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CYTOKINE DIAGNOSTICS IN THE PROGNOSIS OF CRITICAL CONDITIONS IN NEWBORNS BORN TO MOTHERS INFECTED WITH COVID-19

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ABSTRACT

The authors conducted a study of cytokines of newborns born to mothers with coronavirus infection. SARS-CoV-2 infection causes a sharp decrease in the number of lymphocytes, especially a decrease in CD4 T cells, accompanied by uncontrolled release of inflammatory cytokines, which leads to a second stroke and exacerbates pathological changes in the respiratory system. Clinical symptoms vary among the infected population, suggesting that individual immune status is associated with susceptibility to COVID-19 and that immune dysfunction may play a significant role in the development of critical diseases.

KEYWORDS: *COVID-19, SARS-Cov-2, Newborns, Critical Conditions, Coronavirus Disease, Cytokines*

INTRODUCTION

The 2019 coronavirus disease (COVID-19) has spread rapidly around the world. With a sharp increase in the number of infections, the number of pregnant women and children with COVID-19 is also growing [6,23,24].

Since the first reported case of neonatal COVID-19 in February 2020 [20], concerns have been expressed about the possible vertical transmission of SARS-CoV-2 [9,10,12,23].

Early Chinese reports suggested that vertical transmission of SARS-CoV-2 does not occur because amniotic fluid, vaginal mucus, placenta, umbilical cord, umbilical cord blood and neonatal stool samples tested negative for the virus [6,7,11,15,17,19,21,24]. In addition, smears from the nasopharynx of these newborns immediately after delivery were negative. Moreover, there have been no reports of vertical transmission during outbreaks of Severe Acute Respiratory

Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) due to genetically similar coronaviruses [4,16].

In other series of cases, serological testing of seven newborns with limited postpartum exposure (mothers born by caesarean section wore masks, and newborns quickly separated from their mothers) showed the presence of virus-specific antibodies, including three with high IgM levels, despite negative virological testing [9,10]. This may indicate the transplacental passage of SARS-CoV-2, since IgM does not cross the placenta, although IgM assays are difficult to interpret due to frequent false positive results [12]. While postnatal transmission of infection to newborns is most likely, current data are inconclusive regarding intrauterine transmission [5].

It is known that critical conditions of newborns are characterized by organ dysfunction and multiple organ failure, the treatment of which requires urgent aggressive therapeutic measures. Changes in clinical, laboratory and physiological parameters in critical conditions are often considered and interpreted in isolation from each other. Timely adoption of clinical and organizational decisions in the treatment of patients in critical conditions is very important [1-3].

The frequency of critical diseases caused by COVID-19 is about 19%, of which in most cases progress to acute respiratory distress syndrome and respiratory failure, accompanied by acute immune dysfunction. SARS-CoV-2 infection causes a sharp decrease in the number of lymphocytes, especially a decrease in CD4 T cells, accompanied by uncontrolled release of inflammatory cytokines, which leads to a second stroke and exacerbates pathological changes in the respiratory system. Clinical symptoms vary among the infected population, suggesting that individual immune status is associated with susceptibility to COVID-19 and that immune dysfunction may play a significant role in the development of critical diseases. Due to the special immunological status of pregnant women, the inflammatory reaction of the mother to a coronavirus infection can affect the structural and functional development of the fetus and newborn [13,19].

In children, COVID-19 is weak or asymptomatic.12; however, the virus can remain in the body for a long time, and viral nucleic acids can persist in faeces, which suggests the possibility of non-respiratory transmission in children. Immaturity of immunological function in children and newborns leads to their increased susceptibility to viral infections, while immaturity of adaptive immunological development can make their clinical symptoms different from those in adults [8,13].

Together, these aspects raise serious questions about why the clinical manifestations of infected children and newborns differ from those of adults with immunosuppression and what effect the inflammatory response caused by maternal infection has on the immunological function of the fetus [14].

The aim of the study was to study blood and urine cytokines of newborns born to mothers infected with COVID-19 to predict the outcome of critical conditions.

