**Primary (hereditary) hemochromatosis**

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*In medicine, there are many gaps, and pathological processes are so hidden that they can not always be detected even by modern methods of research ...*

*Some serious diseases initially do not give symptoms.*

Hugo Glaser (1881-1976)

**Key words:** iron metabolism, hemochromatosis forms, etiology and pathogenesis, clinical picture, treatment

**Definition.** Accepted definition of primary (hereditarily) hemochromatosis exists. Here are two most accurate, in our opinion, definitions of this disease.

1. Hereditary hemochromatosis is a monoallelic autosomal recessive genetically predisposed disease, leading to the present excessive iron absorption in the gastrointestinal tract and reloading them with cells of internal organs change their structure and dysfunction [2].

2. Hereditary (primary) hemochromatosis is an HLA-associated disease of genetical nature with autosomal recessive inheritance type caused by HFE gene defect that results in increased absorption of iron in digestive tract with its primary deposition in the liver, and then in other internal organs with a change in their structure and breakdown of functions [7].

**Terminology.** For the first time the description of this disease was presented Leno French doctors Troisier Ch. E. (1848-1919) — in 1871 (Bull Soc Anat Paris, 1871) and Hanot V. Ch. (1844-1893) and Chauffard A. M. E. (1855-1932) — in 1882 (Rev Med, 1882; 2:385- 403), which was originally called Troisier-Hanot-Chauffard disease (syndrome) [19].

The term *"hemochromatosis»* (hemochromatosis) was proposed by Recklinghausen F. D. in 1889 (Berlin Klin Wschr, 1889;21:857-872) [4]. In 1935, Sheldon J. N. established the presence of genetic abnormalities in the metabolism of iron in this disease, and in 1964 MacDonald R. G. confirmed the genetic nature of between primary (hereditary) hemochromatosis [4, 10].

3 forms the disease were highlighted in the course of studying hemochromatosis:

1. Primary (classical) genetically caused, — hereditary hemochromatosis, in which the iron penetrates into cells of parenchymatous organs (liver, pancreas, etc.), Causing their damage; 2. Secondary (acquired) iron overload syndrome (siderosis): thalassemia; sideroblastic anemia, characterized by ineffective hematopoiesis and chronic hemolytic anemia; multiple blood transfusion; chronicles cal hemodialysis (hemosiderosis), wherein the iron accumulating etsya predominantly in cells of the reticuloendothelial system — phagocytic macrophages; 3. rare forms of the syndrome Booting iron: neonatal hemochromatosis; aceruloplasminemia; hereditary atransferrinemiya [10].

This article discusses only the primary (hereditary, classical) form of hemochromatosis.

**Synonyms.** At different times this disease was called: bronze diabetes; retinitis cirrhosis (cirrhosis pigmentosa); idiopathic hemochromatosis; diabetic retinitis cirrhosis et al., however, it has established itself and is mainly used, the term *"primary (hereditary)* *hemochromatosis" (primary* *hereditary* *hemochromatosis).*

**Prevalence.** «First-screw (hereditary) gemohro matoz" — is a very common disease. Its frequency w riruet within 1,5-5,9 per 1000 population, which corresponds to 1 in 200-500 people. (0.3-0.5% of the population). A frequency of pathological gene (HFE) is even higher, — 1: 8.10 [2, 5, 6, 8, 29]. The greater the spread of the primary (hereditary) from hemochromatosis labeled with the Nordic countries, at least — in the UK and countries Price southern and southern Europe. In the US, the disease suffers from 0.01- 0.1% of the population. Men are sick 10 times more often than women of tires, and the clinical manifestation of the disease seen in men aged 40-50 years, and for women a little later — usually already in menopause, due to the fact that women lose iron each month with menstruation. Later on the onset of the disease explaining The fact that iron accumulates in the body of sick patients foam — for several decades, until it reaches the Cree level.

