Complications from the cardiovascular system in children who have had COVID-19

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Abstract. The article discusses the state of the cardiovascular system in children who have had COVID-19, depending on the severity of the course of the infectious process. We conducted a retrospective analysis of the case histories of 88 children of various ages who were hospitalized with a confirmed diagnosis of a new coronavirus infection COVID-19 in September-November 2020.There were 48 boys (54.6%), girls - 40 (45.4%). According to the classification, the examined children were divided into 4 groups: pre-preschool period (1-3 years) - 9 (10.2%), pre-school period (from 3 to 7 years) - 32 (36.4%), junior school period (7-11 years old) - 29 (32.9%) and senior school period (from 12 to 16 years old) - 18 (20.4%) . An analysis of the characteristics of the course of COVID-19 depending on the severity showed that the moderate and severe course of the disease mostly developed in boys (58.5 and 60.0%), the mild course was typical for girls (66.7%).

1 Introduction

In recent years, there has been growing concern about the development of multisystem inflammatory syndrome in children infected with coronavirus infection. It should be noted that coronavirus infection is quite often complicated by acute respiratory distress syndrome (ARDS), it proceeds with severe intoxication and cardiomyopathy, the development of acute heart failure, and disseminated intravascular coagulation (DIC). The mechanism of its development is associated with damage to tissues and organs by cells of the immune system, which leads to the development of a systemic inflammatory response (SIR) [1, 2]. According to the literature, during ARDS, the synthesis of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) is expressed in activated alveolar macrophages, which further stimulate the synthesis of IL-6, IL-8 and monocyte chemotactic factor [3]. This is confirmed by the studies of Ronkati I. et al. (2020), who showed that the development of type III hypersensitivity in patients who underwent COVID-19 lies in the development of systemic vasculitis [4]. In the studies of Sushentseva N.N. (2020) when examining 127 patients with septic lesions on the background of COVID-19 and 54 patients with abdominal sepsis, a sharp increase in the level of cytokines in both examined groups, especially with abdominal sepsis, was shown, at the same time, the content of sCD40L and

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vascular growth factor (VEGF) increased more pronouncedly in patients with coronavirus infection [9]. According to the authors, a critically high level of sCD40L and VEGF in patients with COVID-19 indicates the presence of severe endothelial damage, which is confirmed by the clinical course of the disease. Generalized inflammation of the endothelium coincides with a high percentage of complications from the cardiovascular system (CVS). A US CDC report reported that between February 12 and April 2, 2020, laboratory-confirmed cases of COVID-19 in among persons under 18 years of age were 1.7% [5]. However, since March 2020, against the background of the COVID-19 pandemic in Europe and the United States, there have been reports of outbreaks of a disease that meets the criteria for Kawasaki disease: the development of a pronounced hyperinflammatory response associated with SARS-CoV-2 infection in previously healthy children. They had signs of toxic shock syndrome, myocarditis with cardiogenic shock, called "pediatric multisystem inflammatory syndrome (PMIS)" [6]. Children developed fever (>38.5°C), cardiogenic shock or acute left ventricular (LV) dysfunction, LV ejection fraction <50%), C-reactive protein (CRP) content >100 mg/ml [7]. As given in the article, 17% of children had overweight and 9% had bronchial asthma among concomitant diseases. Clinically: 83% - abdominal pain, vomiting or diarrhea, 68% of patients - symptoms of cardiogenic shock, 34% - respiratory manifestations, 31% - meningeal symptoms (31%), chest pain. The laboratory showed high levels of C-reactive protein (CRP), D-dimer, N-terminal part of the brain natriuretic peptide (BNP) prohormone NT-proBNP, IL-6, which corresponded to the criteria for macrophage activation syndrome and the development of a "cytokine storm". An increase in the level of troponin I and an elevation of the ST segment on the electrocardiogram (ECG), a decrease in LV systolic function and its hypokinesia were detected in 89%, dilatation of the coronary arteries in 17% of patients [8]. More than 80% of patients required inotropic support, 29% needed artificial respiration. Shahbaznejad L, Rouhanizadeh H, Navaeifar MR (2020), analyzing sick children with PMIS with coronavirus infection in an Iranian hospital, concluded that COVID-19 can cause symptoms in children in two stages [9]. In the first week, upper and lower respiratory symptoms may occur, which are of lower severity and prevalence compared to adults. But 2-3 weeks after infection, symptoms of PMIS or multisystemic involvement in COVID-19 may occur and should be considered in patient management. The most common sign for hospitalization is fever, rash, and breathing problems. The pathogenesis and pathoanatomical picture of COVID-19 is characterized by the development of generalized microangiopathy, manifested by the development of destructive-productive viral vasculitis and hypercoagulable syndrome. In the future, secondary lesions of the skin, internal organs, central nervous system and hemophagocytosis develop [7, 10, 11]. In this regard, in May 2020, recommendations were developed for the diagnosis and management of patients with PMIS [6, 7]. According to the authors, therapy depends on the clinical manifestations and severity of the disease. Thus, based on the generalization of clinical data and the results of laboratory and instrumental methods of examining patients, the authors concluded that PMIS is a dangerous systemic infectious disease characterized by extreme inflammation, fever, abdominal symptoms, conjunctivitis, and rash [1]. Symptoms of PMIS appear 3 to 4 weeks after infection with SARS-CoV-2, and many of them rapidly develop shock and cardiorespiratory failure requiring treatment in an intensive care unit (ICU). In the republic, there are few scientific studies on the effect of SARS-CoV-2 on CVS in children who have had COVID-19 of varying severity, they are scattered, which requires a detailed study of CVS in children.

