YEVROSIYO PEDIATRIYA AXBOROTNOMASI/ЕВРАЗИЙСКИЙ ВЕСТНИК ПЕДИАТРИИ

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Адрес редакции: 100140

Республика Узбекистан г. Ташкент ул Богишамол , 223 тел: +99871 - 260-28-57; факс: +998971 - 262 - 33-14; www: tashpmi.uz/ru/science/journal pediatry

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RISK FACTORS FOR THE DEVELOPMENT OF CARDIOMYOPATHIES IN CHILDREN

Dilorom Ilhamovna Akhmedova, Dilfuza Mirzabaevna Ruzmatova.

Republican Specialized Scientific-practical medical center of Pediatrics, Ministry of Health of the Republic of Uzbekistan, Tashkent pediatric medical institute, Tashkent city. Uzbekistan

1.ABSTRACT: Cardiomyopathies are the most severe diseases in children, they are characterized by cardiac arrhythmias, thromboembolic complications and a frequent fatal outcome in the form of sudden cardiac death. The study aimed to identify risk factors for developing cardiomyopathies (CMP) in children. Materials and methods: 85 children under 18 years of age with cardiomyopathy were examined, of which 60 children had dilated cardiomyopathy (DCMP), 16 children had hypertrophic cardiomyopathy (HCMP) and 9 children had restrictive cardiomyopathy (RCMP). All children were hospitalized in the cardio-rheumatological department of the Republican Specialized Scientific-Practical Medical Center of Pediatrics of the Ministry of Health of the Republic of Uzbekistan. The control group consisted of 30 healthy children. Research results on biomedical factors showed that the disease is associated with sex: DCMP is more common in boys (63.3±6.2%), while HCMP and RCMP are more common in girls (75.0±10.8% and 77.7±13.8%, respectively). Preeclampsia (33.3%), miscarriages in previous pregnancies (20.0%), stillbirths in previous pregnancies (16.6%), and polyuria (16.6%) were the most unfavorable maternal factors of pregnancy. Thus, among the factors influencing the development of the disease are environmental, biomedical factors, unfavorable maternal factors during pregnancy, and past diseases.

KEYWORDS: risk factors, children, cardiomyopathy, dilated cardiomyopathy.

1.1.INTRODUCTION: Currently, many factors have been identified that affect human health, they can be positive or negative. Such factors are called determining factors or determinants of health. According to the latest World Health Organization (WHO) assessments), policies and laws that affect health and inequality include several areas of regulation, among which the environment and ecology are also noted [53]. Among the factors affecting health, there are medical and biological factors outside the sphere of human influence, for example, age, gender, and genetic predisposition [1,2,5].

In recent years, topical issues in pediatrics are the identification of developmental factors of diseases of the cardiovascular system. According to WHO, «...one of the main causes of death in the world is diseases of the cardiovascular system if current trends continue, the annual number of deaths from cardiovascular diseases will increase from 17.5 million in 2012 to 22.2 million by 2030» [8]. In 1980, WHO experts proposed a classification, according to which MMPs were defined as «myocardial diseases of unknown etiology» and were subdivided into DCMP, HCMP, RCMP, and unclassifiable MMPs [13]. The main principle of division is also structural and functional.

In 1995, experts from WHO and the International Society and Federation of Cardiology recommended using the term «cardiomyopathy» for all cases of myocardial lesions associated with myocardial dysfunction. According to this classification, WHO has distinguished 6 groups of CMDs: 1. Dilated cardiomyopathy (DCMP); 2. Hypertrophic cardiomyopathy (HCMP); 3. Restrictive cardiomyopathy (RCMP); 4. Arrhythmogenic right ventricular dysplasia (ARVD); 5. Specific BMPs and 6. Unclassifiable BMPs. The basic principle of division is unknown/unknown (specific) etiology [14].

In 2008, a new classification of BMPs was published by the American Heart Association (AHA). This classification was based on the etiologic principle with genomic orientation. This classification defines CMPs as «a heterogeneous group of diseases of different etiology accompanied by mechanical and/or electrical myocardial dysfunction» and divided into primary (genetic, mixed, acquired) and secondary CMPs. The main principle of division is primary/secondary [15].