Materials and methods of research:

Under observation were 120 newborns with critical conditions hospitalized in the BODMPMC in the period 2020-2021. A clinical and laboratory examination of 64 newborns was conducted: 33 newborns born to mothers with COVID-19 (group 1), 30 newborns with perinatal CNS lesion

(CNS) (2nd group) and 31 healthy newborns. The exclusion criteria were congenital malformations, prematurity, traumatic lesions of the central nervous system. All newborns underwent conventional clinical and laboratory methods of examination. To determine the molecular markers in the urine, the morning, first portion of urine was collected in special sterile plastic urine collectors with lids. Determination of the content of the main pro- and anti-inflammatory cytokines (IFNy, IL-17A, MCP-1, IFNa, VEGF) in urine and serum (IFNy, IL-17A, MCP-1, IFNa, VEGF) on the 5th day of life was carried out by solid-phase enzyme immunoassay using sets of reagents from Vector-Best (Novosibirsk, RF). The results were expressed in pg/ml. Statistical processing of the obtained results was carried out by methods of variational statistics using the Statistica for Windows application software package. Digital data was processed on an IB MPC personal computer using the memory of Microsoft Exell-97 application programs. The information was considered reliable under the condition that $t \geq 2$ and $P < 0.05$.

Research results and their discussion: To compare the immunological parameters of blood and urine, as well as to determine the dynamics of cytokines and reduce invasive procedures, the study of pro and anti-inflammatory cytokines in blood serum and urine in newborns was carried out. Modern literature says that the immune system in the neonatal period and in the postnatal period is in a state of physiological suppression. The biological meaning of suppressing immune reactions in newborns and in the postnatal period is to prevent the risk of developing severe immunopathological reactions with massive contact of the child with environmental antigens [8]. It has been established that the human immune system is inextricably linked with the interferon system. Interferons-α and -γ affect the activity of natural killers. Also, one of the important properties of interferons is the ability to interfere with intracellular replication of viruses, activating the cell's response to viral infection. Interferon triggers a cascade of biochemical reactions in cells that lead to suppression of the synthesis of viral proteins, as well as to suppression of the assembly and release of viral particles and activation of the process of apoptosis of an infected cell [3,22].

Prognostically unfavorable for the development of infectious and inflammatory diseases of the pulmonary system in premature infants is a decrease in the indicators of alpha and gamma interferons in the blood [4].

As a result of the analysis, it was found that the concentration of INFy increases in newborns of the 1st group to -23.64±0.83 pkg/ml ($p<0.05$), and in the 2nd group to - 29.20±1.28 pkg/ml ($p<0.05$), in relation to the control-20.96±0.66 pkg/ml (Table 1).

At the same time, an increase in the concentration of IFNa was also noted in newborns born to mothers with COVID-19 (group 1) to 33.71±1.22 pkg/ml in relation to the control indicators - 26.49±1.20 pkg/ml ($p<0.05$), and children of group 2 with PPCNS had a statistically insignificant decrease to 24.43±1.36 pkg/ml.

TABLE 1 THE CONTENT OF CYTOKINES IN THE BLOOD OF NEWBORNS

Cytokines pg/ ml	Control groupn=31		1-groupn=33		2-groupn=30	
	min-max	Average	min-max	Average	min-max	Average
IFNγ	14,48-27,35	20,96±0,66	15,27-32,25	23,64±0,83*	17,05-39,63	29,20±1,28*
IFNα	15,83-38,21	26,49±1,20	21,79-47,37	33,71±1,22*	16,92-35,49	24,43±1,36
IL-17A	29,93-64,97	46,99±1,70	55,34-92,06	70,63±1,70*	24,22-56,17	38,74±2,07*
MCP-1	98,29-305,71	196,69±9,92	422,15-1058,15	765,66±33,07*	74,22-166,43	116,47±7,86*
VEGF	19,21-59,93	38,47±2,23	25,17-54,67	40,05±1,49	30,12-54,45	42,15±1,82

