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DIAGNOSIS AND TREATMENT OF DILATED CARDIOMYOPATHY IN CHILDREN

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Abstract. The article presents data on the etiology of dilated cardiomyopathy in children (postmyocardial, metabolic, associated with neuromuscular pathology, idiopathic). The genetic aspects of the disease are covered, a wide range of mutations in genes encoding proteins of various structures of the cardiomyocyte (sarcomeric complex, cytoskeleton, Z-discs, mitochondria), and various inheritance options are described.

Keywords: children, genetic data, etiology, dilated cardiomyopathy, diagnosis, prognosis, method, treatment.

INTRODUCTION

According to modern concepts, dilated cardiomyopathy is understood as a heart disease characterized by non-obstructive dilatation of the left ventricle, reduced contractile ability of the myocardium in the absence of hemodynamic overload (congenital heart defects, arterial and pulmonary hypertension, valvular pathology, ischemic disease heart), which could cause impairment of global systolic function of the left ventricle [1]. Dilated cardiomyopathy is characterized by a continuously progressive course, occupies a leading position in the structure of disability and mortality in children, and is the main cause of chronic heart failure in childhood [2, 3].

MATERIALS AND METHODS

The prevalence of dilated cardiomyopathy varies from 40 cases per 100,000 population in the United States of America to 3.8 per 100,000 per year in Europe. The annual incidence in Europe is 5–7 new cases per 100,000 population per year, in the United States of America – 38 per 100,000 population. In children of the first year of life, the highest prevalence of the disease was observed compared to older children: 4.4 versus 0.34 per 100,000 children of the corresponding age. The disease is more often observed in boys than in girls. The share of dilated cardiomyopathy among other cardiomyopathies is 60% [2, 3].

RESULTS AND DISCUSSION

The etiology of dilated cardiomyopathy is diverse, with acquired and hereditary forms possible, which allows the disease to be classified as mixed forms of cardiomyopathy, according to the classification proposed by the American Heart Association [1]. However, the specific cause of the disease is identified only in 40% of cases (including myocarditis, metabolic and neuromuscular diseases); the remaining forms are idiopathic [2, 3].

The acquired postmyocardial form, according to the pediatric registry of cardiomyopathies, predominates in the structure of dilated cardiomyopathy. The cause of postmyocardial cardiomyopathy in most cases is a viral infection. Endomyocardial biopsy data allows one to isolate the specific genome of the virus that causes the disease. Previously, among the causative agents of myocarditis, enterovirus, Coxsackie viruses B and A predominated; currently, herpes viruses, adenovirus, and parvovirus are more often detected. The viral genome is most often detected in newborns. Viruses that persist in the myocardium contain proteins that are partially homologous to autoantibodies of cardiomyocytes, which triggers the autoimmune mechanism of the disease under conditions of altered immune tolerance [4].

In patients with dilated cardiomyopathy, a high titer of antimyocardial antibodies to a wide range of antigens is detected, such as myosin heavy chains, β-adrenergic receptors, muscarinic receptors, lamin, and a high titer of cardiac organ-specific autoantibodies, such as antimyosin, antiactin, antimyolemma, anti-α-myosin and anti-β-myosin heavy chains [4, 5]. However, the diagnosis of myocarditis as a cause of dilated cardiomyopathy remains a big problem. The greatest potential in this regard is provided by endomyocardial biopsy data, which allow diagnosing inflammatory changes in the myocardium, assessing autoimmune changes and, in some cases, identifying a viral infection. According to modern recommendations, the indications for endomyocardial biopsy are rapidly progressive cardiomyopathy, refractory to standard treatment (class of indication II, level of evidence B2), cardiomyopathy of unknown etiology in children (class of indication IIa, level of evidence C) [1]. At the same time, the invasiveness of this technique, as well as the possibility of focal rather than diffuse inflammation, reduce its informativeness. Thus, endomyocardial biopsy data confirm the clinical diagnosis of myocarditis only in 34% of cases. In this regard, the myocardial cause of the disease often remains undiagnosed during life and dilated cardiomyopathy is considered idiopathic.

Congenital metabolic disorders are an important cause of dilated cardiomyopathy, accounting for 5–10% of cases in the structure of the disease, their share increases to 15% among children with an established genesis of cardiomyopathy. According to the registry, metabolic cardiomyopathies are represented by disorders of oxidative phosphorylation (40%), defects in carnitine transport/disorders of fatty acid oxidation (40%). The most common metabolic forms of dilated cardiomyopathy are in children 1 year of age [3].