In 2008, the European Society of Cardiology (ESC) proposed a new classification based on morphologic and functional changes in ventricular myocardium, and a new definition of MCC was introduced - «These are myocardial diseases accompanied by a disorder of its structure and function in the absence of coronary pathology, hypertension, heart defects». BMPs were subdivided into DCMP, HCMP, RCMP, ADPJ, noncompact myocardium, and unclassifiable BMPs [13]. The main division principle is familial/nonfamilial, structural-functional [15].

In 2014, the latest global European classification of CMP, called MOGE(S) (abbreviation: morpho-functional phenotype; organs and systems involved; genetic nature; etiology; stage), was proposed, aimed at presenting an exhaustive portrait of a patient with non-coronary myocardial disease (NCMD).

Currently, cardiomyopathy occupies a special place among children with cardiovascular diseases. The most common form of cardiomyopathy is dilated cardiomyopathy (DCMP), which is diagnosed annually at a rate of 0.57 per 100,000 children [9]. DCMP is the 3rd most common cause of heart failure and the 1st most common cause of heart transplant [4]. Risk factors for sudden death include polymorphic ventricular extrasystoles. However, cardiac arrhythmias are not an independent risk factor for sudden death, as they are closely associated with left ventricular dysfunction. In the case of sudden death, a high frequency of ventricular fibrillation was noted, its appearance is facilitated by a sharp disorder of the pumping function of the left ventricle and an increase in pressure in its cavity [3,6,7]. The widespread introduction of highly informative instrumental methods of heart examination, primarily Doppler echocardiography, makes it possible to streamline the concept of cardiomyopathy as a nosological unit [10,11,12]. Based on the foregoing, this scientific study aimed to determine the predisposing factors for the development of cardiomyopathies in children.

1.1.1.MATERIALS AND METHODS: We examined 85 children with cardiomyopathy under the age of 18, of which 60 children had dilated cardiomyopathy (DCMP), 16 children with hypertrophic cardiomyopathy (HCMP) and 9 children with restrictive cardiomyopathy (RCMP) hospitalized in the cardio-rheumatological department of the Republican specialized scientific-practical medical center of pediatrics of the Ministry of Health of the Republic of Uzbekistan. The research was conducted from 2018 through 2020.

The diagnosis was made based on complaints, anamnesis data (obstetric anamnesis of the mother, anamnesis of the life and illness of the child, previous diseases, the nature of the course and duration of the disease), functional (ECG, echocardiography, Holter ECG monitoring), biochemical (determination of cardio specific markers - creatine kinase,

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lactate dehydrogenase) , immunological (cytokines - tumor necrosis factor-alpha (TNF), IL-1, IL-6, IL-8,) and instrumental (chest x-ray, chest multispiral computed tomography) research methods.

At the time of assessment, the child's age, sex, body length/height and body weight were considered. Body surface area (BSA, m2) and body mass index (BMI) were calculated based on body length/height and body weight. PPT was calculated using the Du Bois formula: PPT = M 0.425 x P 0.725 x 71.84 x 10-4, where M is body weight (kg), P is body length/growth (cm); BMI- using the formula: BMI = M/P2 (kg/m2). Growth and development of children were assessed according to the standards of growth and development of children recommended by WHO (2006; 2009).

ECG was performed on patients in a planned manner during each hospitalization in the Department of Cardiorheumatology, both during the initial examination and during re-hospitalization to the department on the ultrasound machine Aplio-500 (Toshiba, Japan) with sector sensors 3.0-6.5 MHz Echocardiography was performed according to standard methods per domestic and foreign guidelines and recommendations. Two-dimensional echocardiography with the determination of echometric parameters was used. The contractility of the left ventricular myocardium was assessed by the ejection fraction (EF) by the Teicholtz or Simpson method and the shortening fraction of the left ventricular myocardium (SF) [6]. Transthoracic echocardiographic research included: seroscale M-modal and two-dimensional studies, color, pulsed-wave Doppler studies of blood flows through mitral, aortic and tricuspid valves; tissue Doppler investigation (TDI) of the velocities of fibrous rings of mitral and tricuspid valves. The following echocardiographic parameters were selected and measured to assess systolic and diastolic function: left ventricular (LV) end-diastolic (ED) and left ventricular (LV) end-systolic (LV) volumes, LV ejection fraction (EF), interventricular septal thickness (tSV).

