

FEATURES OF LABORATORY AND BIOCHEMICAL CHANGES BASED ON THE STUDY OF THE HISTORY OF THE DISEASE IN CHILDREN TREATED FOR CORONAVIRUS INFECTION

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ABSTARCT

In most children, the disease is mild, but it is not known whether those who have had COVID-19 asymptotically remain healthy or whether they need special rehabilitation. The clinical picture of the new coronavirus infection COVID-19 is characterized by typical signs of acute respiratory viral infections, with a predominant lesion of the upper respiratory tract, a predominance of mild forms of the disease, which in turn complicates differential diagnosis with other acute respiratory viral infections and requires a mandatory laboratory examination confirming the etiological significance of SARS-CoV-2 in each individual case [3,4,5,6].

Zimmermann and N. Curtis [2020] summarized the epidemiological and clinical features of children infected with SARS-CoV-2, including newborns born to women infected with SARS-CoV-2 during pregnancy. The study included 333 infants (data from 11 centers). The incubation period from the time of contact varied from 2 to 25 days [6,8,9]. The virus could be isolated from the nasopharynx for 22 days, and from feces even for 30 days or more after contact with a SARS-CoV-2 carrier. Coinfections were reported in 79% of children. Approximately 35% of infected children had no symptoms of the disease. The most common symptoms were cough (48%; minimum and maximum frequency values for this symptom were: 19–100%), fever (42%; 11–100%) and pharyngitis (30%; 11–100%). Other symptoms were nasal congestion, rhinorrhea, tachypnea, shortness of breath, diarrhea, vomiting, and headaches. Often, children complained of fatigue (asthenization) for no apparent reason. Children were more likely than adults to have symptoms of gastrointestinal tract damage [7,8,10]. Radiographic findings included unilateral or bilateral infiltrative changes, in some cases there were "ground glass" opacities in the interstitial tissue of the lung or a seal with a halo environment. At the same time, children rarely needed to be transferred to an intensive care unit (3%) [6,8,12]. Comar M, Brumat M, Concas MP (2020) Italian authors evaluate RT-PCR tests for SARS-CoV-2 and identify viral ribonucleic acid (RNA). RT-PCR reagents were readily available after the publication of the viral RNA sequence (Corman 2020). Testing was carried out in central laboratories, a laborious process, with several points in the path of performing a single test, where errors may occur, although some automation of parts of the process is possible. Process Amplification requires thermal cycle equipment to provide multiple temperature changes over the course of the cycle, with the cycles repeated up to 40 times until viral DNA is detected. Although the amplification process for RT-PCR can be completed in a relatively short time, the steps of extraction, sample processing, and data management (including reporting) mean that test results are usually only available after 24-48 hours [12,14]. Where testing is carried out in a centralized laboratory, the transport time is further extended. The lead time for fully automated RT-PCR tests is shorter than for manual RT-PCR, however, most assays still require sample preparation steps that make them unsuitable for point-of-care use [15,16]. Other nucleic acid amplification techniques,

including loop isothermal amplifications (LAMPs) or CRISPR-based nucleic acid detection techniques that allow constant temperature amplification, are also being developed. These methods can reduce the time to obtain test results after sample extraction and processing to a few minutes, but the time for the entire process can still be significant. Laboratory molecular tests are most commonly applied to upper and lower respiratory tract samples, although they are also used on fecal and urine samples[2,3].

