertion with gradually decreasing load tolerance may develop in the disease onset, followed by paroxysmal nocturnal dyspnea (the patient is in a forced position with the elevated head end of the bed (lying on high pillows) — orthopnea); later, dyspnea may emerge even at rest, and pulmonary edema may develop. Patients with higher iron deposition in the right ventricle than the left one may develop right ventricular failure. With isolated right ventricular heart failure, dyspnea is not prominent, and pulmonary congestion is absent. In such patients symptoms include peripheral edema, weakness, and fatigue. Congestive hepatomegaly may cause discomfort, which is usually described as dull pain or heaviness in the right upper abdominal quadrant or epigastrium. This pain may be caused by the hepatic capsule distension; it may be intensive with the quickly increased size of the liver in acute right ventricular failure. Physical signs of chronic heart failure in cardiac hemochromatosis also include increased jugular venous pressure, positive hepatojugular reflux, pleural effusion, and ascites. Cardiomegaly may be accompanied by the lateral point of maximum impulse shift, emergence of pathological additional S3 and S4 heart sounds (gallop rhythm), systolic murmurs or mitral and/or tricuspid regurgitation associated with dilation of the left or right ventricles. These murmurs often decrease or disappear after the restoration of the cardiac function [45].

- **Diagnosis**

Biochemistry tests. Cardiac hemochromatosis should be suspected in any patient with unexplained heart failure. Systemic iron overload should be screened for using serum ferritin and transferrin saturation. If the results of these tests correspond to iron overload, subsequent non-invasive and histological investigations are indicated to confirm organ lesions due to iron overload.

Guidelines recommend that plasma transferrin saturation levels are over 55 %, while serum ferritin levels are over 200 ng/mL in females or 300 ng/mL in males when diagnosing patients with iron overload. As serum ferritin is an acute phase reactant, it is not robust in diseases with active inflammation. Serum iron studies

are beneficial for screening for total iron overload, but are not robust in the diagnosis of organ-specific overload (i.e. cardiac iron). Serum ferritin levels do not correlate with the myocardial iron overload severity. Despite low serum ferritin levels, myocardial deposition levels may be high. A strong correlation exists between plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and iron overload parameters [46].

Tissue biopsy. Liver biopsy is the best method for the quantifying assessment of iron overload. However, there's no correlation between iron deposition in the liver and myocardium. Liver deposition in the myocardium progresses slower than iron absorption by the liver. Endomyocardial biopsy may be required for patients with cardiac manifestations. Myocardial iron is constantly detected in endomyocardial biopsy specimens in patients with left ventricular dysfunction resulting from cardiac hemochromatosis.

Electrocardiography data. Electrocardiography (ECG) is usually not of diagnostic value in early cardiac hemochromatosis. In advanced cardiac hemochromatosis, ECG demonstrates low QRS voltage and non-specific ST/T anomalies. Atrial tachyarrhythmias (especially paroxysmal atrial fibrillation) are commonly observed. Ventricular arrhythmias develop with LVEF decrease. Iron deposition in the conductive system may cause 1st degree, 2nd degree, or complete atrioventricular blocks.

Echocardiography data. In early cardiac hemochromatosis lesions, echocardiography may detect left ventricular diastolic dysfunction associated with the impaired relaxation of the left ventricle or its restriction. Signs typical for dilated cardiomyopathy (phenocopy) with reduced LVEF typically develop later. Patients with cardiac hemochromatosis may demonstrate dilation of the left or right heart chambers and reduced LVEF, or left atrium and right ventricle dilation with increased pulmonary artery pressure and normal LVEF. Eccentric left ventricular hypertrophy may develop as well. Tissue Doppler echocardiography may be used to diagnose diastolic left ventricular dysfunction in early cardiac hemochromatosis stages [29].