Determination of biochemical markers. Determination of lactate dehydrogenase, creatine phosphokinase, creatine phosphokinase MB, alanine aminotransferase, aspartate aminotransferase activity was carried out in blood serum by immunoenzyme method on biochemical autoanalyzer of «HUMAN» company (Germany).

Determination of cerebral natriuretic peptide concentration. Determination of brain natriuretic peptide (BNP) in blood serum was carried out by solid-phase chemiluminescent immunoenzyme method using test kits IMMULITE 2000 «NT-proBNP».

Determination of blood electrolytes

Blood electrolytes (potassium, sodium, calcium) were determined by ionic gas method on Nova Medical device.

Standard (MS Excel 2000, Statistica 6.0) and specially developed programs were used for statistical calculations. Pearson correlation analysis was used. Differences were evaluated using Student's t-criterion. The following significance levels were accepted to assess the statistical validity of the obtained results: $p<0.05$; $p<0.01$; $p<0.001$.

1.1.1.1.RESULTS AND DISCUSSION: Medical and biological factors analysis showed that the disease is associated with sex: DCMP is more common in boys (63.3±6.2%), HCMP and RCMP are more common in girls (75.0±10.8% and 77,7±13.8%, respectively). The age of the parents is also important, so in children with HCMP, the age of mothers in 37.5±12.1% of cases at the time of the birth of this child was over 35 years old, in mothers of children with DCMP - in 38.3±6.3%, and mothers of children with RCMP - in 55.5±16.6% of cases, i.e., severe forms of CMP to a greater extent were due to the age of mothers over 35 years (Fig. 1).

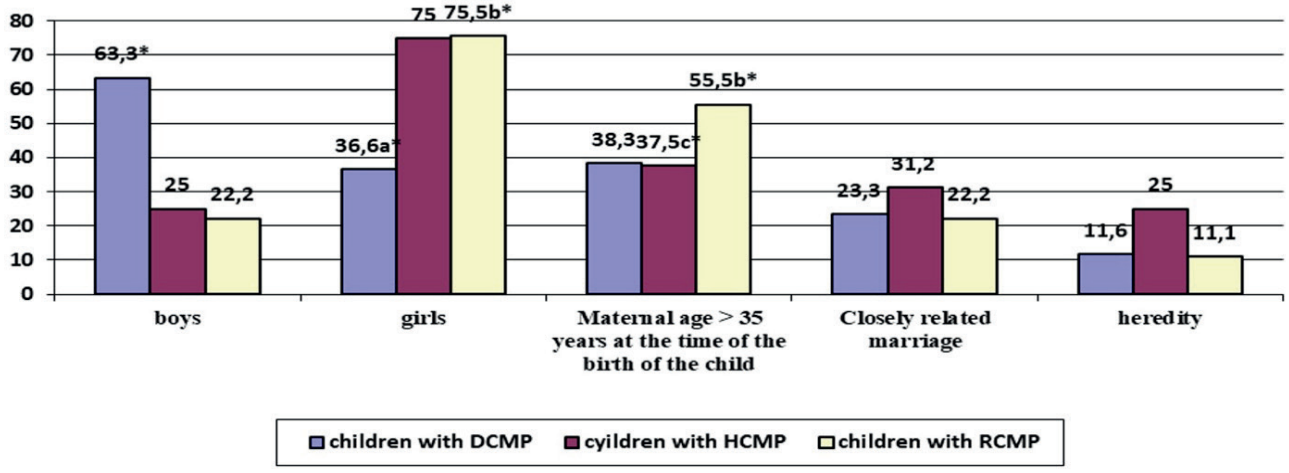

Fig.1 Medical and biological factors in the development of cardiomyopathies in children (%)

Note: a - reliability of differences in indicators between the indicators of children with DCMP and children with HCMP; b-between the indicators of children with DCMP and children with RCMP; c -between the indicators of children with HCMP and RCMP

This pattern is typical regardless of the region of residence of the examined children. The figure shows the reliability of differences in the determinants of health between the regions where children live.

