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Clinical Features and Functional State of the Adrenal Cortex and Thyroid Gland in Children with Covid-19 during the Recovery Period

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The available literature provides limited data on the demographic and clinical features of SARS-CoV-2 infection in children. This information is especially important because pneumonia is the single leading cause of death in children worldwide. Research in this direction is particularly important to clarify and better understand the global impact of COVID-19 on the pediatric population. Unlike adults, most infected children have a milder course and have better results overall. This article also provides an analysis of the violation of the functional state of the adrenal cortex and thyroid gland in children, features of laboratory and biochemical changes based on a study of the history of the disease in children receiving treatment for coronavirus infection. At the

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same time, the level of thyroid-stimulating hormone, total T3, total T4 and cortisol in children who had a coronavirus infection was assessed. The last stage demonstrates the prevention and rehabilitation of children after coronavirus infection.

Keywords: COVID-19 in children; adrenal cortex; thyroid gland; prevention; rehabilitation.

1. INTRODUCTION

1.1 Features of the Clinical Course of Covid-19 in Children

“The acute respiratory syndrome in coronavirus (SARS-CoV-2) pandemic has spread rapidly throughout the world. In contrast to initial reports, recent studies show that children are as likely to become infected with the virus as adults, but have fewer symptoms and less severe diseases” [1-3]. “Experimental studies of SARS-CoV infections indicate that both CD4 and CD8 T cells, as well as antibodies, play an important role in viral clearance. Children have a stronger innate immune response, a higher proportion of total lymphocytes and absolute numbers of T and B cells, as well as natural killer cells, which can help fight the virus” [4]. “However, children are often described as having an "immature" immune system, and for infections with other respiratory tract viruses, such as respiratory syncytial virus or influenza, infants and children are at higher risk of serious illness and hospitalization. This suggests that protective immunity against SARS-CoV-2 is different from immunity against other common respiratory viruses” [5].

“In observing patients with Covid 19, scientists have found that children suffer less from coronavirus disease (COVID-19) than adults; most pediatric cases of SARS CoV-2 are asymptomatic or cause only mild symptoms” [6-8]. “However, a limited number of reports describe severe multisystem inflammatory syndrome in children (MIS-C) developing 1–2 months after acute SARS-CoV-2 infection” [9–12].

According to Moscow authors (Rusinova D.S. et al. 2021), there are currently more than 5 million cases and more than 328 thousand (6.6%) deaths recorded in the world (the mortality rate in the Russian Federation is 0.98%) [13-15]. At the same time, both among the cases and in the analysis of deaths, pediatric patients are rarely mentioned. In European countries, the incidence in the pediatric population is also low. According to observation results, in Switzerland the incidence of children under 10 years of age is 0.4%, among patients 10-19 years old - 2.6% of all those observed with COVID-19. Sweden provided data on 0.5% of children under 10 years of age among the cases and 1.3% among those aged 10-19 years. In Spain, patients under 18 years of age accounted for 0.8% of all cases [16]. The new coronavirus infection COVID-19 in children occurs in a mild form, without complications, under the “mask” of a common viral infection. Up to 11% of children examined by contact had no symptoms at all; they came into the orbit of attention because of sick relatives [17]. According to US data published on April 2, 2020, of the 2572 children under 18 years of age who became ill with COVID-19, 1.7% were children, of whom about 2% required transfer to the intensive care unit [Feldstein LR, Rose EB, Horwitz SM 2021]. This may indicate that if the examination of children were carried out on the same wide front as adults, there could be significantly more identified asymptomatic children. The clinical picture in children is dominated by catarrhal symptoms and a short-term increase in body temperature [18]. Smell impairment, according to observational data, has been registered in children over 10 years of age in 50% of cases. The use of inflammatory markers, traditional for predicting severe disease and justifying the prescription of antibacterial therapy, is ineffective in the case of COVID-19. The course of infection and the development of the clinical picture of COVID-19 disease probably depends on the premorbid background, the presence of concomitant pathology, coinfections, the nature of the immune response and the age of the patient. Possible other factors determining the development trajectory of the pathological process remain to be clarified [19-20]. Thus, the clinical picture of the disease in children, as well as in adults, is dominated by fever and respiratory syndrome. At the same time, the experience of different countries during the 2020 pandemic shows that children, compared to adults, have a smoother course of the disease, damage to the lower respiratory tract in the form of viral pneumonia is less common, symptoms are usually not severe, and deaths are extremely rare. However, it is children of any age who should be the focus of special attention, as they play a huge role in the spread of the disease.

"Scientists have proven that SARS-CoV-2 is detected in only a third (32.9%) of hospitalized patients with respiratory symptoms, in 4.3% of cases - in combination with seasonal CoV-OC43/CoV-229E, in 11.6% - with other respiratory viruses. The source of SARS-Cov-2 infection was more often family members. Among the patients, children with a moderate form of the disease predominated" [21-25]. "The leading symptoms of COVID-19 were fever, catarrhal symptoms, as well as gastrointestinal manifestations and anosmia. A feature of the new coronavirus infection in newborns and children in the first month of life was the absence of fever and intoxication, the lack of severity of catarrhal manifestations when the colon was involved in the pathological process (colitis, rarely - hemocolitis). In the hemogram of children under one year of age, monocytosis predominated, in children over 7 years of age - leukopenia and accelerated ESR. Among the changes in the biochemical blood test, the most common was an increase in C-reactive protein" [16].