Cardiac magnetic resonance imaging. Although echocardiography may be used to detect myocardial iron overload, it does not accurately predict iron levels in the myocardium. MRI provides quantification of the myocardial iron loads. In patients with cardiac hemochromatosis, iron-overloaded myocardium demonstrates changes in the signal intensity and sensitivity with a shorter relaxation time and a quicker image darkening associated with paramagnetic iron effects. The relaxation time may be measured using the spin echo method, in which signals are refocused using a special radiofrequency impulse or small magnetic fields called gradients (gradient echo) in specific time intervals (echo time). Relaxation decay time constant inversely correlates with myocardial iron levels. The larger myocardial iron levels, the shorter are T2 and T2* — spin echo decay time constant and gradient echo-induced relaxation time, respectively. Spin echo is less sensitive than gradient echo to evaluate myocardial iron levels. T2* method is more sensitive and highly specific for quantification and longitudinal follow-up of myocardial iron deposition. A good inverse correlation exists between the T2* in the patient's myocardium and LVEF, as well T2* in the patient's myocardium significantly correlates with the requirements for cardiac hemochromatosis treatment [47].

T2* relaxation time is determined by iron in the hemosiderin form, but not iron in the labile cellular or ferritin form, accurately predicting myocardial iron levels. Clinical severity of myocardial iron overload in cardiac hemochromatosis is evaluated using T2* values. Patients with T2* relaxation time over 20 ms have a low risk of congestive heart failure. Patients with T2* relaxation time 10–20 ms probably have myocardial iron deposits, thus having an intermediate risk of congestive heart failure. Patients with T2* relaxation time less than 10 ms have a high risk of congestive heart failure and require chelation therapy [47].

- **Treatment of cardiac hemochromatosis**

Treatment of iron overload conditions is important to prevent or eliminate cardiac dysfunction. Iron excess removal from tissues in these patients leads to minimum formation of free radicals, decreasing organ damage. The treatment to remove excess iron stores includes therapeutic phlebotomy and iron chelating agents. Treatment of the main disease causing iron overload and diet therapy are also important when treating cardiac hemochromatosis. Diet therapy includes abstaining from taking drug-induced iron, mineral supplements, excess vitamin C, and raw seafood. Congestive heart failure should be treated using the standard drug therapy of heart failure [48].

Therapeutic phlebotomy in cardiac hemochromatosis. Phlebotomy decreases myocardial iron levels and improves left ventricular diameter, left ventricular fractional shortening, LVEF, left ventricular weight, and left atrial size in these patients. Treatment of cardiomyopathy-associated congestive heart failure and serious arrhythmias in patients with cardiac hemochromatosis

should be used until therapeutic phlebotomy (sometimes in combination with iron chelating therapy) decreases excess myocardial iron levels.

Heart transplant in cardiac hemochromatosis. Heart transplant is a therapeutic option for patients with cardiac hemochromatosis and severe heart failure refractory to optimal conservative treatment and cardiac resynchronization therapy. Out of 16 patients that underwent heart transplant associated with iron overload cardiomyopathy, etiology was distributed as follows: primary hemochromatosis in 11 patients, thalassemia major in 4 patients, Diamond-Blackfan anemia in 1 patient. 30-day mortality was 12 %, while 3 deaths were related to infectious complications. Actuarial survival (Kaplan-Meier method) in 1, 3, and 5 years was 81 %, 81 %, and 81 %, respectively. 10-year actuarial survival was 41 % [49].

Congestive heart failure after liver transplant may require the use of a biventricular assist device. Combined heart and liver transplant is indicated in patients with severe cardiomyopathy associated with iron overload and liver cirrhosis. All these patients should continue therapy to decrease iron overload and prevent hemochromatosis of the transplanted heart. In patients with secondary iron overload (i.e. myelodysplastic syndrome, sickle cell anemia, β-thalassemia, Diamond-Blackfan syndrome), hematopoietic stem cell transplant may decrease blood transfusion requirements and slow down the rate of iron overload in these patients [50].