The purpose of the study: to assess the condition of the cardiovascular system in children who had COVID-19, depending on the severity of the course of the infectious process.

2 Material and research methods

We conducted a retrospective analysis of the case histories of 88 children of various ages who were hospitalized with a confirmed diagnosis of a new coronavirus infection COVID-19 in September-November 2020.There were 48 boys (54.6%), girls - 40 (45.4%). According to the classification, the examined children were divided into 4 groups: pre-preschool period (1-3 years) - 9 (10.2%), pre-school period (from 3 to 7 years) - 32 (36.4%), junior school period (7-11 years old) - 29 (32.9%) and senior school period (from 12 to 16 years old) - 18 (20.4%). Depending on the severity of the course, all children were divided into 3 groups: mild - 15 (17.0%), moderate - 53 (60.2%) and severe - 20 (22.7%) children. All patients underwent clinical and anamnestic, functional studies (plain radiography and computed tomography of the chest, electrocardiogram) and laboratory studies. Hematological studies were carried out on a MINDRAY 5000 hematological analyzer (China), general urinalysis on a urinary analyzer, generally accepted biochemical studies of blood serum (activities of ALT and AST enzymes, the content of total bilirubin and its fractions, total protein, glucose, urea, creatinine), as well as special studies (determination of the total activity of LDH, creatine kinase, cardiac MV fraction of creatine kinase) on a biochemical analyzer MINDRAY BA-88A (China) using reagents from CYPRESS Diagnostics (Belgium), as well as determination of the content of interleukin 6 (IL-6) on an enzyme immunoassay analyzer ELIZA (Germany) using reagents of Cytokin JSC (Russia). The digital material was processed by the method of variation statistics.

3 Results and its discussion

Studies have shown that children with mild COVID-19 were treated inpatient and then transferred to outpatient care. Children with moderate and severe forms of COVID-19 received full inpatient treatment, and in our study, patients with a moderate course prevailed - 60.2%, while mild and severe course was noted in 17.1 and 22.7% of children. An analysis of the characteristics of the course of COVID-19 depending on the severity showed that the moderate and severe course of the disease mostly developed in boys (58.5 and 60.0%), the mild course was typical for girls (66.7%) (Table 1). The frequency of concomitant diseases increased, which, apparently, caused a more severe course of the underlying disease.

Table 1. Age-sex and anamnestic distribution of children with COVID-19 depending on the severity of the disease.

Indicators	Severity						Total, n=88	
	Mild, n=15		Moderate, n=53		Severe, n=20			
	n	%	n	%	n	%	n	%
Gender of children								
Male	5	33.3	31	58.5	12	60.0	48	54.5
Female	10	66.7	22	41.5	8	40.0	40	45.5
age								
1-2 years	1	6.7	6	11.3	2	10.0	9	10.2
3-6 years	6	40.0	20	37.7	4	20.0	30	34.1
7-12 years	5	33.3	16	30.2	10	50.0	31	35.2
Over 12 years	3	20.0	11	20.8	4	20.0	18	20.4
Background diseases								

no	5	33.3	6	11.3	6	30.0	17	19.3
one	8	53.3	33	66.3	10	50.0	51	58.0
two	2	13.3	14	26.4	4	20.0	20	22.7
three	0	0.0	0	0.0	0	0.0	0	0.0
Concomitant diseases								
no	12	80.0	40	75.5	12	60.0	64	72.7
one	3	20.0	13	25.5	6	30.0	22	25.0
two	0	0.0	0	0.0	0	0.0	0	0.0
three	0	0.0	0	0.0	2	10.0	2	2.3

