A.V. Pavlova, A.S. Asekritova, E.S. Kylbanova, O.V. Tatarinova, E.V. Shakhtschneider

FAMILIAL HYPERCHOLESTEROLEMIA WITH MOLECULAR GENETIC CONFIRMATION IN THE REPUBLIC OF SAKHA (YAKUTIA)

DOI 10.25789/YMJ.2022.80.09

УДК 616.153.922-008.61

The article presents the first clinical cases with the results of molecular genetic confirmation of the mutation of the low-density lipoprotein receptor gene in patients of the Lipid Cabinet of the GAU RS(Ya) "RCBNo. 3" with a diagnosis of "probable" familial hypercholesterolemia.

Keywords: familial hypercholesterolemia, low-density lipoproteins (LDL), lipidogram, genetic mutation, statins, cascade screening.

Introduction: Familial hypercholesterolemia (CGHS) is characterized by an increase in the level of low–density lipoprotein cholesterol (LDL cholesterol) and it is the most common genetic cause of the early development of myocardial infarction and angina pectoris. This disease is caused by pathogenic mutations, more often in the LDL receptor gene (LDL), less often in the APOB and PCSK9 proteins. GHS significantly increases the risk of developing cardiovascular diseases of atherosclerotic genesis, the clinical manifestation of which occurs at a young age and leads to a 20-fold increase in the probability of cardiovascular mortality [1,6]. About 200 thousand patients die from potentially preventable heart attacks every year in the world [7,8], and timely initiated lipid-lowering therapy significantly prolongs the life of such patients [1,8,9].

According to the results of recent studies, the incidence of heterozygous familial hypercholesterolemia in European countries was on average 1 case per 500 people [8]. According to some literature data, this indicator can reach 1 case per 200-250 people, that is, from 14 to 34 million cases in the world [8,9].

Presumably, in Russia, the number of people with a heterozygous form of Familial hypercholesterolemia is more than 1 million. Nowadays, many of them have not been diagnosed [2,3]. This is due to the fact that in Russia the diagnosis of "Familial hypercholesterolemia" is very rare, there is no unified system of accounting for these patients, and therefore the true prevalence of the disease is still unknown [1,5,6]. According to the ESSE-RF study [4,6], which was conducted in 13 regions of the Russian Federation, the prevalence of "definite" and "probable" Familial hypercholesterolemia was studied only in 3 regions: in the Kemerovo and Tyumen regions it is 1 in 108 people, and in the Primorsky Territory the prevalence of Familial hypercholesterolemia was 1 in 172 people. In the remaining 10 regions, 16360 people were included in the study, of which 10% of the surveyed require further verification of Familial hypercholesterolemia [2]. According to the results of the 3-year work of the Russian RENAISSANCE Registry, 1,691 patients from 17 regions of Russia with diagnoses of "definite" and "probable" Familial hypercholesterolemia were included in the registry [2,3,5].

All over the world, the issue of early diagnosis of Familial hypercholesterolemia is more relevant than ever. The National Health System of Great Britain in its long-term plan (National Health System long-term plan) in 2019 stated that by 2023, 25% of the projected number of identified patients with Familial hypercholesterolemia will be treated [7,10]. This will be ensured by genetic testing of index patients diagnosed with Familial hypercholesterolemia and cascade screening of relatives [7].

Cascade screening has clinical and economic value because it provides identification of people suffering from familial hypercholesterolemia at a young age - before the onset of a cardiovascular catastrophe of atherosclerotic genesis. Early diagnosis provides the patient with the choice of an appropriate lifestyle and the possibility of prescribing lipid-lowering therapy, which gives a chance to reduce the risk of premature coronary heart disease, stroke and possible disability in the future.

Based on the above, the identification of patients with CFS in clinical practice is an important task of primary and secondary prevention of cardiovascular events [4].