Investigated methods of cardiac hemochromatosis treatment

Calcium channel blockers. L-type and T-type Ca2+-channels provide the main pathway for iron influx into cardiomyocytes in iron overload cardiomyopathy. It was demonstrated that amlodipine decreased iron absorption and production of free oxygen radicals in murine hearts with chronic iron overload. Therapy with calcium channel blockers (nifedipine, verapamil, efonidipine) and the divalent metal transporter 1 (ebselen) demonstrated decreased iron deposition in the heart, cardiac malonic dialdehyde and plasma non-transferrin-bound iron levels, as well as improved cardiac rhythm variability and left ventricular function in mice with thalassemia and iron overload. Efonidipine and ebselen decreased mortality in such mice. Further studies are required to determine whether calcium channel blockers may be effective in the prevention and treatment of iron overload cardiomyopathy [51].

Conclusion

Hemochromatosis is a multisystemic disease, which starting symptoms include fatigue, arthralgia, decreased libido, erectile dysfunction, signs of hepatic, cardiac lesions, and diabetes mellitus. These are subsequently followed by organ dysfunction with the emergence of such lesions as liver cirrhosis, cardiomyopathy, pancreatic fibrosis, and osteoporosis. Timely detection of this systemic disease may prevent multiple organ damage. Biochemical parameters and T2* relaxation time in cardiac MRI are not only of diagnostic value, but also help to quantify the therapeutic effect. Treatment includes phlebotomy and iron chelating agents which provide normal survival in pre-clinical and early clinical stages. Specific chelation, red blood cell exchange, and standard treatment of heart failure may demonstrate significant benefits even in the late stage. As symptoms and organ lesions are often irreversible, it is important to start the treatment as soon as possible, before symptoms and organ dysfunction develop.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Резник Е.В.: идея, руководство, организация работы, редактирование рукописи

Лауар М.Х.Э.: анализ публикаций по теме, написание обзора литературы

Воинова В.Ю.: генетическое консультирование, редактирование рукописи

Голухов Г.Н.: организация работы, редактирование рукописи

Author contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Reznik E.V.: idea, leadership, work organization, edition

Laouar M.H.E.: literature review, writing of article

Voinova V.Yu.: genetic consulting, edition

Golukhov G.N.: work organization, edition

Список литературы/References:

1. Barton JC., Parker CJ. HFE-Related Hemochromatosis. 2000 Apr 3 [updated 2024 Apr 11]. In: Adam MP., Feldman J., Mirzaa GM. et al. editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2024. PMID: 20301613.
2. Brissot P., Pietrangelo A., Adams PC. et al. Haemochromatosis. Nat Rev Dis Primers. 2018 Apr 5; 4: 18016. doi: 10.1038/nrdp.2018.16.
3. Малаева В.Г., Адаменко Е.И., Жарская О.М. и др. Полиорганное поражение при гемохроматозе. Проблемы здоровья и экологии. 2022; 19(1): 139-144. doi: 10.51523/2708-6011.2022-19-1-18.