An analysis of the clinical manifestations of COVID-19 in children, depending on the severity of the disease, showed the presence of myalgia and arthralgia, the development of pneumonia, coughing and shortness of breath, a complicated course was observed in all children with moderate and severe course (Table 2). However, some differences have also been identified. So, the frequency of lung damage, fever, tachycardia were 1.33; 2 and 1.42 times, violations of sensory systems were detected 5 times more often in children with severe course. Analysis of respiratory rate and heart rate depending on the age norm showed rapid breathing in 12 (60%) children and tachycardia in 16 (80%) children with a severe course of the disease. The severe course of a new infection in children required the appointment of dexamethasone in 90% of children, which is 1.77 times more often than in children with a moderate course of the infectious process. 2 children with a severe course of the disease developed PMIS, which required transfer to the ICU.

Table 2. The frequency of clinical manifestations of COVID-19 in children depending on the severity of the disease.

Indicators	**Severity**						**Total, n=88**	
	Mild, n=15		**Mild-moderate, n=53**		**Severe, n=20**			
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Clinical manifestations								
Pain in the abdomen	3	20.0	15	28.3	6	30.0	24	27.3
Diarrhea/constipation	3	20.0	14	26.4	6	30.0	23	26.1
Irritability	5	33.3	19	35.8	4	20.0	28	31.8
Weakness	9	60.0	23	43.4	4	20.0	36	40.9
Pain in the region of the heart	2	13.3	23	43.4	20	100.0	45	51.1
Pain in joints	6	40.0	39	73.6	18	90.0	63	71.6
sweating	3	20.0	9	17.0	4	20.0	16	18.2
Lack of appetite	7	46.7	15	28.3	0	0.0	22	25.0
Frequent inflammation	2	13.3	5	9.4	4	20.0	11	12.5
Irritability	4	26.6	10	18.9	2	10.0	26	29.5
Headache	2	13.3	17	32.1	8	40.0	27	30.7
dexamethasone therapy	2	13.3	27	50.9	18	90.0	47	53.4

Our data are consistent with the literature, which shows that the moderate course of pneumonia without respiratory failure is approximately 40%, the frequency of severe course is 2.5-7.6%, and extremely severe is less than 1% [7]. According to the results of a systematic review including 1065 patients under the age of 19 years, this infection occurs in children mainly with mild respiratory and general symptoms or asymptomatic [7, 10]. An analysis of the biochemical parameters of children with showed a tendency to increase the activity of aminotransferases, the level of total bilirubin and its fractions, urea, especially in children with severe infections. Such changes in the biochemical parameters of blood serum, apparently, were associated with the activation of catabolic processes as a result of

an infectious-inflammatory process. This is confirmed by the development of leukocytosis in patients with moderate and severe COVID-19 by 1.25 (P<0.05) and 1.41 (P<0.05) times compared to the values of practically healthy children (Table 3). ESR increased statistically significantly at 1.55 (P<0.05); 1.63 (P<0.001) and 1.94 (P<0.001) times, respectively, in groups with mild, moderate and severe inflammation. The most pronounced changes were revealed in the study of the level of IL-6 in the blood serum. So, if in children with a mild course of the inflammatory process, the level of this cytokine only tended to increase, then in children with moderate and, especially, with severe course of COVID-19, its values exceeded those of practically healthy children by 3.02 (P< 0.001) and 14.43 (P<0.001) times, respectively. In 2 children with the development of PMIS, IL-6 values were 87.1 and 97.5 pg/ml, respectively.

Table 3. Indicators of the activity of the inflammatory process in children with COVID-19 depending on the severity, M+m.

Course	Indicators of the infectious and inflammatory process		
	Number of leukocytes, $x10^9$/l	ESR, mm/hour	IL-6, pg/ml
practically healthy, n=20	5.12+0.36	6.15+0.27	4.12+0.027
COVID-19, mild, n=15	5.29+0.28	9.55+0.52 [a]	4.48+0.68
COVID-19, moderate-severy, n=53	6.38+0.19[a]	10.00+0.70 [a]	12.46+0.36 [a]
COVID-19, severy, n=20	7.21+0.54 [a]	11.95+1.69 [a]	59.46+6.96 [a]

Note: a - the differences between the indicators of practically healthy and sick children are significant (P<0.05).