Note:-significantly relative to the control (p<0.05)*

Consequently, the obtained results of studying the interferon status of observed newborns on the first 5th day of life show activation of interferon formation in full-term newborns born to mothers with COVID-19.Interleukin-17 belongs to proinflammatory cytokines and is involved in many stages of the immune response. It stimulates the production of chemokines and, as a result, stimulates the migration of neutrophils to the site of inflammation. IL-17 triggers an extensive tissue reaction leading to the migration of neutrophils into the inflammatory zone [7]. IL17A is a dimeric glycoprotein (15 kDa) consisting of 155 amino acids. Its biological function is aimed at ensuring the interaction between innate and acquired immunity [18,36].

The study of IL-17A levels in the serum of observed newborns showed a statistically significant increase in group 1 children to -70.63±1.70 pg/ml ($p<0.05$), and in group 2 a decrease to 38.74±2.07 pg/ml ($p<0.05$) versus control-46.99±1.70 pg/ml. The results obtained indicate the presence of an inflammatory process and activation of the phagocytosis system in the first 5 days of life in full-term newborns born to mothers with COVID-19. And a significant decrease in its level in newborns with PCNS confirms an increase in INFy and the absence of inflammation. Thus, full-term newborns born to mothers with COVID-19 are characterized by an increase in the synthesis of INFy and IFNa against the background of an increase in IL-17A, which confirms the activation of phagocytosis and interferon synthesis in response to viral load for the first time 5 days of life.

It is known that monocytic chemotactic protein (MCP-1) is widely involved in physiological (teething, nociception, angiogenesis, etc.) and pathophysiological processes in the body, participates in the pathogenesis of a number of diseases. MCP-1 is mainly expressed by macrophages in response to the action of a wide range of cytokines, such as IL-6, TNF-a and IL-1b. Due to its targeted cell specificity, it has been postulated that MCP-1 plays a pathogenic role in a variety of different diseases characterized by infiltration of mononuclear cells. Elevated levels of MCP-1 were also detected in connection with bone inflammation, as well as in myocardial ischemia and viral infection [5].

In our studies, when studying the concentration of MCP-1 in the blood serum of observed healthy and sick newborns with critical conditions, a statistically significant increase was found

in group 1 children to -765.66±33.07 pg/ml ($p<0.05$), and in group 2 a decrease to 116.47±7.86pg/ml ($p<0.05$) versus control-196.69±9.92 pg/ml.

Consequently, the established increase in the level of MCP-1 in group 1 newborns confirms the development of inflammation at the endothelial level and indicates the onset of systemic inflammatory response syndrome (SIRS).

Currently, seven different CoV strains have been found to infect humans, including HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1, which usually cause self-resolving symptoms. In addition, coronavirus can cause severe acute respiratory syndrome (SARS), Middle Eastern respiratory syndrome (MERS-CoV) and lethal acute respiratory syndrome, which causes the recently identified SARS-CoV-2. Four types of HCoV, including HCoV-229E (α-CoV), HCoVNL63 (α-CoV), HCoV-OC43 (β-CoV) and HCoV-HKU1 (β-CoV), are endemic to humans and usually cause mild respiratory infection with self-resolving symptoms, which accounts for 15-30% of acute respiratory diseases (ARI). As a rule, this type of infection occurs in young people, but in older age, especially in patients with cardiovascular and bronchopulmonary pathology, it can cause hospitalization, including emergency [30]. Vascular Endothelial Growth Factor (VEGF)-activator of angiogenesis, responsible for restoring oxygen supply to tissues in a situation where blood circulation is insufficient. In physiological concentrations, endothelin (ET) acts on endothelial receptors, causing the release of relaxation factors, in higher concentrations it activates receptors on smooth muscle cells, stimulating persistent vasoconstriction primarily at the level of microcirculation [19]. The constrictor activity of endothelin-1 may be a factor of vasospasm enhancement, closing the vicious circle of pathobiochemical reactions and aggravating cerebral ischemia [9].