Malaeva EG., Adamenko EI., Zharskaya OM. Multiple organ lesion in hemochromatosis. Health and Ecology Issues. 2022; 19(1): 139–144. doi: https://doi. Org/10.51523/2708-6011.2022-19-1-18 [in Russian].
4. Sandhu K., Flintoff K., Chatfield MD. et al. Phenotypic analysis of hemochromatosis subtypes reveals variations in severity of iron overload and clinical disease. Blood. 2018 Jul 5; 132(1): 101-110. doi: 10.1182/blood-2018-02-830562.
5. Kemppinen L., Mattila M., Ekholm E. et al. Gestational iron deficiency anemia is associated with preterm birth, fetal growth restriction, and postpartum infections. J Perinat Med. 2020 Dec 21; 49(4): 431-438. doi: 10.1515/jpm-2020-0379.
6. Merryweather-Clarke AT., Pointon JJ., Jouanolle AM. et al. Geography of HFE C282Y and H63D mutations. Genet Test. 2000; 4(2): 183-98. doi: 10.1089/10906570050114902.
7. Wallace DF., Subramaniam VN. The global prevalence of HFE and non-HFE hemochromatosis estimated from analysis of next-generation sequencing data. Genet Med. 2016 Jun; 18(6): 618-26. doi: 10.1038/gim.2015.140. Epub 2015 Dec 3.
8. Kang W., Barad A., Clark AG. et al. Ethnic Differences in Iron Status. Adv Nutr. 2021 Oct 1; 12(5): 1838-1853. doi: 10.1093/advances/nmab035.
9. Pilling LC., Tamosauskaite J., Jones G. et al. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. BMJ. 2019 Jan 16; 364: k5222. doi: 10.1136/bmj.k5222. Erratum in: BMJ. 2019 Oct 23; 367: l6157.
10. Cheng CF., Lian WS. Prooxidant mechanisms in iron overload cardiomyopathy. Biomed Res Int. 2013; 2013: 740573. doi: 10.1155/2013/740573. Epub 2013 Nov 19.
11. Trousseau A. Glycosurie; diabete sucre. Clinique Med de l'Hotel-dieu de Paris (2nd ed) 1865; 2: 663–698. doi: 10.1007/s12072-023-10510-3.
12. Von Recklinghausen FD. Uber haemochromatose. Tageblatt der (62) Versammlung Deutscher Naturforscher und Arzte Heidelberg 1889; 62: 324–325. doi: 10.1007/s12072-023-10510-3.
13. Atkins JL., Pilling LC., Masoli JAH. et al. Association of Hemochromatosis HFE p.C282Y Homozygosity With Hepatic Malignancy. JAMA. 2020 Nov 24; 324(20): 2048-2057. doi: 10.1001/jama.2020.21566.
14. Pilling LC., Tamosauskaite J., Jones G. et al. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. BMJ. 2019 Jan 16; 364: k5222. doi: 10.1136/bmj.k5222. Erratum in: BMJ. 2019 Oct 23; 367: l6157.
15. Atkins JL., Pilling LC., Heales CJ. et al. Hemochromatosis mutations, brain iron imaging, and dementia in the UK Biobank Cohort. J Alzheimers Dis. 2021;79:1203–1211. doi: 10.3233/JAD-201080.
16. Tamosauskaite J., Atkins JL., Pilling LC. et al. Hereditary hemochromatosis associations with frailty, sarcopenia and chronic pain: evidence from 200,975 older UK Biobank participants. J Gerontol A Biol Sci Med Sci. 2019; 74: 337–342. doi: 10.1093/gerona/gly270.
17. Powell LW., Seckington RC., Deugnier Y. et al. Haemochromatosis. Lancet. 2016 Aug 13 ;388(10045): 706-16. doi: 10.1016/S0140-6736(15)01315-X. Epub 2016 Mar 12.