The high indicators of the infectious-inflammatory process that we revealed, in our opinion, are associated with the development of a systemic inflammatory response [2]. This is manifested by increased synthesis of pro-inflammatory cytokines by activated alveolar macrophages [2, 3]. The consequence of this is the development of endotheliitis [11], contributing against the background of hypercoagulation, complications from the cardiovascular system. Considering the literature data, it was of interest to study the biochemical parameters of blood serum, reflecting myocardial damage (Table 4). Studies have shown an increase in creatine kinase activity of 1.42 (P<0.05); 1.66 (P<0.001) and 2.48 (P<0.001) times mild, moderate and severe COVID-19, respectively, relative to the values of apparently healthy children. It should be said that CK reversibly catalyzes the phosphorylation of creatine. Skeletal muscles, cardiac muscle are the richest in CK, less in the brain, thyroid gland, uterus, and lungs. CK isoenzymes have the greatest diagnostic value: CK-MM (muscular), CK-MB (cardiac), CK-BB (brain) [12]. An increase in the activity of CK in the blood serum occurs due to the release of the enzyme from the cells when they are damaged. In recent years, for the differential diagnosis of myocardial infarction from muscle damage, the CK / AST ratio is determined. If cardiomyocytes are damaged, this ratio is less than 10, if this indicator exceeds more than 10, then we can talk about damage to the skeletal muscles. Indeed, the CC/AST ratio was 15.92+1.91; 17.43+0.92 and 23.93+3.50, respectively, for COVID-19 severity, indicating skeletal muscle damage. This is confirmed by the development of myalgia in the children examined by us and literature data on the development of post-Covid musculoskeletal pain [13].

Table 4. Serum enzyme activity in children with COVID-19 depending on severity, M+m.

The course of COVID-19	Serum enzyme levels indicators		
	Creatine kinase, IU/l	**MB-КК, IU/l**	**LDH, IU/l**
practically healthy, n=20	148.25+12.13	9.97+0.58	272.5+17.12
COVID-19, mild, n=15	210.74+13.02[a]	16.07+0.69 [a]	327.07+11.64 [a]
COVID-19, moderate-severy, n=53	246.67+6.85 [a]	27.57+0.99 [a]	490.34+7.32 [a]
COVID-19, severy, n=20	367.08+20.81 [a]	47.90+2.31 [a]	674.75+18.32 [a]

Note: a - the differences between the indicators of practically healthy and sick children are significant.

To confirm the risk of myocarditis in children with COVID-19, we analyzed the activity of the CK MB fraction. Studies have shown an increase in the activity of this isoform in the blood serum of children with COVID-19 by 1.61 ($P<0.05$); 2.76 ($P<0.001$) and 4.80 ($P<0.001$) times, respectively, the severity of the infectious process relative to the values of practically healthy children. According to the literature, an increase in the CK-MB fraction in some cases is possible with myocarditis and myocardial dystrophy [12]. It should be noted that damage to skeletal muscles is accompanied by a significant increase in the activity of the MM fraction, which can "simulate" the MB fraction. Hypoxic muscle lesions are also accompanied by an increase in the activity of CK and CK-MB. Considering that respiratory failure develops due to damage to the lung tissue in COVID-19, it was of interest to study the activity of LDH in the blood serum of infected children, depending on the severity of the course. Studies have shown an increase in total LDH activity by 1.2 ($P<0.05$); 1.8 ($P<0.001$) and 2.48 ($P<0.001$) times, respectively, the severity of the course, relative to the values of practically healthy children. According to the literature, an increase in LDH activity is observed during intense physical exertion, in most patients with acute coronary insufficiency, myocarditis, and chronic heart failure [12]. The source of an increase in LDH activity can be lung tissue in case of embolism, pneumonia, and myopathies. It should be said that violations of the activity of myocardial enzymes in the blood serum are an indicator of a complex process in response to an infectious-inflammatory process, developing hypoxia. In the children with COVID-19 examined by us, X-ray and MSCT showed the development of lung damage of varying severity, the presence of "ground glass", an increase in the cardio-thoracic index of I and II degrees. On the ECG, myocarditis was characterized by combined rhythm and conduction disturbances in the form of sinus tachy- and bradyarrhythmia, complete or incomplete blockade of the left, especially the right bundle branch block, a decrease in the amplitude of the QRS complex teeth, especially in children with severe COVID-19 (Table 5).). On the ECG in children with moderate and severe course of the disease, the most combined rhythm and conduction disturbances in the form of sinus tachy- and bradyarrhythmia were noted.

