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CARDIOLOGY AND GENETICS

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Abstract: Hereditary cardiovascular diseases make a significant contribution to the structure of cardiovascular pathology. The article is devoted to a review of materials on genetically determined cardiac diseases, which were discussed at the First International Congress "Genetics and the Heart". The most current data on hypertrophic and dilated cardiomyopathies and hereditary problems of arrhythmogenesis are presented. The main participants of the congress are listed.

Keywords: hypertrophic cardiomyopathy, dilated cardiomyopathy, channelopathies, arrhythmogenic cardiomyopathy, pulmonary hypertension, genetic myocardial diseases, Congress "Genetics and the Heart".

Hereditary cardiovascular diseases make a significant contribution to the structure of cardiovascular pathology. The cause of sudden cardiac death (SCD) in young patients under 35 years of age is primary cardiomyopathies or channelopathies in 10–15% of cases [1]. The extraordinary progress achieved in the molecular genetics of hereditary cardiovascular diseases makes it possible to identify them in the early stages and determine the management tactics for these patients, as well as their relatives.

Today, genetic diagnosis is included in most international guidelines with a high level of evidence (IB). Currently, indications for genetic studies are included in clinical guidelines for long QT syndrome [2], hypertrophic (HCM) [3], arrhythmogenic (ACMP) [1], dilated cardiomyopathy (DCM) [4], and pulmonary hypertension. Genetic testing of autopsy material is indicated in all cases of SCD when hereditary cardiovascular diseases are suspected [5].

Genetic diagnosis in cardiology is a difficult task, since hereditary cardiovascular diseases are extremely heterogeneous and a large number of different genes are involved in their pathogenesis. For example, the DCM diagnostic panel includes 98 genes, since the disease manifests itself in the form of abnormalities in the cytoskeletal proteins, nuclear envelope, sarcomeres, desmin and other structural proteins. Sequencing, and especially interpretation of the results, is an extremely difficult task. Currently, the main method for diagnosing cardiomyopathies is NGS sequencing (massively parallel sequencing method), which allows simultaneous study of a large number of genes. NGS sequencing is performed using repeated cycles of polymerase-induced chain extension or repeated ligation of oligonucleotides. NGS sequencing can generate up to hundreds of megabases and gigabases of nucleotide sequences in one work cycle. This technology, which began its development 8 years ago and continues to be constantly improved, has made it possible to reduce the cost of large-scale studies by several orders of magnitude. However, in Russia today this type of research is not registered and genetic laboratories do not have the ability to issue certified conclusions, and also do not have sufficient experience in correctly interpreting the data of such studies from a clinical point of view.

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This problem, as well as the growing importance of genetic diagnostics in cardiology, was the reason for the creation in December 2017 of the National Research League of Cardiac Genetics (NRCG). The head of the primary vascular department of the State Clinical Hospital No. 51, head of the department of therapy, cardiology and functional diagnostics of the Federal State Budgetary Institution of Further Professional Education "Central State Medical Academy" of the Administration of the President of the Russian Federation, Professor D.A. Zateyshchikov. Director of the NLKG - Head of the Scientific Information Department of the Federal State Budgetary Institution of Further Education of the Central State Medical Academy I.K. Yosava, secretary of the NLCG - head of development of the international genetic laboratory Health in Code N.A. Sonicheva.

In addition, the presidium of the NLCG included leading cardiologists and geneticists from the largest regions of Russia, as well as international colleagues. The NLCH initiative was supported by the working group on myocardial and pericardial diseases of the European Society of Cardiology (ESC).

The purpose of creating the NLCG is the development of Russian cardiological genetics, attracting specialists interested in this problem. The tasks include organizing information work among cardiologists and geneticists in the form of creating an information portal, conducting educational programs, collaborating with world organizations, providing scientific publications, introducing genetic analysis methods into clinical practice to identify hereditary diseases in patients and their relatives in order to optimize ongoing treatment and prevention of complications, which will certainly lead to the development of personalized medicine and a reduction in mortality from cardiovascular diseases.

The work of the NLCG began with the organization of regional conferences in the largest cities of the Russian Federation: Moscow, St. Petersburg, Kazan, Samara, and the creation of the website www.nlcg.ru, where interested colleagues can register and receive information about all possible methods of genetic research in Russia and abroad , as well as familiarize yourself with the most modern scientific publications on genetics in cardiology. In addition, all current projects and registers in the field of cardiogenetics are published on the website.