In our studies, the study of VEGF concentration showed a tendency to increase, regardless of nosology, to 40.05±1.49 and 42.15±1.82 in relation to control-38.47±2.23 in newborns with critical conditions of the 1st and 2nd groups, respectively (Table 1). The established phenomenon indicates the involvement in the development of CVD during the first 5 days in newborns of the observed group both with coronavirus infection and with PDCNS in the absence of COVID-19.

To reduce invasive manipulations and compare blood serum and urine values in newborns of the observed group, urocytokinodiagnostics was performed.

The studied indicators in urine allowed us to conclude that during the first 5 days of life of full-term newborns with perinatal pathologies, reliable results of urocytokinodiagnostics can be obtained. Thus, in full-term newborns with perinatal pathologies, the concentrations of INFy, IFNa and IL-17A significantly increase in urine both during infection and in the absence of COVID-19 in the mother.The studies revealed a statistically significant 3-fold increase in the level of INFy to 16.84±0.66 pg/ml in children of group 1, and a 2-fold increase (10.21±0.41 pg/ml) in children of group 2, against the control-5.94±0.23 pg/ml ($p<0.05$). This tendency to increase was noted in relation to the level of IFNa in urine: up to 7.60±0.39 pg/ml and 9.49±0.43 pg/ml against the control-5.78±0.23 pg/ml, in newborns of the 1st and 2nd groups, respectively (Table 2).

TABLE 2 THE CONTENT OF CYTOKINES IN THE URINE OF NEWBORNS

Immunologicparametersofurine	Control groupn=31		1-groupn=33		2-groupn=30	
	min-max	Average	min-max	min-max	Average	min-max
IFNγ	4,25-8,75	5,94±0,23	10,08-24,11	16,84±0,66*	6,94-15,42	10,21±0,41*
IFNα	3,68-8,06	5,78±0,23	4,33-11,87	7,60±0,39*	5,48-14,33	9,49±0,43*
IL-17A	20,05-38,48	30,75±0,93	41,15-92,50	65,48±2,30*	23,55-54,67	37,07±1,43*
MCP-1	74,51-130,2	99,25±2,63	16,72-33,10	23,36±0,75*	39,45-71,27	54,75±1,80*
VEGF	18,36-34,97	26,99±0,87	10,26-30,15	19,79±1,02*	14,48-33,05	22,72±0,96*

Note:-significantly relative to the control (p<0.05)*

The study of the concentration of MSR-1 in urine revealed a 4-fold decrease to 23.36±0.75 pg/ml in COVID-19 and a 2-fold decrease to 54.75±1.80 pg/ml in full-term neonates against control-99.25±2.63 pg/ml. And the concentration of VEGF in urine also had a significant tendency to decrease to 19.79±1.02 pg/ml and 22.72±0.96 pg/ml against the control -26.99±0.87 pg/ml, which indicates the absence of an activator for oxygen delivery to tissues and inadequate renal circulation during the first 5 days of life of full-term newborns both in the presence of COVID-19 and in its absence in newborns with PDCNS, respectively.

CONCLUSION

The obtained results of cytokinodiagnostics allowed early diagnosis and prediction of the health status of newborns for the development of critical conditions.

Newborns born from a mother with COVID-19 develop CVD during the first 5 days of life. In critical conditions in newborns with a coronavirus load, an increase in the synthesis of INFy and IFNa was found against the background of an increase in the level of IL-17A, which confirms the activation of phagocytosis and interferon synthesis for the first time 5 days of life.

The established processes are accompanied by an increase in the level of MCP-1 in the blood by 3.89 times, with a decrease in its urine by 4.25 times in newborns born from a mother with COVID-19, which indicates the severity of the course of CVD.Both with COVID-19 infection and with PDCNS in newborns without COVID-19 infection, there is a tendency to increase VEGF in the blood, against the background of a statistically significant decrease in its urine. Consequently, the observed dynamics of cytokines in the blood and urine of newborns with CVD indicates the activation of phagocytosis, interferon formation and inadequate renal circulation during the first 5 days of life.

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