Statistical analysis shows that in the development of cardiomyopathies, the predominant place belongs to diseases associated with lifestyle (%) and the health of future parents (%) and mothers during pregnancy (%).

Studies have shown that one of the medical-biological determinants that significantly impact the development of cardiomyopathy is also the burdened obstetric anamnesis of mothers.

We conducted a comparative analysis of maternal risk factors for developing cardiomyopathies. To assess the prognostic unfavorable anamnestic data, the following were considered: the mother's age, the somatic pathology of the pregnant woman, the presence of infectious diseases during pregnancy, and the nature of the course of pregnancy. The analysis of the state of health of pregnant women was carried out from the standpoint of the concept of perinatal risk.

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As can be seen from Figure 2, in the development of DCMP, the most unfavorable maternal factors during pregnancy were preeclampsia (33.3%), miscarriages in previous pregnancies (20.0%), stillbirths in previous pregnancies (16.6%) and polyhydramnios (16. 6%).

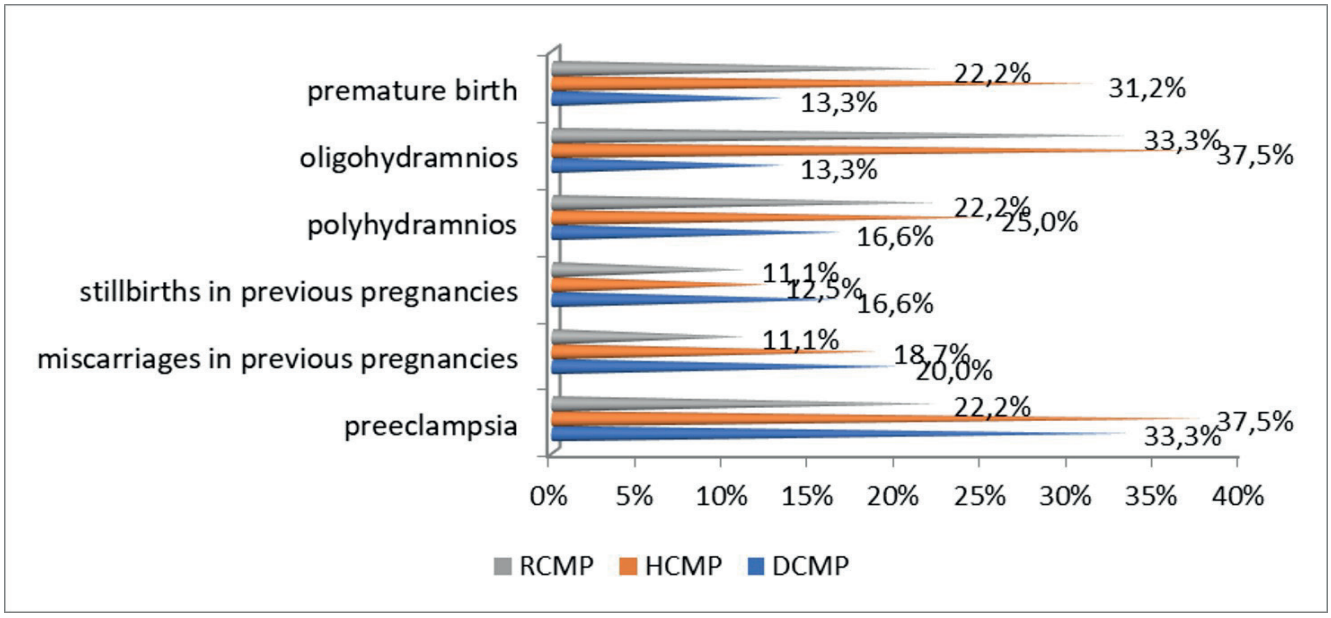

Fig. 2. Obstetric history of mothers of children with cardiomyopathies

In the development of HCMP, the leading factors were preeclampsia (37.5%), oligohydramnios (37.5%), preterm birth (31.2%), polyhydramnios (25.0%), miscarriages in previous pregnancies (18.7%) and stillbirths in previous pregnancies (12.5%). In the obstetric history in children with RCMP, oligohydramnios prevailed (33.3%), preeclampsia, polyhydramnios, preterm labor and stillbirth in previous pregnancies were equally (22.2%) noted; 11.1% had miscarriages in previous pregnancies. As can be seen from these results, the most unfavorable factors in severe forms of CMP are preeclampsia, oligohydramnios, and adverse course and outcomes of previous pregnancies.