18. Doyard M., Chappard D., Leroyer P. et al. Decreased Bone Formation Explains Osteoporosis in a Genetic Mouse Model of Hemochromatosiss. PloS One. 2016; 11: e0148292. doi: 10.1371/journal.pone.0148292.
19. Girelli D., Busti F., Brissot P. et al. Hemochromatosis classification: update and recommendations by the BIOIRON Society. Blood. 2022 May 19; 139(20): 3018-3029. doi: 10.1182/blood.2021011338.
20. Kowdley KV., Brown KE., Ahn J. et al. ACG Clinical Guideline: Hereditary Hemochromatosis. Am J Gastroenterol. 2019 Aug; 114(8): 1202-1218. doi: 10.14309/ajg.0000000000000315.
21. Chin J., Powell L.W. Utility of hepatic or total body iron burden in the assessment of advanced hepatic fibrosis in HFE hemochromatosis. Sci Rep 9, 20234 (2019). doi: 10.1038/s41598-019-56732-0.
22. Bardou-Jacquet E., Morandeau E., Anderson GJ. et al. Regression of Fibrosis Stage With Treatment Reduces Long-Term Risk of Liver Cancer in Patients With Hemochromatosis Caused by Mutation in HFE. Clin Gastroenterol Hepatol. 2020 Jul; 18(8): 1851-1857. doi: 10.1016/j.cgh.2019.10.010.
23. Girelli D., Busti F., Brissot P. et al. Hemochromatosis classification: update and recommendations by the BIOIRON Society. Blood. 2022 May 19; 139(20): 3018-3029. doi: 10.1182/blood.2021011338.
24. Bardou-Jacquet E., Lainé F., Guggenbuhl P. et al. Worse Outcomes of Patients With HFE Hemochromatosis With Persistent Increases in Transferrin Saturation During Maintenance Therapy. Clin Gastroenterol Hepatol. 2017 Oct; 15(10): 1620-1627. doi: 10.1016/j.cgh.2016.12.039.
25. Calori S., Comisi C., Mascio A. et al. Overview of Ankle Arthropathy in Hereditary Hemochromatosis. Med Sci (Basel). 2023 Aug 15; 11(3): 51. doi: 10.3390/medsci11030051.
26. Ravasi G., Pelucchi S., Bertola F. et al. Identification of Novel Mutations by Targeted NGS Panel in Patients with Hyperferritinemia. Genes (Basel). 2021 Nov 9; 12(11): 1778. doi: 10.3390/genes12111778.
27. Sandhu K., Flintoff K., Chatfield MD. et al. Phenotypic analysis of hemochromatosis subtypes reveals variations in severity of iron overload and clinical disease. Blood. 2018 Jul 5; 132(1): 101-110. doi: 10.1182/blood-2018-02-830562.
28. Legros L., Bardou-Jacquet E., Latournerie M. et al. Non-invasive assessment of liver fibrosis in C282Y homozygous HFE hemochromatosis. Liver Int. 2015 Jun; 35(6): 1731-8. doi: 10.1111/liv.12762.
29. Malvarosa I., Massaroni C., Liguori C. et al. Estimation of liver iron concentration by dual energy CT images: influence of X-ray energy on sensitivity. Annu Int Conf IEEE Eng Med Biol Soc. 2014; 2014: 5129-32. doi: 10.1109/EMBC.2014.6944779.
30. Bazzocchi A., Ponti F., Albisinni U. et al. DXA: Technical aspects and application. Eur J Radiol. 2016; 85(8): 1481–1492. doi: 10.1016/j.ejrad.2016.04.004.
31. Yancy CW., Jessup M., Bozkurt B. et al. 2013 ACCF/AHA guidelines for the management of heart failure: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American College of Chest Physicians,

