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Diagnosis of Liver Cirrhosis on the Background of Mutations H63D of the *HFE* Gene and H1069Q of the *ATP7B* Gene associated with Hemochromatosis and Wilson's Disease (Clinical Case)

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The purpose of the study was to ilustrate the analysis of etiological factors of liver cirrhosis using clinical and anamnestic data and the results of instrumental, laboratory and genetic researches.

Materials and methods. The data of anamnesis and objective examination, results of instrumental, laboratory and genetic research methods are evaluated and analyzed. Modern protocols and medical literature were used.

Results and discussion. Clinical case of the patient, 52 years old. Complaints of weakness, pain in the left hypochondrium, taste of iron, convulsions of the upper and lower extremities. Laboratory and instrumental methods of research allowed to establish the following indicators in the patient: erythrocytopenia, thrombocytopenia, neutropenia, persistent lymphocytosis, lecopenia, decreased platelet count, increased average erythrocyte volume and average hemoglobin content in one erythromycin distribution, albuminemia, increased beta globulin, decreased albumin to globulin ratio, increased liver enzymes (ALT, AST, bilirubin direct) and GGT, blood iron metabolism (COPD and iron levels), iron saturation and iron ferritin saturation, negative immunological analysis for antinuclear antibodies (ANA), HbS Ag and anti-HCV were not detected. The patient was consulted by a hematologist, lymphoproliferative diseases were excluded. On the basis of data on hepatosplenomegaly, portal hypertension, varicose veins of the esophagus, lymphadenopathy, excluding nonalcoholic fatty liver disease, alcoholic fatty liver disease, viral hepatitis, autoimmune hepatitis, biliary cirrhosis, diagnosed with a diagnosis on the detection of mutations that cause hemochromatosis and Wilson's disease. Molecular genetic studies have shown the following results: the H63D mutation of the *HFE* gene in the heterozygous state and the H1069Q mutation of the *ATP7B* gene in the heterozygous state were detected.

Mutation testing and phenotype prediction based on genotype opens up prospects not only for personalized therapy, but also for the development of new treatment strategies. The literature provides data about new therapies with different mechanisms of action and discusses studies on Bis-choline tetrathiomolybdate in patients, pre-clinical studies of a novel chelator methanobactin and animal studies exploring cures for WD with gene therapy using adeno-associated vectors that introduce *ATP7B* into liver cells.

Conclusion. The clinical case showed the need to involve specialists in various specialties and a set of research methods to establish the etiology of liver cirrhosis and further etiopathogenetic treatment and the formation of risk groups for primary prevention among relatives.

Keywords: liver cirrhosis, hepatosplenomegaly, hemochromatosis, Wilson's disease, heterozygote.

Introduction. Studies of genetic pathologies are especially relevant because they are found in all countries and ethnic groups. Their prevalence is increasing due to the reduction of selection pressure against the background of improving the level of medical care, the development of modern research and treatment methods [1]. Inbreeding significantly increases the probability of monogenic pathology in offspring. This problem needs special attention, as genetic diversity requires the involvement of 5,000 people, while the population of some settlements does not reach this figure, which increases the risk of consanguineous marriages with the emergence of descendants of genetic pathologies [2]. Genetic diseases, in particular monogenic, have unfavorable effects on public health, require significant material and moral resources for the support, care and treatment of patients, lead to disability and mortality [3].

Among these pathologies a special place is occupied by diseases with predominant affection of the gastrointestinal tract [4]. The issues of interpretation of clinical signs and laboratory parameters, differential diagnosis in patients with hepatosplenomegaly and liver cirrhosis are relevant, without which it is impossible to conduct further adequate etiopathogenetic therapy or prescribe symptomatic therapy. An important tool is genetic research with testing for mutations in various genes, followed by a definitive diagnosis and prognosis in patients with hepatosplenomegaly. It can be caused by metabolic disorders associated with genetic pathologies such as hemochromatosis,

Wilson's disease, Niemann-Pick disease, Gaucher disease, amyloidosis and others.