Anamnestic data on past diseases and their etiology are important for the diagnosis and early detection of CMP. As can be seen from Table 1, viral infections are significant among past diseases for all forms of CMP, and bacterial infections are also significant for HCMP and RCMP.

Table 1
Past diseases of children with cardiomyopathies

Past illnesses	Children with DCMP (n=60) (%)	Children with HCMP (n=16) (%)	Children with RCMP (n=9) (%)	P	P_1	P_2
Acute respiratory viral infection	76 .7±5 .5	100±0 .0	100±0 .0	<0 .05	<0 .05	>0 .05
Chicken pox	33 .3±6 .1	18 .8±9 .8	22 .2±13 .9	>0 .05	>0 .05	>0 .05
Bronchopneumonia	18 .3±5 .0	37 .5±12 .1	33 .3±15 .7	>0 .05	>0 .05	>0 .05
Acute intestinal infections	10±3 .9	31 .25±11 .6	44 .4±16. 6	<0 .05	<0 .05	>0 .05
Purulent tonsillitis	8 .3±3 .6	25±10 .8	33 .3±15 .7	>0 .05	<0 .05	>0 .05
Pyelonephritis	6 .7±3 .2	18 .75±9 .8	-	<0 .05	-	-
Non-rheumatic myocarditis	10 .0±3 .9	18 .75±9 .8	-	>0 .05	-	-
Sepsis	8 .3±3 .6	12 .5±8 .2	22 .2±13 .9	<0 .05	<0 .05	>0 .05
Epid. mumps	-	12 .5±8 .3	-	-	-	-
Viral hepatitis B	-	-	22 .2±13 .9	-	-	-
Viral hepatitis A	-	-	11 .1±10 .5	-	-	-

Note: P - reliability of differences in indicators between the indicators of children with DCMP and children with HCMP; P1 – between indicators of children with DCMP and children with RCMP; P2 - between the indicators of children with HCMP and RCMP

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The study of indicators of physical development of children with CMP revealed the presence of deviations in indicators of growth. body weight and body mass index relative to age norms. The indicators were evaluated using the WHO Antro and Antro Plus software.

The analysis of the obtained results showed that growth delay was detected among patients with CMP - in 13.9% of children. growth rates relative to age ranged from -3SD to -2SD. corresponding to low growth. Low weight relative to age (indicators ranging from -3SD to -2SD) was determined in 30.2% of children. The most reliable indicator in the harmonious development of children is the body mass index (BMI). According to this indicator, 31.0% of children living in the Republic of Karakalpakstan and the Khorezm region have a risk of protein-energy malnutrition (PEM). 24.1% of children have moderate PEM. and 6.8% of children have severe PEM degree (exhaustion). These figures in the aggregate of children living in other regions amounted to 19.2%. 10.5% and 3.5%, respectively.

The physical development of a growing organism is one of the main indicators of a child's health. The more significant disorders in physical development. the greater the likelihood of disease. In turn, the presence of a chronic pathological process always has a significant impact on the physical development of children. At the same time. according to the laws. physical development depends on some factors of a biomedical and environmental nature. as evidenced by our indicators of the physical development of children. depending on the place of residence.

It is important to note that in children of the Aral Sea region. diseases of the circulatory organs against the background of low physical development were diagnosed 4-6 times more often than in children of Tashkent. At the same time. in every third child. chronic forms of circulatory organ pathology were combined with chronic bronchopulmonary diseases, while this combination was not observed in children in Tashkent. Based on complaints, three main clinical syndromes can be equally distinguished in children with all forms of cardiomyopathy: astheno-vegetative, cardiac, and cardiorespiratory. Among the complaints, the most common were general weakness (93%), shortness of breath (81.4%) . and discomfort or pain in the heart region (23.2%) . the latter was most characteristic of older children.

In the course of this study . a differential diagnostic and correlation analysis of the relationship between the parameters of a biochemical blood test . structural and functional remodeling of the cardiovascular system and the clinical and functional status of children with dilated cardiomyopathy and non-rheumatic myocarditis depending on health determinants was carried out with the calculation of Pearson's correlation coefficients.

