

## КАРДИОМИОПАТИИ У ДЕТЕЙ – КЛИНИЧЕСКИЕ, ГЕНЕТИЧЕСКИЕ И МОРФОЛОГИЧЕСКИЕ АСПЕКТЫ

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Кардиомиопатии (КМП) являются одной из серьезных и сложных проблем детской кардиологии. Многие из них – причина внезапной смерти и носят семейный характер. Неутешительная статистика повышает актуальность проблемы КМП и диктует необходимость углубленного изучения этиопатогенеза, структурных основ и опыта клинико-морфологической диагностики данной патологии у детей. Особую значимость, с практической точки зрения, приобретает разработка прогностических факторов при первичных и вторичных КМП. В данном литературном обзоре представлены сведения об этиологии, патогенезе, клинических проявлениях, патоморфологических изменениях и исходах таких КМП как гипертрофическая, дилатационная, некомпактный миокард левого желудочка и гистиоцитозная кардиомиопатия. Показаны особенности структурной перестройки миокарда при анализируемых кардиомиопатиях и их связь с систолической и диастолической дисфункцией миокарда. Детализированы молекулярно-генетические аспекты диагностики этиологии и патогенеза данной патологии у детей. Подчеркивается необходимость систематического патоморфологического исследования сердца с наиболее полным анализом сократительных, проводящих микроциркуляторных и нейровегетативных структур при рассматриваемых вариантах сердечно-сосудистой патологии. Эти данные помогут сформировать будущие исследовательские приоритеты по обсуждаемой группе заболеваний для достижения более ранней диагностики, улучшения клинических результатов и повышения качества жизни этих детей и их семей.

**Ключевые слова:** кардиомиопатия; гипертрофическая; гистиоцитозная; дилатационная; дети; некомпактный миокард.

## CARDIOMYOPATHY IN CHILDREN – CLINICAL, GENETIC AND MORPHOLOGICAL ASPECTS

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Cardiomyopathy is one of serious and complex problems of pediatric cardiology. Many of them are the cause of sudden death and are familial in character. Disappointing statistics increases the relevance of the problem of cardiomyopathy and dictates the need for in-depth study of the etiology and pathogenesis, structural bases and experience in clinical and morphological diagnosis of this pathology in children. Of particular importance from a practical point of view is the development of prognostic factors in primary and secondary cardiomyopathies. This literature review pro-



vides information on the etiology, pathogenesis, clinical manifestations, pathomorphological changes and outcomes of such cardiomyopathies as hypertrophic, dilated cardiomyopathies, non-compact left ventricular myocardium and histiocytoid cardiomyopathy. Peculiarities of restructure of the myocardium in the analyzed cardiomyopathies and their relationship with systolic and diastolic myocardial dysfunction are shown. Molecular genetic aspects of diagnosis of etiology and pathogenesis of this pathology in children are given in detail. The necessity of systematic pathomorphological study of the heart with full analysis of contractile, conducting microcirculatory and neuroautonomic structures in considered variants of cardiovascular pathology is emphasized. These data will help outline future research priorities for this group of diseases to provide earlier diagnosis, improve clinical outcomes and the quality of life of these children and their families.

**Keywords:** *cardiomyopathy; hypertrophic; histiocytoid; children; dilated; non-compact myocardium.*

Cardiomyopathies (CMP) is the term that denotes diseases of the myocardium associated with structural and functional alterations of the cardiac muscle with the absence of pathology of coronary arteries, of arterial hypertension, lesions of the heart valves and of the congenital heart disease. As a rule, CMP clinically manifest in infancy and often have lethal outcome. Despite achievements of the modern medical sciences – genetics, immunology, pathological anatomy – CMP remain the least studied part of pediatric cardiology.

Classification of WHO (1995) distinguishes primary (congenital, idiopathic) and secondary (specific) CMP. The primary CMP include dilated CMP (DCMP), hypertrophic CMP (HCMP), restrictive CMP (RCMP) and arrhythmogenic right ventricular CMP (ARVC). Primary CMP are either genetically determined, or result from *de novo* gene mutations. Further on this leads to destruction of the contractile proteins of the myocardium followed by frustration of the pumping function of the myocardium and dilatation of its chambers. According to the literature data [1,2], the most common in the population are DCMP (up to 60% of diagnosed cases) and HCMP (40% of diagnosed cases). Besides the mentioned groups, there also exists a group of unclassified CMP including non-compact (trabecular) myocardium, histiocytoid cardiomyopathy (HcCMP), endocarp-

dial fibroelastosis, etc. Secondary, or specific, CMP include pathology of the myocardium combined with other diseases of the heart or with systemic processes. These are metabolic CMP (endocrine or amyloidosis-related), associated with systemic diseases of the connective tissue, muscular dystrophies, toxic-allergic reactions, etc.