The journal JAMA published an article by Chinese scientists showing the immunological features of mild and moderate COVID-19 in pediatric patients (Wu H, Zhu H, Yuan C, Yao C.2019) the work was carried out in the Department of Laboratory Medicine, Wuhan Children's Hospital [5,6]. Analysis of clinical and immunological characteristics showed that the number of lymphocytes is closely related to the severity of SARS-CoV-2 infection in adult patients, and in 63-70% of patients with severe disease have lymphopenia and depletion of natural killer cells (NK), while the level of neutrophils, the main player in the so-called cytokine storm, was elevated. Therefore, to support efforts to prevent and control COVID-19 in children, scientists conducted a comprehensive study of the characteristics of 157 patients with laboratory-confirmed SARS-CoV-2 infection upon admission to the hospital and compared the clinical and immune features of mild cases with moderate cases. These findings may help expand our understanding of risk factors associated with the severity of COVID-19 disease in pediatric patients. An analysis of the medical records of 157 pediatric patients admitted to Wuhan Children's Hospital with laboratory-confirmed SARS-CoV-2 infection and a certain clinical outcome (i.e., death or discharge) as of April 18, 2020 is shown [5]. Throat swab and swab samples were collected and tested for SARS-CoV-2 with the recommended kit of the Chinese Center for Disease Control and Prevention. All samples were processed in the laboratory medicine department of Wuhan Children's Hospital. The total RNA was extracted within 2 hours using the Nucleic Acid Isolation Kit (DAAN Gene). Real-time reverse transcription and polymerase chain reaction analysis was performed using a SARS-CoV-2 nucleic acid detection kit according to the manufacturer's protocol (BGI Biotechnology). A cycle threshold in a FAM channel of 38 or less was determined as a positive test result, and a cycle threshold greater than 40 or without a gain curve was determined as a negative test result [6,7,9]. In this study, serum IgG concentrations were significantly reduced in moderate cases compared to mild cases. Notably, Igs, including IgG, IgA, and IgM [11,12,13], were negatively associated with biomarkers associated with liver and myocardial injury in pediatric patients. Antibodies to neuraminidase have been reported to be the main mediators of protection against influenza A virus infection and exhibit broad binding activity spanning the entire history of influenza A virus circulation in humans, including the original pandemic strains of the H1N1 and H3N2 subtypes.²¹ In addition, it was noted that titers and duration of IgG prior to SARS-CoV-2 in pediatric patients showed no significant differences compared to adult patients. These findings suggest that B cells also play an important role in controlling SARS-CoV-2 infection. Further research is needed to determine the effects of B cells in COVID-19 settings.

According to the authors (Kuznik B.I., Sturov V.G.2021), children, unlike adults, are less likely to experience neutrophilia, thrombocytopenia, lymphocytopenia, including a decrease in CD4+, CD8+, Treg cells and memory T-lymphocytes. In children, the content of pro-inflammatory cytokines, including IL-6, moderately increases, without reaching the level of a cytokine storm.

In pediatric patients, there are practically no high levels of D-dimer, indicating the presence of intensive intravascular coagulation. Finally, in children, in most cases, there is no significant increase in CRP, procalcitonin and troponin. In children with a history of obesity, diabetes, heart, kidney or liver failure, etc.), the disease can be very difficult, in some cases leading to death. The same applies to newborns and infants, in which innate immunity plays a significant role in the fight against infection. In children with COVID-19, neutrophils are of primary importance in the early stages of the disease, and Th (CD4+), including Treg (CD4+CD25+), which synthesize suppressive IL-4 and IL-10, which not only prevent the occurrence of a cytokine storm [12,14], but also contribute to the synthesis of antibodies that block the action of the SARS-CoV-2 virus. Of course, the therapy of children with COVID-19 should be prescribed based on the severity and age of the child. Immunomodulatory drugs (INF- γ , tocilizumab, azithromycin, doxycycline, etc.), as well as antiviral drugs (favipiravir, etc.) play a significant role in the fight against severe and extremely severe COVID-19 in children. A complex of polypeptides from the thymus gland - thymalin, which has proven itself in pneumonia and various infectious diseases in both adults and children, and has also been successfully used for the first time for therapy in elderly patients with coronavirus infection, can claim the role of an immunocorrector in children with COVID-19 (Kuznik B.I., Sturov V.G.2021)