**Exchange of iron in the body of healthy people.** Body of healthy adult contains 4-5 g of iron, most of it (over 50%) is found in erythrocyte hemoglobin (1700 — 2000 mg), 15% — in muscle — in myoglobin (iron, not including The occurs in a gem). The blood plasma contains more than 20 mg of iron, including a freely circulating — more than 7 mg. Capture iron modulates *protein* *HFE.* Iron is in the composition *transferrin,* which is synthesized in the liver and is a plasma protein, saturating with iron at 30-35%. Iron enters into cells due to endocytosis via transporter bivalent metals — DMT-1, creating a common pool of nonheme iron and geminovogo; part of the iron with the participation of another carrier — *ferroportin* derived from cells and oxidized associated with transferrin i form enters through the bloodstream to organs and tissues. Transferrin is the main transporter of iron in the human body. It is saturated with iron and after the transfer of iron into the cells of an organ returns to the total blood flow. In cells, iron de is reduced in a complex with *ferritin,* which is synthesized poppy profaphagi. Normally, as a part of ferritin iron is deposited in number of 12-200 g / l (20-25% of iron, — a spare iron). In the physiological conditions, the higher the iron content in transferrin (serum), the less it is absorbed in the small intestine [3, 6, 18]. The transferrin composition is the 4 mg climb. 35% iron (500 mg) is deposited in the liver, spleen and bone marrow. The minimum amount of iron is not which enzymes (cytochromes, catalase).

Within a day, a person loses 0.7 to 1.0 mg of iron with feces. Female of tires during menstruation lose an additional 1.5-2.0 mg iron monthly. A minor portion of iron excreted in the urine and through the skin. With the destruction of red blood cells, their obsolete term recycled to 97% iron.

Under normal feeding the body receives 10- 20 mg of iron, but only absorbed 1.2 mg (10%) in the small intestine.

In primary (hereditary) hemochromatosis adsorbed increased amounts of iron, which is deposited in the liver and other organs (pancreas e, heart, etc.), As well as re tikuloendotelialnoy system (stellate cells — cells Ito) as a pigment — *hemosiderin* brownish color and having a granular structure. In the norm it is not. In the liver, hemosiderin located in the periportal zone — in lysosomes of hepatocytes is determined by Perls reaction [4, 8, 10, 18].

In men suffering from primary (legacy nnym) gemohroma tozom, resulting in excessive absorption of iron to 50 years of age is accumulated up to 20 mg of iron in the liver and other tissues and organs, causing damage to their structure and function of the growing tional disorders [3].

**Etiology and pathogenesis.** Etiology of the primary (hereditary) hemochromatosis is unknown. At the heart of its pathogenesis is *pathological gene* *HFE,* identified at the molecular genetic studies, which encodes a protein structure that is identical or similar in structure molecule (or complex) MHC (Major Histocompatibiliti Complex) class 1 [16, 18]. The HFE gene mutations were found C 282 Y 63 H and D in various combinations [2, 22, 30]. In normal HFE proteinmodulates iron associated with transferrin, while the mutation Y 282 C broken iron capture intestinal crypt cells.

Most patients (85-90%) are homozygous for th tantnomu gene C 282 Y, wherein the substituted tyrosine tsistsin polo zhenii 282, and 10-15% — mixed heterozygotes: C 282 Y / H 63 D.

While all children are sick homozygous primary (hereditary) hemochromatosis, heterozygous children, almost as a rule, manifest forms do not develop the disease. Mouth Credited incomplete penetrance hemochromatosis gene — up to 60%,

If the father and mother are heterozygous — media de fektnogo HFE gene, the probability of occurrence of homozygous children with defective gene HFE, is 1:4, while heterozygous children — 1:2 [3].

The mutant gene C Y 282 communicates with 2-macroglobulin (2m) firmly enough that reduces the expression of HFE-2m on plazmati membrane. At the same time, the mutant gene 63 H D in this process has no effect.

HFE gene is produced in all tissues of the body, except for the first First of all, in the deep crypts of the duodenum hydrochloric intestine [25, 30]. HFE gene — a protein that interacts with the transferrin receptor — TfR, and association of the HFE gene with TfR CNI zhaet affinity of the receptor for transferrin, which is provided transport of iron in the human body.

Mutation C 282 Y HFE gene robs its ability to bind to the receptor TfR, and to a much greater extent than mu ting H 63 D. This is because the mutation Y 282 C causes break disulfide bond (bridge) in the alpha-3 domain, disturbing the binding process mutant receptor gene TfR [23]. While healthy people HFE gene modulates seizure iron svya bound to transferrin at the mutation Y 282 C seizure iron GCO sredovanny receptor, TfR, is broken. In this case there are boxes ny signal supposedly low iron content in blood serum, which increases the ab sorption of iron in the intestine 2- 3 times [2, 5 8]. A surplus absorption of iron, in turn, with It leads to a significant increase in transferrin saturation jelly Zoom (100%),amount of rise of serum iron and its deposition in target organs (liver, pancreas, heart, etc.). Iron acts ka to toxin, amplifying processes ne rekisnogo lipid peroxidation (LPO) in response to stimulation of free radical oxidation (CPOJI).