Hemochromatosis (OMIM 235200) is an autosomal recessive disorder of iron metabolism, in which the body accumulates its excess with subsequent deposition in various organs, due to excessive absorption of iron due to hepcidin deficiency, which leads to organ failure and the development of debilitating conditions [5]. The genetic heterozygosity of hemochromatosis is described – the number of genes, *HFE, HJV, HAMP, TFR2,* and *SLC40A1* have been identified as causative of HH types 1, 2a, 2b, 3, and 4, respectively. All of them have an autosomal recessive inheritance, except for type 4 with autosomal dominant inheritance [6]. The prevalence of hemochromatosis among Europeans is about 1:500 [4]. The frequency of heterozygous carriers of mutations that cause the development of hemochromatosis is 1:20. Wilson's disease (OMIM 277900) is an autosomal recessive disease characterized by the accumulation of intracellular copper in the liver with subsequent hepatic and neurological disorders due to decreased levels of ceruloplasmin in blood plasma [7], that is caused by homozygous or compound heterozygous mutation in the *ATP7B* gene (OMIM 606882) on chromosome 13q14. The prevalence of Wilson's disease in the world is 3:100,000 [8]. Frequency of heterozygous carrier of the mutation causing development of Wilson's disease is 1:90 [9].

The purpose of the study was to illustrate the analysis of etiological factors of liver cirrhosis using clinical and anamnestic data and the results of instrumental, laboratory and genetic research.

Materials and methods. The patient was observed in the municipal non-profit enterprise «City Clinical Hospital No.13» of the Kharkiv City Council in 2021-2022. Clinical and genealogical, instrumental – ultrasound (Philips 550, Philips), MSCT (Philips Brilliance 64, Philips), laboratory – biochemical (Cobas 6000, Roche Diagnostics), enzyme-linked immunosorbent assay (Eurostar UN Plus Plus fluorescence microscope, EUROIMM), molecular genetic research methods were used. Genetic testing was performed to determine the H1069Q mutation (rs76151636, according to HGVS nomenclature c.3207C> A, p.His1069Gln) in the *ATP7B* gene (OMIM 606882), associated with the Wilson's disease, the C282Y (rs 1800562, according to HGVS nomenclature c.845G>A, p.Cys282Tyr) and the H63D mutation (rs1799945, according to HGVS nomenclature c.187C> G, p.His63Asp) in the *HFE* gene (OMIM 613609), associated with the hemochromatosis. The data of modern recommendations and clinical protocols [10, 11], medical literature and genetic databases (OMIM) were analyzed.

Informed consent was obtained from the patient. Ethical considerations.

The study conforms to the Helsinki Declaration (1997), the Convention on Europe on Human Rights and Biomedicine (1997), the International Code of Medical Ethics (1983), ICHGSP (2002), and Commission for Ethics and Bioethics, School of Medicine, V. N. Karazin Kharkiv National University (protocol No. 5 dated 04.13.2022).

Research results. Clinical case: patient V., 52 years old, after suffering from acute respiratory disease for the first time complained of weakness, pain in the left hypochondrium, taste of iron in the mouth, cramps in the lower and upper extremities. From the anamnesis it is known that the patient has bronchial asthma and early menopause, from the age of 46, although the first manifestations appeared at the age of 44. According to the patient, she had allergic reactions in the form of erythema and itchy skin, subconsciously avoids iron-containing products, does not drink alcohol.

Overall condition is relatively satisfactory. Body mass index is 19.5, skin and mucous membranes are pale pink, palmar erythema. She had vesicular respiration in the lungs, clear heart tones, rhythmic, heart rate – 80, blood pressure – 120/80. The tongue is moist, covered with white plaque at the root, the abdomen is soft, sensitive to palpation in the left and right hypochondriums, the liver protrudes are three centimeters below the edge of the costal arch, the spleen is one and a half centimeters. Defecation and diuresis are without features. There is no peripheral edema.

The patient was assigned the following laboratory tests: general blood test, biochemical blood test, immunological test, HbS Ag and anti-HCV test and the following results were obtained (**Table**).

Table – Patient V., 52 years old. Results of laboratory tests

Indicator	Result	Norm
General blood test		
Leukocytes	**3.4*10^9/L**	4.5-10.0*10^9/L
Erythrocytes	**3.94*10^12/L**	4.1-5.1*10^12/L
Hemoglobin	130 g/L	120-140 g/L
Hematocrit	393	350-500
Platelet level	**71*10^9/L**	150-400*10^9/L
Thrombocrit	**58**	100-500
Average volume of erythrocytes	**100 fL**	80.00-99.00 fL