The organizers of the congress were the FSBI DPO TSMA and NLKG. The congress was supported by the working group on myocardial and pericardial diseases of the EOC, and among the guests and participants of the congress were the president of the working group, Professor Yehuda Adler, and the vice-president of the cardiologist, Professor Antonis Pantazis.

The main idea of the congress was to unite pediatric and adult cardiologists, geneticists, and general practitioners. It was the multidisciplinary approach to work that aroused great interest among all participants of the event.

The congress was attended by 650 participants, and 900 people tuned in to the online broadcast, which significantly surpassed all previous events on this topic, showing the relevance of the development of genetic diagnostics in Russia and emphasizing that such events should be done on an annual basis.

Leading cardiologists from Azerbaijan, Belarus, Bulgaria, Great Britain, Germany, Israel, Spain, Italy, USA, and Uzbekistan took part in the congress.

The Congress allowed us to come close to creating an international consortium for the study of cardiac diseases of predominantly genetic origin.

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At plenary sessions and symposiums, congress participants discussed the risks of sudden death in patients with genetically determined diseases; prognosis for cardiomyopathies; problems of real clinical practice in assessing the risk of SCD in patients with HCM; hereditary disorders of lipid metabolism; problems of hereditary cardiovascular diseases in children; interventional treatment methods for patients with hereditary diseases; the problem of amyloidosis, pulmonary hypertension, pericarditis; some aspects of cardio-oncology; as well as the problem of hereditary cardiovascular diseases in athletes and many other topics.

The main topics of the symposiums and reports were cardiomyopathies, channelopathies, pulmonary hypertension, hereditary dyslipidemias and diseases of the pericardium and connective tissue.

Most of the topics of the congress were devoted to cardiomyopathies, taking into account the frequency of occurrence of these pathologies and their connection with SCD.

William John McKenna, Emeritus Professor of Medicine at the University of Aberdeen and Associate Professor of Cardiovascular Medicine at Yale University, CEO and Medical Director of the Hamad Medical Corporation Cardiology Clinic (Doha, Qatar), spoke in detail about the classification and genetic diversity of hereditary cardiomyopathies, with an emphasis on HCM. The professor shared his experience at the origins of the discovery of this complex disease, its modern classification, genetic diagnosis and treatment.

HCM is the most common cause of SCD [6]. Definition: HCM is characterized by left ventricular (LV) hypertrophy of unknown etiology, not related to pressure loading or valvular lesions. Diagnosis of this type of myocardial disease is based on recording echocardiographic changes in the already advanced stage of the disease - the criterion is the presence of thickening ≥15 mm of one or more LV segments. In some cases, the diagnosis of this disease is very difficult, and the first manifestations of the disease are not always visible on an echocardiogram. Professor W. McKenna emphasized in his report the role of ECG diagnostics in cardiomyopathies, especially the role of the T wave and its inversion as an early manifestation in I, aVL, V4–6 in HCM and in V1–3 in ACM. He gives a special role in such and other cases of diagnosing HCM to genetic diagnosis. Today, the international expert community recognizes mandatory genetic testing of a patient with HCM and all related relatives (evidence class IB). It is genetic testing that can identify the problem of early and timely diagnosis of HCM, since this is quite difficult to do using clinical criteria alone. Most often, involvement of the interventricular septum is noted, as well as the phenomenon of disarray (disorderly arrangement) of cardiomyocytes and fibrosis. Atrial fibrillation is a common complication of this disease, and such patients appear to have a higher risk of thromboembolic complications [3].

Type of inheritance - autosomal dominant, mutations in genes encoding sarcomeric proteins, most often cardiac type myosin binding protein C - MYBPC3 (15-30%) or b-isoform of the myosin heavy chain - MYH7 (15-30%). However, modern genotyping technologies make it possible to identify the genetic causes of the disease in 50–70% of patients with clinical HCM [1, 3]. The likelihood of obtaining a positive result is higher if the patient has a clear clinical picture of the disease and a family history of the disease or cases of SCD in the family.