The close connection of the primary (hereditary) hemochromatosis antigens MHC — HLA (Human Leucocyte Antigen) — with haplotypes A3, B14, and (in Men (degree of immunity) B17 (immunogenetic factor). In 1978, it was found (SimonN. et Bourel M.) that HFE gene controlling with holding the iron in the human body, located on the short arm of chromosome 6 th [2, 3, 4, 6, 8, 24]. The presence of two haplotypes HLA proband indicates a high risk of the disease in Degree sibowls, but not in the offspring [4, 24].

**Clinical picture.** Despite the hereditary nature of the disease, clinical symptoms of primary hemochromatosis develops as an adult — after 50 years, because it takes many years of increased iron absorption and its excess deposits in the organs and tissues, to cause damage and impairment of the function [6].

In the development of primary (hereditary) with hemochromatosis *distinguish four stages:*

I. *latent (hidden) stage,* when there is a genetic defect, but has not yet developed *an iron overload syndrome;*

II. *asymptomatic stage* during which no clinical manifestations disease but laboratory parameters witness There is a syndrome of iron overload;

III. *low-syptomatic* *stage,* when there are signs of *asthenia* (general weakness, malaise, apathy, etc.), but no clinical symptoms suggestive of time to different organs.

IV. *symptomatic* *stage* manifested as an signs of asthenic syndrome, and symptomatology, from reflects the loss of various organs (liver, pancreas, heart, etc.) [1, 2, 4, 8, 18].

For the primary (hereditary) hemochromatosis *is characterized by the systematic destruction* with involvement in the pathological process of many organs and tissues.

Most researchers indicate this disease *"triad" signs* for its most characteristic clinical manifestations: 1. Choose cirrhosis, 2. diabetes type II and 3. hyperpigmentation of the skin [1, 3, 6, 8, 18].

Back in 1951 Heilmeyer L. et al. data on the incidence of various organs in the primary governmental) hemochromatosis:

1. The increase in size of the liver (hepatomegaly) — 100% SLE teas; 2. skin hyperpigmentation — 96%; 3. symptomatic diabetes mellitus type II — 64%; 4. heart disease — 86%; 5. lesion endocrine glands — 37% [17].

Recently indicate a slightly different frequency of involvement cheniya pathological process in various organs: 1. liver (hepatitis tomegaliya, cirrhosis) — 95-100%; 2. skin hyperpigmentation and (rarely) mucosal — 55- 90%; 3. diabetes type II — 80%; 4. splenomsgaliya — 25-50%; 5. heart disease — 75%; 5. on expressions endocrine glands — 30-35% [2, 4].

*In the expanded (4* *th* *step)* clinical *disease* per between primary (hereditary) hemochromatosis results from the following clinical manifestations.

*1.* *Fatigue syndrome:* weakness, fatigue, lethargy, weight loss (60%) [4].

*2.* *Skin:* hyperpigmentation of the skin, becomes golden brown (bronze) or grayish-bluish (smoke chaty) color with predominant accumulation of pigment in the skin of the face, extremities (especially the hands), reproductive organs due to deposition of hemosiderin and gemofustsina; there is dry skin and its atrophic changes, hair loss.

*3.* *Liver:* hepatomegaly, dense texture, smooth surface often, at least — bumpy; mild tenderness with palm tions; in the terminal phase — metabolic cirrhosis with signs of portal hypertension, ascites, rarely — with the blood flow cheniyami ofvaricose's esophagus and stomach; hepatitis totsellyulyarnaya failure; Fig raised to development gepatotsel lyulyarnoy carcinoma (30% of patients in stage cirrhosis); dysproteinemia; moderate signs of cytolysis and cholestasis.

*4.* *Endocrine glands:* dysfunction of the pituitary, thyroid, adrenal glands; gipogenitalizme (impotence), atrophy, dis- and amenorrhea and infertility — women; gipokorti tsizm (reduced cortical functions over pochechnikov flowing with hypo tensor, general weakness and cutting, etc.); a small part of the patients — hypothyroidism.