End of table

Indicator	Result	Norm
Average content of hemoglobin in one erythrocyte	**33.0 pg**	26.5 pg
Average concentration of hemoglobin in erythrocytes	332 g/L	320.00-360.00 g/L
Width of the distribution of erythrocytes by volume	13.6%	10.00-15.00 %
Average platelet volume	8.1 fL	7.00-11.00 fL
Width of distribution of thrombocytes by volume	**9.3%**	10.00-18.00 %
Lymphocytes	**52.2%**	20-45 %
Monocytes	4.8%	2-10 %
Granulocytes	43.0%	40.00-70.00 %
Lymphocytes	1.7*10^9/L	0.6-4.1*10^9/L
Monocytes	0.1*10^9/L	0.10-0.90*10^9/L
Granulocytes	**1.6*10^9/L**	2.00-7.80*10^9/L
Erythrocyte sedimentation rate	5 mm/hr	2-15 mm/hr
Rod nuclear granulocytes	1%	1-5%
Segmental granulocytes	41%	40-70%
Basophils	0%	0-1%
Eosinophils	1%	1-5%
Lymphocytes	**53%**	20-45%
Monocytes	4%	3-11%
Biochemical analysis of blood		
Albumin	**42.7%**	56.6-66.8 %
Albumin	38.6 g/L	35-52 g/L
Ceruloplasmin	39.1 mg/dL	15-60 mg/dL
Alpha globulins 1	4.6%	3.0-5.6 %
Alpha globulins 2	7.6%	6.9-10.5 %
Beta globulins	**31.6%**	7.2-12.5 %
Gamma globulins	13.5%	12.8-19.2 %
A/G	**0.74**	1.55-1.64
Total bilirubin	20.43 micromoles/L	5-21 micromoles/L
Bilirubin indirect	13.03 micromoles/L	3.4-15.4 micromoles/L
Bilirubin direct	**7.4 micromoles/L**	up to 6.8 micromoles/L
Alanine aminotransferase	**88.53 U/L**	up to 32 U/L
Aspartate aminotransferase	**90.98 U/L**	up to 31 U/L
Gamma-glutamyl transferase	**70.14 U/L**	7-32 U/L
Total iron binding capacity of blood	**72.4 micromoles/L**	45-72 micromoles/L
Iron	**39.69 micromoles/L**	9.0-30.4 micromoles/L
Saturation of transferrin with iron	**51%**	15-50 %
Creatinine	60.17 micromoles/L	53-97 micromoles/L
International normalized relationship (INR)	1.10	0.85-1.25
Prothrombin index according to Quick	92%	85-125%
Prothrombin time	13.0 seconds	8.5-14 seconds
Glucose on an empty stomach (T34025)	3.4 mmol/l	up to 5.5 mmol/l
Blood test for hormones		
Ferritin (FER)	**204 ng/mL**	6-159 ng/mL
Immunological analysis		
Antimitochondrial antibodies (AMA, IFT method)	<1:100	<1:100 – negative result
Antinuclear antibodies (ANA, IFT method)	1<100	<1:100 – negative result
Analysis for HbS Ag and anti-HCV		
Hepatitis B (PCR method) (plasma EDTA)	Not found	Not found
Hepatitis C, PCR qualitative study (plasma EDTA)	Not found	Not found

The patient also underwent ultrasound and MSCT and the following results were obtained:

Ultrasound: diffuse changes in the liver parenchyma of the fibro-fatty type, it is impossible to exclude cirrhosis. Hepatosplenomegaly. Visceral lymphadenopathy.

MSCT: hepatosplenomegaly, CT signs of portal hypertension. Varicose veins of the distal 1/3 of the esophagus, liver cirrhosis. Few lymph nodes of the retroperitoneal space and abdominal cavity, paracardiac and lower paraesophageal groups of the thoracic cavity, which require differential diagnosis with lymphoproliferative disease. Hematologist consultation is recommended. Dolichosigma. Diverticulosis of the sigmoid colon. CT signs of organic pathology of the brain were not detected. CT signs of polysegmental osteochondrosis, spondyloarthritis, initial manifestations of spinal spondylosis.

Laboratory and instrumental methods of research allowed to establish the following indicators in the patient: erythrocytopenia, thrombocytopenia, neutropenia, persistent lymphocytosis, *leukopenia*, decreased platelet count, increased average erythrocyte volume and average hemoglobin content in one erythromycin distribution, albuminemia, increased beta globulin, decreased albumin to globulin ratio, increased liver enzymes (ALT, AST, bilirubin direct) and GGT, blood iron metabolism (COPD and iron levels), iron saturation and iron ferritin saturation, negative immunological analysis for antinuclear antibodies (ANA), HbS Ag and anti-HCV were not detected.