Ambiguous epidemiological picture of the given pathology can be due to the difficulties of the lifetime and postmortem diagnosis of CMP. According to different authors [3,4], the rate of identification of the primary CMP in children ranges from 0.65 to 1.24 cases per 100000 children.

CMP presents a serious problem of pediatric cardiology: 40% of patients with verified diagnosis need surgical treatment (heart transplantation) within the first two years from the moment the disease manifested. Without the operation the most part of patients die [3,5]. In early antenatal diagnosis of the pathology 13% of pregnancies are interrupted, and the most part of fetuses (up to 63%) die in the perinatal period [4]. Disappointing statistics emphasizes the relevance of the problem of cardiomyopathy and dictates the need for in-depth study of the etiology and pathogenesis, structural bases and experience in clinical and morphological diagnosis of this pathology in children.

The *aim* of the given literature survey is to elucidate the clinical and morphological

aspects of the most common variants of cardiomyopathies in children – hypertrophic and dilated cardiomyopathies, and also of such rare diseases as histiocytic cardiomyopathy and left ventricular non-compaction.

### ***Hypertrophic Cardiomyopathy***

The disease characterized by hypertrophy of the walls of the left and/or right ventricle that is mostly asymmetric and usually involves the interventricular septum (IVS). HCMP is the most common disease of the myocardium in pediatric practice. According to the data of epidemiological studies conducted in the countries of the Western Europe, Australia and the USA, the annual incidence rate of the disease ranges from 0.24 to 0.47 per 100000 [2-5]. According to different authors, from 30% to 60% of HCMP are familial, with autosomal-dominant transmission in most cases [5,6]. Increase in the amount of recorded cases of this pathology is due to both wide introduction of modern diagnostic methods into practice and, what is most likely, to true increase in the amount of patients [5,7]. By the moment, there are identified 14 genes which mutations may lead to HCMP: myosin-bound protein C (MYBPC3),  $\beta$ -myosin-heavy chains (MYH7), cardiac troponin T (TNNT2),  $\alpha$ -tropomyosin (TPM1), cardiac  $\alpha$ -actin (ACTC) and others. The majority of the mentioned genes code for proteins of cardiac sarcomeres and structural proteins of filaments [3,5,8]. Most common are mutations of gene of  $\beta$ -myosin of heavy chains – up to 50% of families of patients with HCMP. A role in the pathogenesis is assigned to matrix metalloproteinases (MMP). There are found disorders in the balance between the amount of MMP and their tissue inhibitor (TIMMP-1) in the myocardium that leads to disorders in the isomeric composition of components of the extracellular matrix, to accumulation of collagens and to development of fibrous tissue in the heart [9].

HCMP that develop in disorders of metabolism, in genetic syndromes and neuromuscular diseases, are referred to non-genetic

forms. Into the same category there are also referred metabolic forms of HCMP accounting for 10% of cases. Metabolic disorders associated with HCMP are mainly glycogenoses (in particular, Pompe's disease) and also mucopolysaccharidoses and disorders in metabolism of fatty acids. Often HCMP is a manifestation of *MELAS*, *Barth*, *Sengers* syndromes and of other mitochondrial diseases [10]. Characteristic peculiarities of heart lesion in these diseases are symmetrical hypertrophy of the myocardium, rapid progress of systolic dysfunction and development of dilatation.

Clinical manifestations of HCMP vary from a prolonged asymptomatic course to a sudden cardiac death. As a rule, the disease manifests by dyspnea on physical exertion, pain syndrome, arrhythmias, dizziness and syncopal conditions. The spectrum of arrhythmias in children is wide, they may be both bradyarrhythmias and tachyarrhythmias [11]. Diagnosis of HCMP rests on the data of electrocardiography (ECG) and echocardiography (EchoCG). It is the changes in ECG that often become one of starting points in the diagnosis of the disease. The most informative changes in EchoCG are the thickness of IVS and of the wall of LV.