*5.* *Diabetes mellitus type II often* insulin from rare — insulin resistance; possibly complicated course (acidosis, coma)

*6.* *Heart:* increase in its size (cardiomegaly); cardio — myopathy, occurring with lesions of the cardiac conduction system, and right ventricular fibrillation (congestive) failure.

*7.* *Joints:* arthropathy, const rovozhdayuschiesya arthralgia (from 20 to 25%); chondrocalcinosis large joints (30-35%), osteoporosis.

*8.* *Neuropsychiatric disorders:* different psychoneurological violations.

Part of the patients may have non-localized abdominal pain.

During primary (hereditary) hemochromatosis — slowly but steadily progressing.

The cause of death of all ashche h n is the development patotsellyulyarnoy carcinoma (in 25-35% cases). When the hepatic tissue is overloaded with iron against the background of the formed cirrhosis ne Cheney's risk of developing hepatocellular carcinoma increased 200 times (!) as compared to a population of healthy individuals [3].

In addition, it was found that with the primary (hereditary) hemochromatosis is often determined by the presence of viral n patita B and C (marked presence of HBsAg in the liver) to over which is accompanied by immunodeficiency, especially in the background Accurate accumulation of iron in the hepatic tissue, which also can sobstvovat development of hepatocellular carcinoma [21].

Sherlock S. and J. Dooley. Developed and *clinical and pathogenetic classification of* primary (hereditary) hemochromatosis, koto paradise provides for the allocation of its four types.

*I.* *Type* *HFE* *1* (classical form); it is characterized by the presence of a triad of typical signs of the disease (see above), which are often with defeat of heart and endocrine glands on a background exchange rates of iron.

*II.* *Type* *HFE* *2* (juvenile form), which is inherited in an auto-chromosomal type diagnosed at an early age, manifested resistant abdominal pain, lagging physical and sexual development; symptoms of myocardium with irregular rhythm and conductivity (very rare).

*III.* *Type* *HFE* *3:* clinically difficult to distinguish from the classical form of the disease; is inherited by an autosomal recessive type.

*IV.* *Type* *HFE* *4* (autosomal dominant hemochromatosis); when this form of the disease deposited iron predominantly in reticuloendothelial system (Kupffer cells) infestation chapters nym way liver [8].

**Diagnostics.** AT diagnosis of primary (hereditary) hemochromatosis using clinical data set forth above, taking into account the multiplicity involved in the pathological process organs and tissues, especially the "triad" characteristic lesions (cirrhosis, diabetes type II; hyperpigmentation of skin) [1, 4, 8 18]. In addition, it is necessary to study the family history and find out whether analogicalo disease in blood kinship of the first degree relatives.

*Laboratory diagnosis* is very important, sometimes Resch the importance of establishing a clinical diagnosis.

To confirm the initial diagnosis (hereditary) hemochromatosis used:

1. determination *of iron concentrations in serum* — it should exceed 200 mg / dl (normal 50-150 mg / dL), but the diagnostic method can not be considered reliable;

2. determination of *iron binding ability of a transferring* (Tf) — its iron saturation (determined after 12-hour fasting): it is usually above 62 % and is an important proof stances correct diagnosis;

3. determining *the concentration of ferritin* (acute phase protein) in the serum: it exceeds 300 g / l; sensitivity of the method is 94 %, and specificity — 89 %.

4. histological study of *liver biopsy specimens* with the use of a special color for the presence of iron in hepatocytes and bile duct epithelium (in secondary forms of iron overload, it accumulates mainly in the cells of the reticuloendothelial system, and not in the liver);

5. quantitative determination of iron in liver biopsy specimens (with the help of a spectrophotometer): confirms the diagnosis of an increase in its amount to 1000 μg / 100 g of dry weight (in healthy people 50-100 μg / 100 g of dry weight);

6. determination (calculation) of the iron index in the liver (Hii) by decreasing the amount of iron concentration (amount) found in liver biopsies (in μg / 100 g of dry weight) by the patient's age (in years) — in patients with primary (hereditary) hemochromatosis, this index is more than 2.0, and for other diseases — less than 1.6;

7. morphological study of liver biopsy specimens revealing the presence of large-nodular liver cirrhosis and indistinctly expressed fibrosis of portal zones with iron deposition at periportal hepatocytes and (to a lesser extent) in Kupffer cells;