Sarcomeric gene mutations are the most common causes of the disease, which is why HCM is often called sarcomeric disease. However, mutations in many other genes may also be responsible for the development of HCM [3]. Comprehensive genetic screening for HCM should consider RAS genes (Noonan, Costello, other cardiovascular syndromes), mitochondrial diseases

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(mitochondrial genome or nuclear genome), transcription factors, cytoskeletal structural proteins (DES, FLNC, etc.), calcium regulatory proteins (PLN), glycogenic diseases (Danon disease, PRKAG2, Pompe disease, Fabry disease), amyloidosis (TTR) and many others [1–3, 6–8].

To date, a complete targeted panel for diagnosing HCM in specialized laboratories includes 118 genes. If the result of the genetic study is positive, then this confirms the diagnosis 100% and allows us to begin screening relatives and dynamic monitoring of carriers, taking into account the severity of each identified variant. If it is negative, you need to re-analyze the clinical picture of the disease, the family history of the disease (in some cases, new de novo mutations occur, more often characteristic of phenocopies of HCM), the selected panel for the study and the laboratory where such a study was carried out. A negative result does not eliminate the diagnosis of HCM, as information about new genes and variants continues to accumulate, so in any case, genetic testing is an additional diagnostic method that does not exclude other research methods.

Diagnosis of all rare hereditary diseases requires specific knowledge not only in the field of clinical medicine, but also in the field of molecular biology and genetics, as well as a multidisciplinary approach. Fabry disease can be diagnosed by knowing the early symptoms of the disease, which will allow genotype-specific therapy to be initiated before severe organ damage develops [11].

The diagnosis and treatment of amyloidosis, a difficult to diagnose disease with a poor prognosis, was also widely covered at the congress, taking into account its etiology, diagnosis and new promising treatment methods [12].

One of the innovative reports on new genes recently discovered in the genetic diagnosis of HCM was the report of scientist Juan Pablo Ochoa, PhD, cardiologist, researcher at the Health in Code genetic laboratory, A Coruña, Spain.

The scientist, together with colleagues, in 2018 identified the possibility of the involvement of mutations in the Formin homology 2 domain containing 3 (FHOD3) gene, which is involved in the organization of the sarcomere (myofibrillogenesis) and supports the contractile apparatus of cardiomyocytes. The role of this gene in the development of HCM was proven as a result of NGS sequencing of 3189 probands with HCM: 1915 patients had other cardiomyopathies or SCD and 2777 were present in the control group. The results of the study revealed that this gene is responsible for 1–2% of cases with HCM, so it must be included in the main panel of genes for HCM [10].

Treatment of HCM, regardless of genetic disorders, is currently symptomatic, but existing studies have already shown the prospect of gene therapy in the near future. Treatment includes eliminating complications and preventing the development of life-threatening arrhythmias. Currently, pathogenetic treatment methods based on gene therapy are being developed [9].

One of the most important plenary reports was the report by Antonis Pantazis, vice-president of the EOC working group on myocardial and pericardial diseases, on hereditary cardiovascular diseases and sports.

Problems of the genetics of arrhythmogenesis were also raised during the congress. ACM is an inherited disease characterized by progressive fatty and fibrous replacement of cardiomyocytes and leading to life-threatening arrhythmias and heart failure. Until recently, it was believed that with this disease the right ventricle, the RV, was involved in the process (the disease was called arrhythmogenic dysplasia of the RV). However, recently, in connection with the development of genetic diagnostics and the discovery of genes for desmosomal proteins (anchor

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connections between cardiomyocytes), it has been proven that the LV can also be involved in the process and can be dominant, causing a high risk of developing life-threatening arrhythmias leading to sudden death at a young age.

The incidence of ARVC is 1:5000 in the general population, but it should be noted that there is heterogeneity in the geographical distribution and a higher incidence of ARVC in some regions. The mode of inheritance is autosomal dominant, and the main genes causing the disease are plakophilin (PKP2) - in approximately 40% of cases, desmoplakin (DSP), desmoglein (DSG2), desmocolin (DSC2), plakoglobin (JUP). In total, the panel includes 26 genes, but it is constantly updated due to the continuous development of genetic diagnosis of this disease [8].