HCMP is classified to symmetrical and asymmetrical forms. The latter is subdivided to obstructive form, or idiopathic hypertrophic subaortic stenosis, and apical form. Obstructive HCMP is manifested by hypertrophy of primarily apical part of IVS, sometimes in combination with hypertrophy of the anterior-lateral wall of the left ventricle, and is accompanied by obstruction of the outflow tract. The apical variant of HCMP is characterized by predominant hypertrophy of the apical part of the LV. Here, obstruction of the outflow tract is absent. Asymmetrical form of HCMP is characterized by a pronounced hypertrophy of the myocardium of LV and of IVS without dilatation of the heart chambers. Macroscopically, the heart is considerably increased in mass and dimensions, with hypertrophy of LV and

IVS, histologic examination reveals chaotic arrangement of cardiomyocytes and of shortened muscle fibers [6,12], and also cardiosclerosis and focal necroses of cardiac myocytes. Sometimes branching cardiac myocytes of irregular or stellular shape are detected. Alteration of the cytoarchitectonics of the myocardium with alternation of narrow longitudinal and wide transverse muscle fibers is associated with increase of the area of the myocardial stroma. Pronounced hypertrophy is associated with disorder in the function of the coronary arteries (first of all of the anterior left descending branch) and, as a result, with myocardial ischemia [13].

Symmetrical HCMP is characterized by a considerable increase in the mass of the heart with uniform thickening of its wall, dilatation of atria and reduction of the volumes of ventricular chambers. The pathomorphological picture of the disease is determined by a combination of the focal myocardial sclerosis and focal necroses of cardiac myocytes with the underlying hypertrophy of muscle fibers. The latter may have mutually orthogonal arrangement forming 'nodes' and 'vortices'. The cytoplasm of cardiac myocytes contains perinuclear vacuoles assumed to be due to accumulation of atypical granules of glycogen [13].

The prognosis of the disease is rather poor – HCMP is associated with high mortality rate. The mortality rate data given by different authors are contradictory. According to B. Maron, et al., the risk of death is maximal in the individuals of postpubertal and young age [14]. Results of the extensive study of Swiss scientists indicated the death rate from HCMP in children at the age from 8 to 16 to be comparable with that in adults and making 0.112 per 100000 of population. The death rate among children under 8 is minimal and makes 1.6%, then it increases and by the age of 10 reaches 9.7% [15]. A sudden cardiac arrest accounts for 18% of direct causes of death and may be the first and the only manifestation of the disease [15].

### *Dilated Cardiomyopathy*

DCMP is characterized by dilatation of the chamber of the LV and by reduction of the global contractility of the myocardium in the absence of any hemodynamic overload which could induce a disorder in the systolic function of the LV. This form is dominating in the structure of disability and death of children and is the main cause of development of chronic cardiac failure in childhood [2, 16]. The incidence of DCMP ranges from 3.8 cases per 100000 of population in Europe to 40 cases per 100000 of population in the USA [16]. The disease affects boys more often than girls.

According to different authors, up to 30% DCMP are familial [17,18]. The disease is considered to be transmitted by autosomal-dominant pattern, but autosomal-recessive, X-linked and mitochondrial transmission patterns are also possible [17,18]. By the present moment, information have been accumulated about mutation of genes of the cardiac proteins (desmin, dystrophin, lamin A/C) participating in the embryofetogenesis of the myocardium [17,19].

An important role in the pathogenesis of DCMP is assigned to activation of apoptosis, endothelial dysfunction and alterations of the extracellular matrix [19]. Disorders in the structural and functional condition of the extracellular matrix are diagnosed by imbalance in the content of matrix metalloproteinases (MMP). Increased content of MMP-1 in the matrix provokes cleavage of I type collagen leading to imbalance of collagen with increase in III type collagen. The latter possessing the property of enhanced elasticity, becomes a factor that facilitates distensibility of the myocardium and dilatation of the LV. Increase in the content of MMP-2 and MMP-9 indicates activation of cleavage of the matrix components which leads to dilatation of ventricles and atria thus worsening systolic and diastolic dysfunction of the heart [19].

A significant share in the structure of the disease is taken by non-hereditary forms

caused by myocarditis, disorders in metabolism and neuromuscular diseases. Postmyocarditis DCMP is confirmed by the data of endomyocardial biopsy that permits to isolate the genome of the virus that caused the disease. The predominating causative agents are enteroviruses, A and B Coxsackie viruses, and also herpes viruses. Neuromuscular diseases running with development of DCMP include progressing Duchenne dystrophy and Becker muscular dystrophy [16].

DCMP debuts with reduction of the contractility of the myocardium, of systolic activity, and with diastolic dysfunction. Symptoms of chronic heart failure first appear in the pulmonary circulation and further on spread to the systemic circulation.