Among the violations of intraventricular conduction, the most common was complete and incomplete blockade of the right branch of the His bundle, somewhat less often blockade of the left branch of the His bundle. In children with severe COVID-19, there was a decrease in the amplitude of the QRS complex waves, which was more pronounced on standard and enhanced unipolar limb leads, indicating an acute and diffuse nature of myocardial damage, especially in children with PMIS.

Table 5. The frequency of occurrence of ECG changes in children who have had COVID-19 depending on the severity of the course.

Indicators	**Mild course, n=15**		**Moderate-severe course, n=53**		**Severe course, n=20**	
	n	**%**	**n**	**%**	**n**	**%**
Morphology of the ventricular complex						
Depolarization phase: - pathological. Q wave	0	0.0	2	3.8	0	0.0
- low QRS voltage	0	0.0	2	3.8	0	0.0
Repolarization phase: - T wave changes	0	0.0	2	3.8	0	0.0
- ST changes	0	0.0	0	0.0	0	0.0
Conduction disorders of the heart						
Arrhythmia	0	0.0	6	11.3	4	20.0
Sinus tachycardia	4	26.7	11	20.8	4	20.0
Sinus bradycardia	4	26.7	17	32.1	6	30.0
AV blockade	0	0.0	0	0.0	0	0.0
- Left His bundle branch block	0	0.0	0	0.0	6	30.0
-Right His bundle branch block	0	0.0	5	9.4	15	75.0
Extrasystole	0	0.0	0	0.0	0	0.0
Sick sinus syndrome	0	0.0	0	0.0	0	0.0
ventricular hypertrophy						
right ventricle	1	6.7	7	13.2	0	0.0
left ventricle	0	0.0	9	17.0	2	10.0
Both chambers	0	0.0	0	0.0	0	0.0
Exchange disorders	1	6.7	4	7.5	0	0.0

The changes we identified may be associated with a high inflammatory burden, COVID-19 can cause vascular inflammation, since, according to the literature, most patients who have had COVID-19 develop endothelitis, leading to the risk of developing cardiovascular complications [2, 14]. Apparently, this is due to the autoxidation of high concentrations of fibrinogen with the formation of free radicals that damage the vascular endothelium and the subsequent development of endothelial dysfunction. On the other hand, the use of certain drugs can lead to acute myocardial injury and cardiac arrhythmia, therefore, in the publications of Whittaker E et al. (2020) reviewed the main provisions for conducting echocardiography during a pandemic [15]. The pathophysiology of myocardial injury caused by SARS-CoV-2 is still unknown, although several theories have been put forward. The first is associated with direct myocardial injury, similar to those previously documented in COVID patients caused by another coronavirus in 2005, when viral RNA in heart muscle cells was found in 35% of infected subjects [2, 16]. The specific mechanism underlying SARS-CoV-2 replication in cardiomyocytes is still debated, despite appearing similar to other coronaviruses [17]. It has recently been suggested that SARS-CoV-2 can enter myocardial cells simply by binding to ACE-2 receptors on the surface of cardiomyocytes [18]. According to the authors, patients taking ACE-1 inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) have type 2 overexpression and are at high risk of cardiovascular events when infected with SARS-CoV-2. A viral infection can damage heart cells in both the early and late stages of the infection. In the early stages,

this is associated with direct myocardial damage by hyperinflammation and hyperactivation of the immune system, the development of systemic inflammation due to a "cytokine storm" that directly affects the ST interval. In later stages, this may be due to other relevant factors: vasculitis, vascular microthrombosis, widespread intravascular coagulation, hypoxia, electrolyte imbalance, myocardial ischemia, and ACE-2 deficiency disorders. The latter can lead to dysfunction of ion channels in various tissues, including the heart and lungs [19]. Overall, further research is needed to better understand the consequences of pediatric forms of COVID-19, and rigorous follow-up and ongoing monitoring of these children is needed. Based on the data obtained, it can be concluded that the moderate and severe course of COVID-19 is typical for adolescent children. In this contingent of children, there is a pronounced induction of IL-6, activation of catabolic processes, manifested by hypoproteinemia, an increase in the content of urea and creatinine in the blood serum. According to the severity of COVID-19, the activity of total LDH and CK increases in the blood serum, which indicates the presence of hypoxia in the tissues, manifested by severe myalgia. In addition, according to the severity of COVID-19, the CK-MB fraction increases, indicating myocardial damage in the examined children. This is manifested by a violation of the morphology of the ventricular complex, cardiac conduction and overload of the ventricles.

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