Materials and methods: In the lipid cabinet of the Center for Predictive Medicine and Bioinformatics of the State Autonomous Institution of the Republic of Sakha (Yakutia) "Republican Clinical Hospital No. 3" for 2021 and 2022, we examined 535 patients, 355 of them women and 180 men. The average age of women was 63 years, for men – 67 years. 42 patients out of 535 examined persons were diagnosed with early myocardial infarction (men under 50 and women under 55). The clinical examination included: assessment of lipidogram, blood glucose, thyroid hormones, ECG; if available: Holter ECG monitoring, echocardiography, ultrasound examination of brachiocephalic arteries and vessels of the lower extremities, coronary angiography. The majority of the examined were of Yakut nationality and belonged to the

PAVLOVA Anna Vladimirovna – cardiologist of Center for Predictive Medicine and Bioinformatics Republican clinical hospital No.3, e-mail – pavlovaav11@gmail.com; **ASEKRITOVA Aleksandra Stepanovna** – chief of Center for Predictive Medicine and Bioinformatics Republican clinical hospital No.3, PhD in medical sciences, associate professor of the Department of therapy, Institute of Medicine, M.K. Ammosov North-Eastern Federal University. E-mail – aleksaykt@mail.ru; **KYLBANOVA Elena Semenovna** – MD, Professor, Head of the Department of therapy, Institute of Medicine, M.K. Ammosov North-Eastern Federal University. E-mail: kyles@list.ru; **TATARINOVA Olga Viktorovna** – MD, chief physician of the Republican clinical hospital No.3, e -mail – tov3568@mail.ru; **SHAKHTSHNEIDER Elena Vladimirovna** – PhD in Medical Sciences, head of the Sector for the study of monogenic forms of common human diseases, FSBSI Federal Research Center Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences; deputy Head of the branch for scientific work Research Institute of Therapy and Preventive Medicine- branch of FSBSI Federal Research Center Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences, e-mail: 2117409@mail.ru

polyclinic department of the GAU RS(Ya) "RCB No. 3". 9 patients were selected, according to Dutch diagnostic criteria with a diagnosis of "probable" and "definite" hereditary familial hypercholesterolemia, who underwent direct automatic sequencing of the promoter and exons of the LDLR gene on the methodological and instrument base of the sector for the study of monogenic forms of common human Diseases of the Institute of Cytology and Genetics SB RAS (Novosibirsk). According to the results of a molecular genetic study, pathogenic mutations in the LDLR gene in a heterozygous form were detected in 2 patients.

Results: Two clinical cases of Familial hypercholesterolemia are presented.

Patient 1. Woman C, 68 years old, in July 2021, applied for an appointment in the Lipid Cabinet for high blood cholesterol. It is known from the anamnesis that CHD has been suffering for a long time. She suffered a myocardial infarction in 2002. In 2003, the left ventricle was reconstructed with plastic surgery according to Dore, mitral valve plastic surgery according to Alfieri, mammary coronary bypass surgery of the anterior interventricular branch, coronary artery bypass grafting of the diagonal branch of the right coronary artery. In 2011, stenting of the proximal segment of the envelope artery. The last coronary angiography was performed in 2017, according to the results of which: Coronary sclerosis. Stenosis of the trunk of the left coronary artery up to 25%. Stenosis of the envelope artery in the middle segment is up to 30%, stenosis of the mouth of the branch of the obtuse edge is up to 40%. The left-handed type. The shunts are functioning.

In 2018, life-threatening cardiac arrhythmias were diagnosed, and therefore the patient was implanted with a biventricular EX with defibrillator function in the endocardial version of Medtronic Protecta CT-D PSF 625220S in DDD mode. The defibrillator was triggered in 2019. In 2020, an electrode displacement was diagnosed and its replacement was carried out. The first control after correction of the left ventricular electrode for resynchronizing stimulation of the heart was carried out in 2021.

Increase of total serum cholesterol to 14 mmol/L for a long time. Previously, familial hypercholesterolemia was not diagnosed. According to the Dutch criteria, 8 points were obtained – a "certain" SGHS.