Pathomorphological alterations of DCMP are cardiomegaly and dilatation of the heart chambers (most commonly of ventricles, less commonly in combination with atria). Chambers of the left ventricles are rounded, the walls may be thinned, myocardium becomes flaccid. The heart mass increases by 25-50% and more. The valvular leaflets also become thin. Such alterations of histoarchitectonics are accompanied by reduction of the contractile function of the myocardium with development of cardiac failure. Accumulation of a significant end diastolic volume of blood in the heart chambers leads to congestion and formation of parietal thrombi. The outcome of DCMP is interstitial and/or subendocardial cardiosclerosis [6]. Histological examination reveals unchanged or hypertrophied cardiac myocytes, local myocytolysis with perifocal macrophagal reaction, eosinophilia of cardiac myocytes. Muscle fibers are predominantly arranged in order, the diameter of myofibrils is unchanged, but the nuclei may be hyperchromic like in hypertrophy. Focal disarrangement of myofibrils may present like either alternation of narrow longitudinal and wide transverse bundles, or their interweaving. Morphological equivalent of hypertrophy in the form of amitosis with formation of double-nuclear myofi-

brils is twice as rare than in the norm [6]. Processes of dystrophy and cytolysis may spread to cells of the conducting system and to vascular endothelium that leads to outgrowth of the connective tissue with formation of cardiosclerosis. On the ultrastructural level, alterations of the myofibrils in cardiac myocytes are described (in the form of local destruction or lysis) and of mitochondria [6,20]. There occur either dystrophy of mitochondria, or hyperplasia of the smallest organelles as reflection of energy deficit in the myocardium.

The prognosis is rather poor and depends on the age of the onset of the disease and on the severity of cardiac failure. On the basis of the results of 10-year observation of children of the age from 15 months to 15 years, favorable course was seen in 14% of children mostly of early age, relative clinical stabilization was noted in 21.1%, unfavorable course with lethal outcome – in 64.8% of cases [16]. However, in recent years a tendency to increase in the survival rate of children is noticed owing to a wider introduction of heart transplantation into the practice [21].

#### *Histiocytoid Cardiomyopathy*

This form of CMP belongs to the category of the so called ‘mitochondrial’ myopathies and is a rare form of myocardial diseases. According to classification of American Heart Association, AHA (2006), it is referred to the primary genetically determined CMP. The disease was first described in 1962 by D. Voth under the name of ‘arachnocytois of the cardiac muscle’ [22]. In the literature some synonyms to this CMP may be encountered: infantile, infantile xanthomatous, oncocytic, focal fatty CMP, isolated cardiac lipidosis, multifocal cardiac tumor of Purkinje cells, hamartoma of the myocardium and of the conducting system, foamy transformation of the myocardium. Most researches refer this form of CMP to genetically determined mitochondrial cardiomyopathies. A high incidence rate of this form of cardiomyopathy among representatives of the Caucasoid race (up to



80%) with predomination of the disease in girls (3:1) is an evidence of genetic determination of HcCMP and of X-linked transmission with localization of the gene in Xp22 segment [23]. Active search for determinant genes and mutations inducing the development of HcCMP resulted in identification of a genetic constituent of the defect of the mitochondrial transport of electrons in the given form of cardiomyopathy, in particular, mutation in G15498A gene of mitochondrial DNA coding for mitochondrial cytochrome B. An assumption is made about direct and mediated influence of gene mutations on activation of apoptosis of cardiac myocytes, development of hypertrophy and cardiofibrosis in the given disease through the system of coded proteins IL-33/st2/p38-MAPK/S100A8-S100A9. The role of gestation age in the development of HcCMP is emphasized. Gestation age 5-6 weeks is indicated as the stage of anlage of the sinus and atrioventricular nodes and of differentiation of embryonic Purkinje fibers into cells of the conducting system [24]. The authors emphasize the provoking role of prophylactic vaccination and of viral infections in exacerbation and worsening of the course of the disease [25].

Manifestations of the disease are in a sense polymorphic. This form of CMP may manifest by the syndrome of sudden death, but most common clinical manifestations are disorders in cardiac rhythm in the form of ventricular and supraventricular tachyarrhythmias refractory to antiarrhythmic treatment, with probable development of fibrillation of ventricles [26]. Often this form of CMP is manifested by appearance of symptoms of cardiac insufficiency among full health and in 19-22% of cases the disease starts with the syndrome of sudden infantile death [27]. In 16% of observations histiocytic CMP combines with defects of the interventricular and interatrial septa, with myocardial fibroelastosis and hyperplasia of the left chambers of the heart. In 17% of cases extracardiac pathology is reported: microphthalmia, cataract,

aphakia, hydrocephaly, agenesis of the *corpus callosum* [23]. In 7 observations heterotopias of extracardiac histiocyte-like cells in exocrine and endocrine glands (adrenals, thyroid, adenohypophysis, trachea and salivary glands) were described.