Table 2
Correlation relationship between laboratory and functional parameters in children with CMP

Indicators	DCMP			HCMP			RCMP		
	EF <40%	EDS LV	EDV LV	EF >55%	EDS LV	EDV LV	EF >55%	EDS LV	EDV LV
Na+	0 .19	-0 .45	-0 .36	0 .02	0 .14	0 .01	0 .01	0 .15	0 .18
CPK-MB	-0 .46	0 . 38	-0 .42	-0 .06	0 .10	0 .13	-0 .06	0 .13	0 .12
ALT (<40)	-0 .34	0 .25	0 .26	0 .01	0 .00	0 .2	0 .01	0 .00	0 .10
AST (<35)	-0 .35	0 .22	0 .19	0 .00	0 .05	0 .13	0 .00	0 .04	0 .14
De Ritis ratio (AST/ALT)	- 0 .39	-0 .23	-0 .13	-0 .24	-0 .05	-0 .06	-0 .12	-0 .04	-0 .05
NT-pro BNP	-0 .45	0 .42	0 .45	0 .12	-0 .11	-0 .1	0 .12	-0 .12	-0 .1
HR	- 0 .39	- 0 .17	0 .38	- 0 .21	-0 .14	0 .12	- 0 .21	-0 .24	0 .22

An analysis of correlation relationships showed that an increase in the concentration of brain natriuretic peptide (BNP) . reflecting the activity of neurohumoral mechanisms of progression of CHF . is associated with an increase in the diameter of the LV EDS (r = 0.42; p<0.01) . LV EDV (r = 0.40; p<0.01) in children with DCMP. LV EF (r=-0.35; p<0.05) also significantly decreased with increasing BNP concentration. The concentration of BNP significantly negatively correlated with sodium level in the blood . reflecting (r = -0.28) kidney damage typical for patients with CHF. Also . the sodium concentration significantly negatively correlated with the potassium concentration (r = -0.32; p<0.05) . reflecting multidirectional electrolyte imbalance and indirectly confirming the trend towards an increase in potassium concentration . characteristic of CHF. A negative relationship was found between the sodium concentration and such indicators of the structural and functional restructuring of the heart as the LV EDS diameter (r=-0.35; p<0.05) . LV EDV (r=-0.26).

HR positively correlated with LV EDV diameter (r=0 .38; <0.05) and negatively with LV EF (r=-0 .29; p<0.05) . which confirms the proposition that an increase in heart rate is associated with impaired central hemodynamics and a decrease in the effectiveness of systolic contraction.

Structural and functional parameters of the heart showed close relationships between disorders of LV systolic function . increased pressure in the pulmonary artery and dilatation of the heart cavities.

It was found that the frequency of polyhydramnios positively correlated with LV EDS (r=0.42; <0.01) . LV EDV (r=0.32; <0.05) in children with HCMP. This relationship indicates a possible illness (idiopathic) transferred during pregnancy. Also . the frequency of preeclampsia during pregnancy was positively correlated with EF (r=0.41; <0.01) in children with DCMP.
In turn . these indicators are in a strong correlation with such determinants of health as place of residence - an ecologically unfavorable zone of the Aral Sea region (r=0.72; p<0.001) . mother's age over 35 years (r=0.58; p< 0.001) . and in the average correlation relationship with closely related marriage (r=0.44; p<0.01) and heredity (r=0.32; p<0.05).
Table 3 shows the correlation dependence of functional indicators and health determinants. The most reliable echocardiographic parameters of DCMP were selected.