Family history: the patient's mother had a myocardial infarction at 62, she died at 64, probably from a myocardial infarction. The patient's father died of an acute heart attack at the age of 60. Probanda's grandmother died in 84, there is no information about her grandfather. The patient's sister died at the age of 50, possibly from a vascular catastrophe. The patient's niece has elevated blood cholesterol up to 10 mmol/l. The patient (according to the words) has 3 children: the daughter (39 years old) has a moderate increase in cholesterol to 5 mmol / l, the sons 5.3 (44 years old) and 4.8 mmol / l (30 years old) – all are somatically healthy.

For genetic verification of the diagnosis, targeted direct sequencing of coding and non-coding regions of LDLR genes by Sanger was performed. Bioinformatic analysis of the obtained data revealed the replacement of rs773328511 (NM_000527.5 LDLR c.810C>A p.Cys-270Ter) in a heterozygous form in the LDLR gene.

Current status of the patient: Height: 170 cm, weight: 62 kg, BMI 21.5 kg/m2. At the moment, the patient is receiving treatment for coronary heart disease according to clinical recommendations, including valsartan + sacubitril 50 mg, against which stable hemodynamics is noted. According to the planned daily monitoring of the electrocardiogram in May 2022, the patient had short runs of ventricular tachycardia from 3 complexes. Brain natriuretic peptide 258 pg/ml. Exercise tolerance is moderately reduced, no further progressive decrease has been observed over the past 2 years. The level of total cholesterol is 10.3 mmol / l, LDL is 7.69 mmol / l while taking rosuvastatin 20 mg, the dose could not be increased due to signs of myopathy. When conducting a pharmacogenetic study of the SLCO1B1*5 gene, a combination of C.521CC alleles was found in the patient, which indicates a very high risk of liver damage and striated musculature. About 5 years ago, in combination with rosuvastatin 20 mg, ezetimibe was prescribed at a dose of 10 mg, the effectiveness of which could not be established retrospectively. The patient was unable to take this drug permanently due to the high cost. The patient-initiated combination therapy with rosuvastatin 20 mg per day and evolocumab 140 mg once every 2 weeks. After the first injection of evolocumab, the patient has complaints of myalgia, arthralgia, which limit daily activity. During examination: creatinine phosphokinase, ALT, AST, creatinine, and other biochemical parameters within normal values. Lipidogram indicators: OHS 8.33 mmol/l, LDL 6.22 mmol/L, TG 1.47 mmol/l, HDL 1.53 mmol/L. The patient resumed taking evolocumab 140 mg once every 2 weeks, the dose of rosuvastatin was reduced to 10 mg. Planned face-to-face consultation of the Research Institute of the PC named after Ak. Meshalkin E.N., further conservative management is recommended.

Clinical diagnosis: Heterozygous familial hypercholesterolemia, defined (the Dutch criteria were 16 points, according to S.Broome there is a definite diagnosis of heterozygous hypercholesterolemia). Coronary heart disease. Angina of tension. 2 Functional class. Post-coronary cardiosclerosis from 2002. Complete blockade of the left leg of the Gis bundle. Frequent ventricular extrasystole with unstable short paroxysm of ventricular tachycardia. Transient WPW syndrome.

Operations:

1. Reconstruction of the left ventricle with Douro plastic surgery, Alfieri mitral valve plastic surgery, mammary coronary bypass surgery of the anterior interventricular branch, coronary artery bypass grafting of the diagonal branch of the right coronary artery in 2003.

2. Selective coronary angiography from 2017: Coronary sclerosis. Stenosis of the trunk of the left coronary artery up to 25%. Stenosis of the envelope artery in the middle segment is up to 30%, stenosis of the mouth of the branch of the obtuse edge is up to 40%. The left-handed type. The shunts are functioning.

3. Implantation of an electronic pacemaker with defibrillator function in the endocardial version of Medtronic Protecta CT-D PSF 625220S in DDD mode in 2018. Defibrillator activation in 2019.

Background: Hypertension 3st. Controlled arterial hypertension. Risk of cardiovascular complications 4.

Complication: Chronic heart failure with an intermediate ejection fraction of 42% (S), stage 2a. Functional Class II (NYHA). Secondary dilation of the heart cavities.