Heart Rhythm Society, and International Society for Heart and Lung Transplantation. Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation. J Am Coll Cardiol. 2013; 62: 1495–539. doi: 10.1161/CIR.0b013e31829e8807.
32. Husar-Memmer E., Stadlmayr A., Datz C. et al. HFE-related hemochromatosis: an update for the rheumatologist. Curr Rheumatol Rep. 2014 Jan; 16(1): 393. doi: 10.1007/s11926-013-0393-4.
33. Rombout-Sestrienkova E., Koek GH., Neslo R. et al. Course of iron parameters in HFE-hemochromatosis patients during initial treatment with erythrocytapheresis compared to phlebotomy. J Clin Apher. 2016 Dec; 31(6): 564-570. doi: 10.1002/jca.21451.
34. West KA., Eder AF. Accepting hereditary hemochromatosis blood donors: ask not why, ask why not. Transfusion 56, 2907–2909 (2016). doi: 10.1038/nrdp.2018.16.
35. Bardou-Jacquet E. Worse outcomes of patients with HFE hemochromatosis with persistent increases in transferrin saturation during maintenance therapy. Clin. Gastroenterol. Hepatol 15, 1620–1627 (2017). doi: 10.1016/j.cgh.2016.12.039.
36. Rombout-Sestrienkova E., De Jonge N., Martinakova K. et al. End-stage cardiomyopathy because of hereditary hemochromatoss successfully treated with erythrocytapheresis in combination with left ventricular assist device support. Circ Heart Fail. 2014; 7: 541–3. doi: 10.1161/CIRCHEARTFAILURE.114.001198.
37. Pennell D., Carpenter J., Roughton M. et al. On improvement in ejection fraction with iron chelation in thalassemia major and the risk of future heart failure. J Cardiovasc Magn Reson 13, 45 (2011). doi: 10.1186/1532-429X-13-45.
38. El Sayed SM., Abou-Taleb A., Mahmoud HS. et al. Percutaneous excretion of iron and ferritin (through Al-hijamah) as a novel treatment for iron overload in beta-thalassemia major, hemochromatosis and sideroblastic anemia. Med Hypotheses. 2014; 83: 238–46. doi: 10.1016/j.mehy.2014.04.001.
39. Gelderman MP., Baek JH., Yalananoglu A. et al. Reversal of hemochromatosis by apotransferrin in non-transfused and transfused Hbbth3/+ (heterozygous B1/B2 globin gene deletion) mice. Haematologica. 2015; 100: 611–22. doi: 10.3324/haematol.2014.117325.
40. Lucijanić M., Pejša V., Mitrović Z. et al. Hemochromatosis gene mutations may affect the survival of patients with myelodysplastic syndrome. Hematology. 2016 Apr; 21(3): 170-4. doi: 10.1080/10245332.2015.1101964.
41. Резник Е.В., Нгуен Т.Л., Устюжанин Д.В. и др. «Красные флаги» диагностики инфильтративных заболеваний сердца. Российский кардиологический журнал. 2023; 28(1S): 5259. doi: 10.15829/1560-4071-2023-5259.
Reznik E.V., Nguyen T.L., Ustyuzhanin D.V. Red flags to diagnose infiltrative cardiomyopathies. Russian Journal of Cardiology. 2023; 28(1S): 5259. doi: 10.15829/1560-4071-2023-5259 [in Russian].
42. Lakhal-Littleton S., Wolna M., Carr CA. et al. Cardiac ferroportin regulates cellular iron homeostasis and is important for cardiac function. Proc Natl Acad Sci USA. 2015; 112: 3164–9. doi: 10.1073/pnas.1422373112.
43. Daniłowicz-Szymanowicz L., Świątczak M., Sikorska K. et al. Pathogenesis, Diagnosis, and Clinical Implications of Hereditary Hemochromatosis-The Cardiological Point of View. Diagnostics. 2021; 16: 1279. doi: 10.3390/diagnostics11071279.
44. Aronow WS. Management of cardiac hemochromatosis. Arch Med Sci. 2018; 14(3): 560–568. doi: 10.5114/aoms.2017.68729.
45. Carpenter JP., Grasso AE., Porter JB. et al. On myocardial siderosis and left ventricular dysfunction in hemochromatosis. J Cardiovasc Magn Reson 2013; 15: 24. doi: 10.1186/1532-429X-15-24.
46. Balkan C., Tuluce SY., Basol G. et al. Relation between NT-proBNP levels, iron overload, and early stage of myocardial dysfunction in beta-thalassemia major patients. Echocardiography. 2012; 29: 318–25. doi: 10.1111/j.1540-8175.2011.01584.x.
47. Kirk P., Roughton M., Porter JB. et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation. 2009; 120: 1961–8. doi: 10.1161/CIRCULATIONAHA.109.874487.
48. Yancy CW., Jessup M., Bozkurt B. et al. 2013 ACCF/AHA guidelines for the management of heart failure: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American College of Chest Physicians, Heart Rhythm Society, and International Society for Heart and Lung Transplantation. Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation. J Am Coll Cardiol. 2013; 62: 1495–539. doi: 10.1161/CIR.0b013e31829e8807.
49. Caines AE., Kpodonu J., Massad MG. et al. Cardiac transplantation in patients with iron overload cardiomyopathy. J Heart Lung Transplant. 2005 Apr; 24(4): 486-8. doi: 10.1016/j.healun.2004.02.009.
50. Jermyn R., Soe E., D'Alessandro D. et al. Cardiac failure after liver transplantation requiring a biventricular assist device. Case Rep Transplant. 2014; 2014: 946961. doi: 10.1155/2014/946961.
51. Kumfu S., Chattipakorn S., Chinda K. et al. T-type calcium channel blockade improves survival and cardiovascular function in thalassemic mice. Eur J Haematol. 2012 Jun; 88(6): 535-48. doi: 10.1111/j.1600-0609.2012.01779.x.