Macroscopically, in 95% of cases the given form of CMP is associated with cardiomegaly, dilatation and enhanced trabecularity of the LV. Subendocardially, rounded yellowish-white or yellowish-brown micronodules are detected in the papillary muscles of the LV, on the leaflets of the atrioventricular valves and in both atria. Often the structure of the nodules is presented by hamartoma-like proliferation of polygonal foamy and granulated cells. Localization of these structures inside the conducting system of the heart is a prognostically unfavorable factor. In this variant of CMP, pathological alterations also develop in the valvular apparatus. Here, additional chordal fibers of atrioventricular valves are detected, dysplasia of the tricuspid valve, fibrohyalinosis of tricuspid and mitral valves and focal endomyocardial fibrosis.

A characteristic ultrastructural peculiarity of cardiac myocytes in HcCMP is the existence of a considerable amount of abnormal deformed and enlarged mitochondria with disorganized cristae containing dense inclusions and low content of cytochrome B. In electronic microscopy, enlarged hypertrophied cardiac myocytes with a small amount of myofibrils are seen [28].

Immunohistochemical identification of actin, desmin and myoglobin in histiocytoid cells evidences their muscular origin. In their cytoplasm glycogen granules, lipids and a significant amount of scattered pigment are determined. Moderate focal accumulations of histiocytoid cells combine with foci of fibrosis in the myocardium [28,29]. Cells of this type were proved to possess arrhythmogenic potential. For this reason elimination of nodular aggregations of these cells may lead to disappearance of arrhythmias. Clinicians note that without treatment HcCMP

ends in death within the first two years of life. However, in the literature a case of 7-year catamnesis in a patient with HcCMP was reported. To note, in case of diffuse spread of pathological alterations with involvement of significant areas of the heart into the pathological process, the surgical intervention often appears to be useless.

### ***Non-Compact Cardiomyopathy***

This anomaly of the structure of the heart is characterized by the bilayer structure of the myocardium – the internal non-compact, or trabecular, layer and the underlying compact layer. In the literature the following synonyms can be encountered: LV non-compactness (LVNC), persisting spongy myocardium, fetal myocardium.

Non-compact myocardium was first described by S. Bellet in 1932. The spongy structure of the myocardium was diagnosed by him in autopsy of a newborn with aortic atresia and coronary-ventricular fistula. In 1984, R. Engderding and F. Bender diagnosed non-compact myocardium in an adult using two-dimensional echocardiography [30]. Since 1995, according to the WHO classification, LVNC has been referred to the group of unclassified CMP. The true prevalence of the disease is unknown, given that diagnostic criteria are not standardized. According to C. Lilje, et al. [31], the prevalence of the disease in the children's population is 1.26%, and according to Swiss researchers – 0.014% [32]. The share of this pathology reaches 9.2% of all diagnosed cases of CMP, ranking third after hypertrophic and dilated CMP [33]. Along with an isolated form of LVNC, it may combine with congenital heart diseases or neuromuscular diseases. Among congenital heart defects, the most common are defects of the interatrial and interventricular septum, congenital stenosis of the pulmonary artery, less often – Ebstein's anomaly, and congenital aortic valve defects [31]. The mechanisms of LVNC are still not studied. Both sporadic and familial cases of the disease with different types of inheritance are known: autosomal