Concomitant diseases: Dyscirculatory encephalopathy of the 2nd degree on the background of atherosclerosis and Hypertension. Genetically determined high risk of statin-induced myopathy.

The patient was taken on dispensary registration, included in the Republican Register of familial hypercholesterolemia. In terms of cascade screening (with the consent of the patient), evaluation of the effectiveness and safety of combined cholesterol-lowering therapy.

Patient 2. Male F., 29 years old. Married, no children. I applied to the lipid cabinet in December 2021 for a high level of total cholesterol up to 11 mmol/l. Obese 2 art . During physical examination of the corneal lipoid arch, no tendon xanthomas were detected. According to

the results of a biochemical blood test, the patient had high lipidogram values: total cholesterol: 9.72 mmol/l; TG 1.83 mmol/l; LDL:7.31 mmol/l. When collecting a hereditary history, it was found that the patient's father had an early non-fatal myocardial infarction in 42, but his further fate is unknown. There were no cases of early vascular catastrophes on the part of maternal heredity. The patient does not have siblings. According to the Dutch criteria, the patient has 6 points - "probable" familial hypercholesterolemia. In the future, the patient underwent ultrasound examination of the heart, brachiocephalic arteries, daily monitoring of the electrocardiogram, where deviations were not detected. Thyroid pathology and diabetes mellitus are excluded.

Current status of the patient: Height 185 cm, weight 123 kg. BMI 36 kg/m2. At the moment, he is taking treatment: atorvastatin 60 mg, adherence to therapy is low, does not follow a diet, the level of physical activity is low. According to the latest test results against the background of irregular intake of atorvastatin 60 mg: total cholesterol 9.28 mmol / l, LDL 6.76 mmol / l, HDL 1.5 mmol / l, TG2.92 mmol / l, ALT and AST indicators are normal. When conducting a pharmacogenetic study of the SLCO1B1*5 gene, a combination of alleles of C.521CC was obtained in the patient, which indicates a very high risk of liver damage and striated musculature. The dose of atorvastatin has been reduced to 40 mg and regular intake is strongly recommended. After evaluating the effectiveness and safety of statin therapy, the tactics of further drug treatment will be determined.

For genetic verification of the diagnosis, targeted direct sequencing of coding and non-coding regions of LDLR genes by Sanger was performed. Bioinformatic analysis of the obtained data revealed the replacement of rs121908038 (NM_000527.5 LDLR c.1202 T>A p.Leu401His) in a heterozygous form in the LDLR gene.

Clinical diagnosis: Heterozygous familial hypercholesterolemia, defined (the Dutch criteria were 14 points, according to S.Broome – a definite diagnosis of heterogeneous familial hypercholesterolemia). Obesity of the 2nd degree (BMI 36 kg/m2).

The patient was taken on dispensary registration, included in the Republican Register of familial hypercholesterolemia. The purpose of treatment is the primary prevention of atherosclerotic cardiovascular complications. Cascade screening is not possible. In terms of: genetic counseling on family planning, selection of effective lipid-lowering therapy.

Conclusion. Despite the absolute need for early detection of familial hypercholesterolemia for the primary prevention of atherosclerotic cardiovascular diseases, I would like to note that in our practice we are faced with the same problem that was identified in the RENAISSANCE study: despite the presence of familial hypercholesterolemia and pronounced hypercholesterolemia, patients do not want to take lipid-lowering therapy, and there is also a low the index patient's interest in conducting cascade screening [5]. This problem is being solved, but it requires an individual approach and long-term confidential contact with the patient.

Previously, no targeted identification of patients with familial hypercholesterolemia was carried out in the Republic of Sakha (Yakutia), the ethnic features of this disease remain unexplored, which requires further research.

Reference

1. Karpov Yu.A., Kukharchuk V.V., Boytsov S.A. [et all.] Zaklyuchenie soveta ekspertov Nacional'nogo obshchestva po izucheniyu ateroskleroza (NOA). Semejnaya giperholesterinemiya v Rossijskoj Federacii: nereshennye problemy diagnostiki i lecheniya [Consensus statement of the Russian national atherosclerosis society (rnas) familial hypercholesterolemia in Russia: outstanding issues in diagnosis and management]. Ateroskleroz i dislipidemii. 2015;2(19):5-16. (In Russ.).]