Информация об авторах

Резник Елена Владимировна — д.м.н., доцент, заведующий кафедрой пропедевтики внутренних болезней лечебного факультета / Института клинической медицины ФГАОУ ВО РНИМУ имени Н.И. Пирогова, врач-кардиолог, терапевт, врач функциональной диагностики ГБУЗ ГКБ № 31 им. Акад. Г.М. Савельевой ДЗМ, Москва, e-mail: elenaresnik@gmail.com, ORCID ID: http://orcid.org/0000-0001-7479-418X

Лауар Мохамед Хусем Эддин — аспирант кафедры пропедевтики внутренних болезней лечебного факультета / Института клинической медицины ФГАОУ ВО РНИМУ имени Н.И. Пирогова, Москва, e-mail: houssemlaouar23@gmail.com, ORCID ID: https://orcid.org/0009-0000-8300-6616

Воинова Виктория Юрьевна — д.м.н., заведующая отделом клинической генетики Научно-исследовательского клинического института

педиатрии и детской хирургии имени академика Ю.Е. Вельтищева ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России, заведующая кафедрой общей и медицинской генетики Медико-биологического факультета ФГАОУ ВО РНИМУ им. Н.И. Пирогова Минздрава России, Москва, e-mail: vivoinova@yandex.ru, ORCID ID: https://orcid.org/0000-0001-8491-0228

Голухов Георгий Натанович — президент ГБУЗ ГКБ № 31 им. Акад. Г.М. Савельевой ДЗМ, заместитель председателя Общественного совета при Департаменте здравоохранения города Москвы, Москва, ORCID ID: 0000-0002-0161-005X

Information about the authors

Elena V. Reznik — MD, Head of the Department of Propedeutics of Internal Diseases of the medical faculty/Institution of Clinical Medicine of the Russian national research medical University named after N.I. Pirogov of the Ministry of healthcare of the Russian Federation, Moscow; Cardiologist of the GBUZ «City Clinical Hospital № 31» named after. Academician G.M. Savelyeva of Healthcare Department of Moscow, Moscow, e-mail: elenaresnik@gmail.com, ORCID ID: http://orcid.org/0000-0001-7479-418X

Laouar Mohamed Houcem Eddine — PhD student, Department of Propaedeutics of Internal Diseases of the medical faculty of the Russian national research medical University named after N.I. Pirogov of the Ministry of healthcare of the Russian Federation, Moscow, e-mail: houssemlaouar23@gmail.com, ORCID ID: https://orcid.org/0009-0000-8300-6616

Victoria Y. Voinova — MD, PhD, Head of the Department of Clinical Genetics, Research Clinical Institute of Pediatrics and Pediatric Surgery named after Academician Yu.E. Veltishchev Federal State Autonomous Educational Institution of Russian National Research Medical University named after. N.I. Pirogova, Ministry of Health of Russia, Head of the Department of General and Medical Genetics, Faculty of Medical Biology, Federal State Autonomous Educational Institution of Higher Education Russian National Research Medical University named after. N.I. Pirogov, Ministry of Health of Russia, Moscow, e-mail: vivoinova@yandex.ru, ORCID ID: https://orcid.org/0000-0001-8491-0228

Georgy N. Golukhov — President of the GBUZ "City Clinical Hospital № 31" named after. Academician G.M. Savelyeva, Deputy Chairman of the Public Council under the Department of Health of the City of Moscow, ORCID ID: https://orcid.org/0000-0002-0161-005X

Автор, ответственный за переписку / Corresponding author