8. determination of HLA-A3 and B14 haplotypes, characteristic of primary (hereditary) hemochromatosis: although these studies do not have diagnostic significance, they allow to establish the degree of risk of the disease development in blood relatives of the 1st degree of kinship [1, 2, 3, 4 , 8, 12, 13, 15, 20, 26, 28];

9. Recently, a genetic testing method for the presence of C 282 Y and H 63 D mutations of the HFE gene has been used to diagnose the primary (hereditary) hemochromatosis: if the subject is a homozygous carrier of the mutant gene C 282 Y or a mixed heterozygous carrier C 282 Y / H 63 D, then the diagnosis of the disease can be considered established [6]

In addition, there is a moderate increase in cyto enzymes Lisa (ALT and AST), hyperglycemia and glycosuria, porfirinemiya.

*Instrumental methods of diagnosis* at least of information are effective. With the help of computed tomography (CT) or magnetic resonance imaging (MRT), an increased density of liver tissue can be determined. In addition, you can install (or ­to see) the development of hepatocellular carcinoma.

*The differential diagnosis* is necessary to distinguish primary (hereditary) hemochromatosis liver cirrhosis different etiologies (viral, alcohol, etc.); from Banti syndrome (hepatolienal liver fibrosis); from Addison's disease (insufficient accuracy of the adrenal cortex, often referred to as "bronze disease" New); from porphyria cutanea tarda, and others.

**Treatment.** *Clinical nutrition* provides exclusion from the diet products containing iron (meat, liver), as well as ascorbic acid, reinforcing iron absorption in the small intestine; protein enrichment of food.

In addition, you must refrain from drinking alcohol beverages that have a toxic effect on the liver, stop tobacco smoking.

To reduce absorption of iron in the intestine, it is recommended also use foods that contain calcium (cheese, milk), assign pharmacotherapy containing calcium [1, 3, 4, 8, 18].

With the help of pharmacotherapy, there is no significant effect on the excess absorption of iron in the small intestine.

The basis of therapeutic interventions *in* *primary* *(hereditary)* *hemochromatosis* *are* regularly held bleeding (therapeutic fibrotomiya). Of course, bleeding is not a pathogen matic and symptomatic treatment, but it is effective, and alternatives to it yet.

Bloodletting is carried out 1-2 times a week for 500 ml. Over 4 me The hemoplegia can be removed from the body of the patient up to 1 g of iron.

*The goal of treatment:* using a bloodletting decrease in serum levels of ferritin and 50 mg / L (150 mg / dl or 30 ng / ml) or below. Thus, for 1 year, can be removed from the body of 10-12 g of iron and up to 15 g for the next 2 years. After reaching this goal bloodletting should continue on a regular basis, but with a frequency of 2-4 treatments during the year — *to stop* *bleeding* *in any case it is impossible,* because the primary (hereditary) hemochromatosis — an incurable disease.

If it is impossible to carry out exsanguination (in the presence of deep lesions of liver and heart, severe hypoalbuminemia) patients designate plazmoeritrotsitoferez and / or chelating preparation *Desferal* (desferrioxamin) — 5-10 ml of 10% solution intramuscularly for 20-40 days. However, its effectiveness is incomparable with the effect of regular bloodletting, — with its help it is possible to remove not bo Lee 20 mg iron / day, while in single bloodletting removed and 200 mg of iron (10 times more!). Furthermore, treatment desferalom accompanied by many adverse phenomena tions. Sometimes Desferal is administered intravenously at a rate of not more than 15 mg / kg / hr [1, 2, 3, 4, 6,8, 11, 12, 18, 27].

At the same time (according to the indications), cirrhosis treatment is performed Cheney, type II diabetes, congestive heart failure cardiac arrhythmias, etc. Sometimes there is a need for liver transplantation.

The search for more effective methods for the treatment of primary (hereditary) hemochromatosis continues...

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**Key words:** iron metabolism, hemochromatosis forms, etiology and pathogenesis, clinical picture, treatment

The lecture presents modern ideas on hereditary hemochromatosis. In particular, the metabolism of iron in normal and pathological conditions is described, as well as the definition and terminology of hemochromatosis, its etiology and pathogenesis. Particular attention is paid to the clinical picture, including pancreatic lesion, diagnostics and differential diagnosis. A separate section is devoted to treatment, both dietotherapy, and bloodletting, drug therapy.