The patient was consulted by a hematologist. Lymphoproliferative diseases were excluded.

On the basis of data on hepatosplenomegaly, portal hypertension, varicose veins of the esophagus, lymphadenopathy, excluding NAFLD, alcoholic fatty liver disease, viral hepatitis, autoimmune hepatitis, biliary cirrhosis, diagnosed with a diagnosis on the detection of mutations that cause hemochromatosis and Wilson's disease.

Molecular genetic studies have shown the following results: the H63D mutation of the *HFE* gene in the heterozygous state and the H1069Q mutation of the *ATP7B* gene in the heterozygous state were detected.

Discussion. The results obtained by us on clinical and laboratory signs and genotype of the patient and their relationship should be analyzed together with the experience of other researchers to determine further adequate pathogenetic and symptomatic therapy and understand the prognosis.

The literature describes cases of a combination of several hereditary diseases in patients. The work of Tuluzanovskaya et al. (2018) presents the results of a clinical genetic study of 90 patients with mixed and abdominal forms of Wilson's disease, which revealed mutations in the *HFE* gene in 30% of patients. The data show that 25 patients are heterozygotes by mutations in the *HFE* gene and 2 patients are homozygotes and compound heterozygotes [12].

The research by Makukh, Gaibonyuk et al. (2019) is devoted to determining the prevalence of the H1069Q mutations of the *ATP7B*, C282Y and H63D genes of the *HFE* gene and to establishing the contribution of hereditary hemochromatosis and Wilson's disease to the etiology of hepatobiliary disorders of unknown origin. A study of a group of 120 patients showed that the frequency of the HFD mutations in the *HFE* gene is 28.57%. As a result of a genetic study of the major in the European population mutation of the H1069Q gene *ATP7B* was found in four people (4%), who later confirmed the diagnosis of Wilson-Konovalov disease [4].

The data obtained by colleagues indicate a significant proportion of patients with lifelong progressive hepatocyte damage due to mutations and the need for continuous monitoring and treatment, the formation of risk groups for primary prevention among relatives.

Results of genetic analysis of a patient with hemochromatosis and Wilson's disease at the same time, described by Abuzetun et al. (2008), showed that the patient was heterozygous for mutations C282Y and H63D. Laboratory studies of this patient showed an increase in ferritin levels, transferrin saturation >90%, and subsequent liver biopsy showed diffuse fibrous changes. Although the mutation that causes Wilson's disease in this patient differs from the patient's mutation in our clinical case, they have similar clinical manifestations [13].

In the work of Dib et al. (2006) it is stated that hemochromatosis was detected in patients aged our patient and at the age close to this indicator – 52, 55 and 57 years [14].

A clinical case of a genetic disorder of combined metal metabolism – Wilson's disease and hemochromatosis caused by heterozygous carriers of the C282Y and H63D mutations of the «hereditary hemochromatosis gene», described by Grechanina et al. (2019) has both common and distinctive features. The clinical picture of the patient described by other authors is characterized by neurodegenerative symptoms, while the patient described by us showed limb cramps, which is a sign of damage to the nervous system, and there are other symptoms and results of laboratory tests that coincide: signs of liver cirrhosis, splenomegaly, portal hypertension, skin rashes, regarded as a history of allergies, elevated iron levels, AST, ALT [15].

Among the clinical variants and conditions described in the literature [16] in patients with mutations associated with hemochromatosis, except different types of hemochromatosis, were noted: hereditary cancer-predisposing syndrome, abdominal pain,

peripheral neuropathy, pain, abnormal peripheral nervous system morphology, abnormality of the male genitalia, behavioral abnormality, abnormality of the nervous system, cutaneous photosensitivity, porphyrinuria, porphyria cutanea tarda, susceptibility to porphyria variegata, susceptibility to Alzheimer disease, susceptibility to transferrin serum level quantitative trait locus 2, microvascular complications of diabetes 7, not provided, Alzheimer disease, cardiomyopathy, bronze diabetes.

Information on the conditions described above, which are the result of the pleiotropic effect of the studied mutations, will be useful for differential diagnosis and prevention of their development and symptomatic therapy.

According to the literature on hemochromatosis [16], the distribution of heterozygous and homozygous variants of carrriers showed that the majority of patients are aged 50-65 years, especially the age group 50-55 years. Therefore, it is important to monitor patients, in particular, with hepatosplenomegaly of the appropriate age groups to determine their future prognosis.