2. Kross-sekcionnoe issledovanie po ocenke rasprostranennosti semejnoj giperholesterinemii v otdel'nyh regionah Rossijskoj Federacii: aktual'nost', dizajn issledovaniya i iskhodnye harakteristiki uchastnikov [Cross-sectional study to estimate the prevalence of familial hypercholesterolemia in selected regions of the russian federation: relevance, design of the study and initial characteristics of the participants]. Racional'naya farmakoterapiya v kardiologii [Rational Pharmacotherapy in Cardiology 2020.16(1):24-32. (In Russ.)] DOI 10.20996/1819-6446-2020-02-17.

3. Yezhov M.V., Bliznyuk S.A., Tmoyan N.A. [et all.] Registr pacientov s semejnoj giperholesterinemiej i pacientov ochen' vysokogo serdechno-sosudistogo riska s nedostatochnoj effektivnost'yu provodimoj gipolipidemicheskoj terapii (RENESSANS) [Register Of Patients With Familial Hypercholesterolemia And Patients Of Very High Cardiovascular Risk With Lipid-Lowering Therapy Underperformance (Renessans). Russian Journal of Cardiology 2019;24 (5):7–13. (In Russ.)] DOI 10.15829/1560-4071-2019-5-7-13

4. Rozhkova T.A., Zubareva M.Yu. Vyyavlenie pacientov s semejnoj giperholesterinemiej v ambulatornoj praktike [Identification of patients with familial hypercholesterolemia in outpatient practice]. Evrazijskij kardiologicheskij zhurnal [Eurasian Journal of Cardiology. 2016, No.3:74-75. (In Russ.)]

5. Chubykina U.V., Ezhov M.V., Duplyakov D.V. [et all.] Serdechno-sosudistye oslozhneniya i effektivnost' gipolipidemicheskoj terapii u pacientov s semejnoj giperholesterinemiej i pacientov ochen' vysokogo serdechno- sosudistogo riska: tri goda nablyudeniya registra RENESSANS [Cardiovascular events and effectiveness of hypolipidemic therapy in patients with familial hypercholesterolemia and patients of very high cardiovascular risk: 3-year follow-up of the renaissance registry]. Kardiologicheskiy vestnik [Russian Cardiology Bulletin. 2020,3(15): 27-36. (In Russ.)] DOI 10.36396/MS.2020.16.3.004.

6. Khripunova A.A., Boeva O.I., Dzhanibekova A.R. [et all.] Epidemiologiya i osobennosti diagnostiki semejnoj giperholesterinemii v rossijskoj populyacii [Epidemiology And Diagnostics Of Familial Hypercholesterolemia In The Russian Population. Therapy. 2020. 5(39):147-156. (In Russ.)] DOI 10.18565/therapy.2020.5.147-156.

7. MartaFutema. Genetic testing for familial hypercholesterolemia—past, present, and future. Marta Futema, Alison Taylor-Beadling, Maggie Williams, Steve E. Humphries, Journal of lipid research. 2021; 62-100139: https://www.jlr.org/article/S0022-2275(21)00121-8/fulltext

8. Nordestgaard B.G. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. / Nordestgaard B.G., Chapman M.J., Humphries S.E. et al.// Eur Heart J. 2017; 34(45): 3478-90a. DOI: 10.1093/eurheartj/eht273

9. Mach F. 2019 ESC/EAS Guidelines for the management of dyslipidemias: lipid modification to reduce cardiovascular risk. /Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, DeBacker GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O, //ESC Scientific Document Group. Eur Heart J. 2020; 41(1): 111–188. DOI: 10.1093/ eurheartj/ehz455. https://www.atherosclerosis-journal.com/article/S0021-9150(19)31459-5/fulltext

10. About the long-term plan NHS URL: https://www.longtermplan.nhs.uk/ (date of application: 30.07.2022).