dominant, autosomal recessive, and sex-linked [34]. Autosomal dominant inheritance is more common than X-linked inheritance. Among children, familial forms of non-compact CMP are observed in 50% of cases [35]. There are more than 60 known genes, mutations in which lead to the development of LVNC. Up to 20% of familial cases of non-compact myocardium are caused by mutations in genes coding for sarcomere proteins. X-linked transmission of this pathology is most often associated with Bart's syndrome, a multi-system disease caused by mutations in G 4.5 gene (TAZ). In addition, in individuals with non-compact CMP, mutations in the mitochondria, cytoskeleton, Z-line, and chromosomal abnormalities are reported [36]. The pathogenetic basis for the formation of LVNC is the concept of imperfect embryogenesis. Normally, between the 5th and 8th weeks of embryogenesis, the spongy layer is compacted and a compact layer is formed in the direction from the epicardium to the endocardium. The intertrabecular spaces are reduced to the size of capillaries. The volume of non-compact spongy myocardium within the ventricles is determined by the time of frustration of embryonic morphogenesis. The trabecular layer is compacted more actively in the LV, and the right ventricular myocardium normally has a more spongy structure. However, there is a hypothesis, confirmed by a number of studies, that implies formation of a non-compact layer of the myocardium during life. So, increased trabecularity in young athletes may be a consequence of myocardial remodeling. Hypertrabecularity of LV can also be observed in pregnant women as a response to increased load [37]. Abnormal structure of non-compact myocardium of LV forms the structural basis for its dysfunction and leads to progressive heart failure. The disease may manifest both in the neonatal period and later in life. Clinical manifestations of LVNC are reduced to arrhythmias (ventricular and supraventricular arrhythmias), decreased LV function, and systemic thromboembolism.

Here, in children, cyanosis of skin, negative dynamics of body weight and dysmorphic signs are additionally noted. Diagnosis is based on the results of EchoCG, magnetic resonance imaging, and LV angiography. The course of the disease may vary from asymptomatic to rapidly progressing heart failure. Thromboembolic complications are common, which is associated with congestion of blood in deep intertrabecular spaces. The myocardium is macroscopically spongy with numerous trabeculae and intertrabecular depressions lined with endothelium that continue to the endocardium. In trabeculae, the capillary network is represented by sinusoids arranged into a single system. Often, excessive formation of connective tissue and fibrous structures in the endocardium is observed, histologically resembling fibroelastosis. The prognosis of the disease depends on the volume of the affected areas, the contractile function of the myocardium, the time of occurrence and the rapidity of buildup of symptoms of heart failure. In the works of different authors, the predictive value of the main signs is ambiguous. For example, in the work of S. Brescia, et al. [38], an unfavorable prognostic factor was the manifestation of the disease in the

first year of life. At the same time, in the works of other researchers [39], the age of manifestation did not correlate with the outcome of the disease. According to C. Lilje, et al., mortality from LVNC in children's population for one year of observation was 17.1% [31]. One of the realistic ways to reduce this parameter, as well as to reduce the risk of thromboembolic complications and manifestations of heart failure in this heart disease, is early diagnosis and timely treatment.

### Conclusion

Summarizing the above, it should be emphasized that the given forms of cardiomyopathies are encountered more often than diagnosed, since they often run under the mask of other diseases. This pathology remains to be relatively unknown to a wide range of clinicians despite a considerable amount of works in this direction. Etiology and pathogenesis of cardiomyopathies require further study, as well as development of basics of personified approaches to treatment of this pathology of the cardiovascular system. Here, a priority direction remains to be early diagnosis and treatment of these diseases. Such patients require a more thorough observation and special attention and approach.

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#### Дополнительная информация [Additional Info]

**Источник финансирования.** Бюджет ФГБУ Ивановский НИИ материнства и детства им. В.Н. Городкова Минздрава России. [Financing of study. Budget of V.N. Gorodkov Ivanovo Research Institute of Maternity and Childhood.]

**Конфликт интересов.** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, о которых необходимо сообщить, в связи с публикацией данной статьи. [Conflict of interests. The authors declare no actual and potential conflict of interests which should be stated in connection with publication of the article.]

**Участие авторов.** Сарыева О.П. – сбор, перевод и анализ материала, написание текста, концепция литературного обзора, Кулида Л.В. – написание текста, редактирование, Проценко Е.В. – редактирование. [Participation of authors. O.P. Saryeva – collection, translation and analysis of material, concept of the review, writing the text, L.V. Kulida – writing the text, editing, E.V. Protsenko – editing.]

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**Цитировать** Сарыева О.П., Кулида Л.В., Проценко Е.В., Малышева М.В. Кардиомиопатии у детей – клинические, генетические и морфологические аспекты // Российский медико-биологический вестник имени академика И.П. Павлова. 2020. Т. 28, №1. С. 99-110. doi:10.23888/PAVLOVJ202028199-110

**To cite this article:** Saryeva OP, Kulida LV, Protsenko EV, Malysheva MV. Cardiomyopathy in children – clinical, genetic and morphological aspects. *I.P. Pavlov Russian Medical Biological Herald.* 2020;28(1):99-110. doi:10.23888/PAVLOVJ202028199-110

**Поступила/Received:** 10.07.2019  
**Принята в печать/Accepted:** 31.03.2020