In the case of long QT syndrome, genetic diagnosis plays a crucial role in therapeutic recommendations, since patient management approaches depend on the affected gene. Variants of types 2 and 3, as well as recessive forms of the disease and cases with compound (biallelic) mutations, have a more unfavorable prognosis. The effectiveness of genetic research is 75–80%. In 1/2 of untreated and undiagnosed patients, the first arrhythmic episode develops before the age of 40. To treat all types of prolonged QT interval, beta-blockers are used, among which nadolol (not available in the Russian Federation) has shown the greatest effectiveness. For type 3 long QT syndrome with QTc≥500 ms, the use of sodium channel blockers, in particular mexiletine (evidence class IIB), is recommended.

Genetic studies, with correct clinical interpretation in laboratories that have a sufficient database of patients with hereditary cardiovascular diseases, make it possible to determine the prognosis of the course of the disease for the proband and relatives, knowing the pathogenic variant that led to the development of the disease. Based on the clinical picture, this is difficult to do, given the significant heterogeneity of the disease, the often lack of family history, and the impossibility of determining a 5-year prognosis due to the changing clinical picture of the disease. In addition, it became possible to use the database to evaluate the time of diagnosis, as well as the degree of manifestation of certain clinical symptoms (for example, the degree of hypertrophy of the LV interventricular septum, the degree of QT prolongation on the ECG, the degree of LV dilatation, etc.). Carrying out genetic diagnostics in specialized laboratories is included in the guidelines for HCM as class of evidence IIC [3].

A major challenge among cardiologists is the limited ability to integrate genetic information into treatment regimens for patients with inherited cardiovascular diseases and risk stratification and quantification of SCD risk [6]. For this reason, genetic laboratories must have clinical cardiologists who can provide the correct interpretation of genetic testing to translate it into clinical practice. It is also necessary to conduct family screening of the disease in relatives when a pathogenic variant is detected for early identification of carriers and prevention of SCD. Early identification of carriers makes economic and psychosocial sense. Healthy non-carrier relatives should be excluded from further observation.

Management of patients with hereditary arrhythmias in adulthood requires: adjustment of therapy depending on changes in the clinical picture of the disease and anthropometric parameters of the patients; discussions with female patients about the specifics of pregnancy management; family screening; genetic testing in the absence of a verified genotype, as well as timely testing of antiarrhythmic devices and monitoring the timing of their replacement; knowledge of the features of programming an implantable cardioverter-defibrillator in patients with primary electrical diseases.

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REFERENCES

1. Charron P, Arad M, Monserrat L et al. Genetic counselling and testing in cardiomyopathies: A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2010; 31 (22): 2715–28.

2. Ackerman M et al. HRS/EHRA Expert Consensus Statement on Genetic Testing. Heart Rhythm 2011; 8 (8).

3. Elliott PM, Anastasakis A, Borger MA et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014; 35 (39): 2733–79.

4. Jan Haas et al. Atlas of the clinical genetics of human dilated cardiomyopathy. Eur Heart J 2015; 36: 1123–35.

5. Priori SG et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2015; 8 (9): 746–837.

6. Manonelles P et al. Estudio de la muertesúbita en deportistas españoles. Investig Cardiovasc 2006; 9 (1): 55–73.

7. Hayashi M et al. The spectrum of epidemiology underlying sudden cardiac death. Circ Res 2015; 116: 1887–906.

8. Monserrat L. Perspectives on current recommendations for genetic testing in HCM. GCSP 2018; 23.

9. Cerrone M, Priori SG. Genetics of sudden death: focus on inherited channelopathies. Eur Heart J 2011; 32: 2109–18. DOI: 10.1093/eurheartj/ehr082

10. Bezzina CR, Lahrouchi N, Priori SG. Genetics of Sudden Cardiac Death. Circulation 2015; 116: 1919–36. DOI: 10.1161/CIRCRESAHA.116.304030

11. Charron P, Carrier L, Dubourg O et al. Penetrance of familial hypertrophic cardiomyopathy. Genet Couns 1997; 8: 107–14.

12. Maron BJ, Maron MS, Semsarian C. Double or compound sarcomere mutations in hypertrophic cardiomyopathy: a potential link to sudden death in the absence of conventional risk factors. Heart Rhythm 2012; 9: 57–63. DOI: 10.1016/j.hrthm.2011.08.009