It is important to note that until the age of 52 the patient had no complaints of signs of gastrointestinal disorders, but the treatment revealed an irreversible stage of the disease – cirrhosis of the liver, which required treatment with diet, L-ornithine-L-aspartate, lactulose, beta-blockers, venotonics, enterosorbents, diuretic therapy, intestinal decontamination, zinc salts [17].

The mutant allele frequency, associated with hemochromatosis, ranges from 0.00015 in East Asian to 0.05766 in the European (non-Finnish) population [16], which indicates the relevance of carriers identification in Eastern European countries, including Ukraine. According to OMIM, the H1069Q mutation of the *ATP7B* gene is the most common relative to others in this gene, in Eastern Europe, so it is important in our country to determine it [18].

Mutation testing and phenotype prediction based on genotype opens up prospects not only for personalized therapy, but also for the development of new treatment strategies. The literature [19] provides data about new therapies with different mechanisms of action and discusses studies on Bis-choline tetrathiomolybdate (TTM) in patients, pre-clinical studies of a novel chelator methanobactin and animal studies exploring cures for WD with gene therapy using adeno-associated vectors (AAVs) that introduce ATP7B into liver cells.

Conclusion. The clinical case showed the need to involve specialists in various specialties and a set of research methods to establish the etiology of liver cirrhosis and further etiopathogenetic treatment and the formation of risk groups for primary prevention among relatives.

Perspectives of further research. Mutations and their combinations associated with the gastrointestinal tract pathologies, in particular, the liver, in patients and persons from risk groups cause a higher severity of the developing pathology, and their timely detection allows predicting the course of the disease, conducting differential diagnostics and choosing an adequate therapy regimen.

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Діагностика цирозу печінки на тлі мутацій H63D гена *HFE* та H1069Q гена *ATP7B*, пов'язаних з гемохроматозом та хворобою Вільсона (клінічний випадок)

Дорофєєва В. Р., Борисенко Т. В., Федота О. М.

Резюме. *Мета.* Ілюстрація аналізу етіологічних факторів цирозу печінки з використанням клініко-анамнестичних даних та результатів інструментальних, лабораторних та генетичних досліджень.

Матеріали та методи. Оцінено та проаналізовано дані анамнезу та об'єктивного обстеження, результатів інструментальних, лабораторних та генетичних методів дослідження. Використано сучасні протоколи і медичну літературу.

Результати. Клінічний випадок, пацієнтка, 52 р. Скарги на слабкість, біль у лівому підребер'ї, присмак заліза, судоми верхніх та нижніх кінцівок. Лабораторні і інструментальні методи дослідження дозволили встановити у пацієнтки таки показники: еритроцитопенія, тромбоцитопенія, нейтропенія, стійкий лімфоцитоз, лейкопенія, знижений тромбокрит, збільшені середній об'єм еритроцитів та середній вміст гемоглобіну в одному еритроциті, зменшена ширина розподілу тромбоцитів за об'ємом, гранулоцитопенія, альбумінемія, підвищення глобуліну бета, зниження відношення альбумінів до глобулінів, підвищення печінкових ферментів (АЛТ, АСТ, прямий білірубін) та ГГТ, показників обміну заліза у крові (ЗЗЗК та рівень заліза в організмі), насичення трасферину залізом та рівень феритину, негативний імунологічний аналіз на антинуклеарні антитіла (ANA, метод IFT), HbS Ag та anti-HCV не виявлені. Хвору проконсультовано гематологом, лімфопроліферативні захворювання виключено. На підставі отриманих даних щодо гепатоспленомегалії, портальної гіпертензії, варикозного розширення вен стравоходу, лімфоаденопатії, при виключенні неалкогольної жирової хвороби печінки, алкогольної жирової хвороби печінки, вірусних гепатитів, аутоімунного гепатиту, біліарного цирозу печінки, встановлений діагноз цироз, що дало привід для подальшої диференційної діагностики провести генетичне тестування щодо виявлення мутацій, які обумовлюють гемохроматоз та хворобу Вільсона. Генетичне тестування виявило мутації H63D гена *HFE* та H1069Q гена *ATP7B* в гетерозиготному стані.

Висновки. Клінічний випадок показав необхідність залучення фахівців різних спеціальностей та комплексу методів дослідження для встановлення етіології цирозу печінки та подальшого етіопатогенетичного лікування та формування груп ризику для проведення первинної профілактики серед родичів.

Ключові слова: цироз печінки, гепатоспленомегалія, гемохроматоз, хвороба Вільсона, гетерозигота.

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