W.J. Guan et al. (2020) analyzed laboratory data from 1099 patients with COVID-19 infection. 926 of them had a mild course, 173 had a severe course of the disease. In a comparative analysis of clinical blood test indicators, leukocytosis was found in 4.8% of patients with a mild course of the process and 11.4% of patients with a severe course of the process, leukopenia was observed in 28.1 and 61.1% of cases, respectively. Lymphopenia was characteristic of patients of both groups and was observed in 80.4% and 96.1% of cases, respectively. Thrombocytopenia in mild course of the process was detected in 31.6%, and in severe - in 57.7% of patients. When analyzing biochemical parameters in the blood serum, the authors found that the level of C-reactive protein (CRP) >10 mg / l increased in 56.4% of patients with mild course and 81.5% with severe course of the process. An increase in the level of procalcitonin was detected in 3.7 and 13.7% of patients, respectively, lactate dehydrogenase (LDH) activity in 37.2 and 58.1% of cases, alanine aminotransferase (ALT) in 19.8 and 28.1%, aspartate aminotransferase (AST) in 18.2 and 39.4%, total bilirubin in serum in 9.9 and 13.3%, creatinine in 1.0 and 4.3% of cases, respectively. The content of potassium, sodium and chlorine in both groups was within normal limits, no significant differences were observed between the compared groups [Guan W.J., Ni Z.Y., Hu Y. et al. 2020].

Belarusian authors (Loginova I. A., Ustinovich A. A., Alferovich E. N.2021) analyzed the features of the course of the neonatal period in children from mothers with confirmed COVID-19 infection (PCR RNA of the SARS-CoV-2 coronavirus), detected in them either during pregnancy or in the postpartum period[18]. When examining children, clinical, laboratory, biochemical research methods were used. It was revealed that children whose mothers fell ill with COVID-19 coronavirus infection immediately before childbirth had a burdened neonatal period compared to children from mothers who had been ill in the middle of pregnancy, and the manifestations of intrauterine infection and posthypoxic syndrome were more pronounced.

Laboratory methods of research in newborns from mothers who fell ill on the eve of childbirth testified in favor of acute viral inflammation.

D. Wang et al. (2020) studied in a comparative aspect changes in laboratory parameters in 138 patients with COVID-19 infection during 19 days of hospitalization. Patients were divided into 2 groups (needy and not in need of resuscitation). When analyzing the indicators of a clinical blood test, it was found that in patients who needed resuscitation in the intensive care unit (ICU), the frequency of elevated leukocyte counts was 1.5 times higher, neutrophils – 1.7 times, and a decrease in lymphocytes was also more often detected. The authors also reported that lymphopenia and leukocytosis were observed in all deceased patients (n = 5). Analysis of blood biochemical parameters in patients who needed help in the ICU showed that an increase in LDH activity was observed 2.1 times, ALT – 1.5 times, AST – 1.8 times more often compared to the group that did not need resuscitation. In addition, the authors found that in patients of the 1st group, the concentration of total bilirubin increased by 1.2 times, creatinine by 1.1 times, cardiac troponin by 2.2 times, procalcitonin by 1.2 times more often compared to patients of the 2nd group [Wang D., Hu B., Hu C. et al.]

Y. Liu et al. (2020), examining adults and children with COVID-19, found that lymphopenia was most often detected in a clinical blood test, which, depending on the course of the process, occurred in 75% of cases; there was also an acceleration of ESR (85%) and a decrease in hemoglobin levels (50%). In the biochemical analysis of blood, the frequency of an increase in the level of CRP was observed in 93%, LDH activity in 92%, and a decrease in the concentration of serum albumin in 98% of patients. The index of fibrinolytic activity of blood (D-dimer) increased in 43% of patients. The authors concluded that the severity of the disease can be predicted by the presence and severity of lymphopenia, low albumin values, as well as elevated LDH and CRP values (Liu Y., Yang Y., Zhang C. et al.2020)

The results of clinical observations of patients with COVID-19 demonstrate a mild or asymptomatic course of SARS-CoV-2 infection in the majority of children.

Thus, the analysis of literature data allows us to conclude that in patients with COVID-19, changes in the indicators of clinical and biochemical blood tests, as well as hemostasis and fibrinolysis systems, have their own characteristics and are closely interrelated with the nature of the course of infection. The most pronounced changes are detected in the severe course of the process. When assessing the indicators of a clinical blood test, first of all, it is necessary to pay attention to the number of leukocytes, lymphocytes, platelets and ESR, since leukopenia, lymphopenia and thrombocytopenia are most often observed in patients of this category. Among the biochemical parameters of blood in COVID-19, an increase in the level of CRP and ferritin, as well as a decrease in albumin levels, are more often detected. The content of procalcitonin at the onset of the disease is uninformative, but with the progression of the disease (due to the addition of a bacterial infection), its value increases significantly.

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