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Table 3
Correlation between health determinants and functional indicators in children with CMP

Indicators	DCMP			HCMP			RCMP		
	EF <40%	EDS LV	EDV LV	EF >55%	EDS LV	EDV LV	EF >55%	EDS LV	EDV LV
Aral region	- 0 .61	0 .72	0 .70	-0 .24	0 .25	0 .36	- 0 .22	0 .12	0 .00
Maternal age > 35 years	-0 .52	0 . 53	0 .62	-0 .16	0 .24	0 .23	-0 .05	0 . 22	0 .62
Closely related marriage	-0 .34	0 .46	0 .42	-0 .19	0 .18	0 .19	-0 .12	0 .05	0 .00
Heredity	-0 .35	0 .34	0 .32	-0 .21	0 .15	0 .17	-0 .05	0 .05	0 .15
Preeclampsia	- 0 .41	0 .36	0 .47	-0 .24	0 .24	0 .15	- 0 .12	0 .12	0 .14
Polyhydramnios	-0 .28	0 .24	0 .27	-0 .18	0 .42	0 .32	-0 .15	0 .01	0 .15

As can be seen from Table 3. . in children with DCMP . strong correlations (p<0.001) of such EchoCG indicators as LV EDS and LV ECV with the indicators of children living in the Aral Sea region were revealed (r = 0.64 and r = 0.72 - respectively) and a strong negative relationship with EF <40% (r = -0.61) . as well as average correlations (p<0.01) with maternal age . closely related marriage and preeclampsia . a weak correlation (p<0.05) with heredity. In children with HCMP . only the LV EDV indicator was significantly associated with the Aral Sea region (r = 0.36; p < 0.01).

Table 4
Correlation between health determinants and laboratory parameters in children with CMP

Indicators	DCMP			HCMP			RCMP		
	EF <40%	EDS LV	EDV LV	EF >55%	EDS LV	EDV LV	EF >55%	EDS LV	EDV LV
Aral region	0 .68	0 .64	0 .22	0 .15	0 .18	0 .36	0 .12	0 .18	0 .12
Maternal age> 35 years	0 .56	0. 53	0 .32	0 .26	0 .24	0 .32	0 .06	0 .12	0 .32
Closely related marriage	0 .44	0. 48	0 .30	0 .24	0 .19	0 .28	0 .12	0 .06	0 .05
Heredity	0 .28	0 .32	0 .27	0 .18	0 .19	0 .27	0 .11	0 .19	0 .07
Preeclampsia	0 .32	0 .36	0 .34	0 .19	-0 .21	0 .32	0 .19	-0 .12	0 .06
Polyhydramnios	0 .25	0. 28	0 .27	0 .18	0 .22	0 .36	0 .18	0 .14	0 .06

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As can be seen from Table 4 . a similar trend of correlations was observed with laboratory indicators. In children with DCMP . strong direct correlations (p<0.001) of such indicators as CFK-MB and NTpro BNP with those of children living in the Aral Sea region (r=0.68 and r=0.64 . respectively) . as well as medium correlations (p<0.01) with maternal age. close marriage and preeclampsia were revealed. Weak correlations of SRO (p<0.05) with preeclampsia.

1.1.1.1.1. Discussion. It was determined that the age of parents is also important . so in children with HCMP the age of mothers in 37 .5±12 .1% of cases at the time of birth of this child was older than 35 years . in mothers of children with DCMP - in 38 .3±6 .3% . and in mothers of children with RCMP - in 55 .5±16 .6% of cases . i.e. . severe forms of CMP to a greater extent were caused by the age of mothers older than 35 years. Preeclampsia (33.3%) . miscarriages in previous pregnancies (20.0%) . stillbirths in previous pregnancies (16.6%) . and polyuria (16.6%) were the most unfavorable maternal factors in the period of pregnancy for the development of DCMP. In children with DCMP . strong direct correlations (p<0.001) of such indicators as CFK-MB and NTpro BNP with those of children living in the Aral Sea region (r=0.68 and r=0.64 . respectively) . as well as medium correlations (p<0.01) with maternal age . close marriage and preeclampsia were revealed. Weak correlations of SRO (p<0.05) with preeclampsia.

1.1.1.1.1.1.Conclusion: Thus . among the factors influencing the disease's development are environmental . medical and biological factors . unfavorable maternal factors during pregnancy . and past diseases. The presence of a chronic pathological process always has a significant impact on the physical development of children. But at the same time . it should be noted that the prescription of the disease also causes growth delay and development in children. In addition to obeying the laws . physical development depends on several factors of a socio-economic . biomedical and environmental nature. Also . the study confirmed the presence of close pathogenetic relationships between indicators of structural and functional remodeling of the heart . endothelial function and the activity of neurohumoral mechanisms of progression of CHF . the severity of which is largely due to health determinants.

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