Neuromuscular pathology as the cause of dilated cardiomyopathy, according to the pediatric cardiomyopathy registry, accounts for 10% [3]. Most often, dilated cardiomyopathy develops with progressive Duchenne and Becker muscular dystrophies, and less often with progressive Emery-Dreyfus muscular dystrophy. Progressive Duchenne muscular dystrophy occurs in 1 in 3–3.5 thousand newborn boys, usually manifesting at the age of 1.5–3 years. Dilated cardiomyopathy develops slowly, but is progressive. Typically, shortening of the P–R interval, deviation of the electrical axis of the heart, and widespread fibrous changes in the myocardium. The clinical picture is dominated by myopathic syndrome, which leads to immobility of children. As motor function is lost, the progression of cardiac dilatation and heart failure symptoms slows somewhat. With Becker's myodystrophy, the loss of motor functions occurs much more slowly, at the same time, heart damage

develops at a faster pace, characterized by severe systolic dysfunction, severe heart failure, and diffuse cardiosclerosis.

Idiopathic dilated cardiomyopathy: in 50–60% of patients, a specific etiology of the disease is not identified, in these cases the cardiomyopathy is classified as idiopathic [3]. According to recent studies, among this group of patients, familial aggregation of the disease varies from 20 to 30% of cases. The empirical risk of having a similar pathology in other family members is at least 6%; if more than one first-degree relative is affected, the risk of cardiomyopathy increases to 50%. Moreover, in a number of relatives the disease can be subclinical. The familial form should be considered if dilated cardiomyopathy is detected in the proband and in one of the first-degree relatives, as well as if there are cases of sudden cardiac death in the pedigree before the age of 35 years. In this case, major criteria are taken into account: expansion of the left ventricular cavity (more than two standard deviations), a decrease in ejection fraction of less than 45%, as well as minor criteria: unexplained arrhythmia - fibrillation, supraventricular tachycardia (with a heart rate of more than 120 per minute) , ventricular extrasystole, increase in end-diastolic pressure of the left ventricle more than 112%, decrease in ejection fraction less than 50% (according to Teicholtz), segmental systolic dysfunction, atrioventricular block type IIb II degree, sudden cardiac death before the age of 50 years . The diagnosis of familial dilated cardiomyopathy is made on the basis of two major criteria or one major + one minor or three minor criteria.

Genetic aspects. Recent years have been characterized by significant progress in the study of genetic factors of the disease. The range of genes is extremely wide, which makes molecular genetic testing difficult. Mutations were identified in genes encoding proteins of various structures of cardiomyocytes: cytoskeleton (gene DMD - dystrophin protein, Des - desmin, VCL - metavinculin, SGCD - sarcoglycan complex), sarcomeric complex (ACTC1 - actin, MYH6 - alpha subunit). Myosin heavy chain, MYH7 – beta subunit of myosin heavy chain, MYPN – myopalladin, TNNT2 – troponin, TTN – titin), inner nuclear membrane (LMNA – lamin A/C, EMD – emerin), Z-discs (ACTN2 - alpha actin 2, TCAP - titin cap, CSRP3 - cysteine and glycine enriched protein 3), mitochondrial membrane (TAZ - tafasin) [3, 4]. The type of inheritance of the disease and the identified mutation are currently indicated using the MOGE(S) classification of cardiomyopathies, (M – morphofunctional characteristics, O – organ involvement, G – type of inheritance, E – mutation in a specific gene, S – functional class of heart failure according to NYHA) [5].

Table 1.

Mutations of the main genes in dilated cardiomyopathy with an autosomal dominant type of inheritance

Gene	Protein	Function	OMIM No.	Mutation frequency
LMNA	Lamin A/C	Structure/stability gene of the inner nuclear membrane	150330	0,06
MYH6	alpha-myosin heavy chains	Sarcomere protein; muscle contraction	160710	0,043
MYH7	beta-myosin heavy chains	Sarcomere protein; muscle contraction	160760	0,042
MYPN	myopalladin	Sarcomere protein; muscle contraction; Z-disc	608517	0,035

TNNT2	cardiac troponin T	Sarcomere protein; muscle contraction	191045	0,029
SCN5A	sodium channels	Control of sodium ion channels	600163	0,026
MYBPC 3	C myosin binding protein	Sarcomere protein; muscle contraction	600958	0,02
RBM20	RNA binding protein	Spliceosome RNA binding protein	613172	0,0019

CONCLUSION

Dilated cardiomyopathy is one of the most severe myocardial diseases and is characterized by extremely high disability and mortality. The etiology of the disease is extremely broad and is associated both with previous myocarditis and with metabolic disorders and neuromuscular pathology. Unfortunately, the true cause of the disease is established only in 40–50% of cases. In recent years, significant progress has been made in the diagnosis of metabolic forms of dilated cardiomyopathy based on the introduction of new laboratory diagnostic methods. Early diagnosis of the metabolic causes of the disease allows timely prescribing pathogenetic treatment and improving the prognosis. In addition, there has been progress in studying the genetic nature of cardiomyopathy. A large number of genes (more than 30) have been identified that encode proteins of various myocardial structures, defects of which lead to dilated cardiomyopathy. Wide variability in the types of inheritance of the disease has been shown. It is hoped that the reduction in the cost of genetic testing will facilitate its wider implementation in clinical practice.

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