1.2 Disorders of the Functional State of the Adrenal Cortex and Thyroid Gland in Children

Assessing hormonal status in the early neonatal period is a complex task, since hormone levels are subject to significant fluctuations depending on the gestational and postnatal age of the newborn, the method of delivery and anesthesia in the mother, birth weight and many other factors. To date, data on the early hormonal response in preterm infants are sparse and often contradictory [12,26].

Congenital adrenal dysfunction (CAD) is a group of inherited autosomal recessive diseases in which, due to mutations in the genes encoding steroidogenesis enzymes in the adrenal cortex, there is a shift in the production of the main steroid hormones from corticosteroids to androgens. The result of these defects is the absence or varying degrees of reduction in the synthesis of cortisol from its precursor, cholesterol. Due to the lack of circulating cortisol, the anterior lobe of the pituitary gland (according to the feedback principle) secretes increased amounts of CAD, under the influence of which adrenal hyperplasia develops [27]. The severity of the disease depends on the location of the gene damage, which determines the degree of loss of 21-hydroxylase activity. Enzyme deficiency leads to a deficiency of the two main end products of steroidogenesis (cortisol and aldosterone) and an excess of precursors that accumulate before the defective enzyme reaction, i.e., at the stage of conversion of 17-hydroxyprogesterone to 11-deoxycortisol and progesterone to 11-deoxycorticosterone. 17-Hydroxyprogesterone can be converted to testosterone and other corticosteroids through alternative biosynthetic pathways in the adrenal cortex and other tissues. That is why such patients may experience an incomplete absence of certain steroids in the blood. For example, in patients with severe 21-hydroxylase deficiency, near-normal levels of 21-hydroxylated steroids were found, which was the result of 21-hydroxylation of precursors outside the adrenal gland [28]. Recent studies have shown that a number of endocrine organs can become targets for coronavirus, namely the pancreas, thyroid gland, testes, ovaries, adrenal glands and pituitary gland, since their epithelium expresses angiotensin converted enzyme 2 (ACE 2) [29]. "ACE2 is expressed in the pancreas, with higher mRNA levels in the pancreas than in the lung. ACE2 expression is observed in both exocrine pancreatic cells and endocrine islet cells. Damage to the exocrine pancreas is manifested by increased levels of serum amylase and/or lipase in 1-2 and 17% of patients with mild and severe disease, respectively. Immunohistochemistry and in situ hybridization identified SARS-CoV in the pancreas of patients who died from SARS" [30]. "Although any serious illness may be associated with stress-related hyperglycemia, Yang et al. previously described that patients with SARS (caused by SARS-CoV, a "cousin" of SARS-CoV-2) who had never received glucocorticoids had significantly higher fasting plasma glucose levels compared with patients with pneumonia without SARS. In addition to direct damage to ß cells, changes in autoantigens and subsequent immune-mediated destruction of ß cells may be involved. In addition, infection of the surrounding exocrine pancreas by SARS-CoV and SARS-CoV-2 can cause random ß-cell death by releasing mediators such as tumor necrosis factor-a (TNFa) and interferon-γ. A systemic proinflammatory response, as evidenced by high amounts of interleukin-γ, monocyte chemoattractant protein-1 (MCP-1), and inducible protein-10 even in patients with mild COVID-19, may play an additional role in accentuating this process" [31-33].

"One of the main immunoinvasive strategies used by SARS-CoV, like the influenza virus, is to

suppress the body's stress response to cortisol. A very interesting hypothesis that has been proposed is the expression of certain amino acid sequences of SARS-CoV, which are molecular mimics of the host adrenocorticotropic hormone (ACTH). This form of molecular mimicry may actually blunt the stress-induced increase in cortisol levels, as antibodies produced against viral particles inadvertently destroy circulating ACTH" [34].

"The data published so far do not take into account the possibility of direct aggression of this virus against the adrenal glands in previously healthy people" [35]. "In the examined autopsies of people who died from severe forms of infection with signs of acute adrenal insufficiency, hemorrhages in the adrenal glands were often detected, and in one case we discovered lymphocytic adrenalitis. Viral, bacterial and fungal sepsis can cause bleeding, necrosis or thrombosis of the adrenal vessels with subsequent acute hypoadrenalism. In addition, recent data indicate the possibility of venous thromboembolism in COVID-19 patients and its beneficial treatment with heparin in some of them. Therefore, it should be taken into account that acute adrenal insufficiency can also be caused by a thrombotic event at the level of the adrenal glands" [29]. "Data on damage to the thyroid gland by coronavirus are extremely scarce. A study conducted during the 2003 SARS outbreak found that serum T3 and T4 levels were lower in SARS patients compared to controls in both the acute and convalescent phases. An autopsy study of five patients with SARS showed severe destruction of follicular and parafollicular cells of the thyroid gland" [36]. "Follicular cell destruction will manifest as low T3 and T4 levels; damage to parafollicular cells would theoretically lead to low serum calcitonin levels, which may be a likely mechanism for osteonecrosis of the femoral head observed in recovered SARS patients; calcitonin deficiency leads to disinhibition of osteoclasts, leading to osteonecrosis" [37].

"Data on thyroid function or thyroid pathology in COVID-19 are not yet available. It is well known that a number of viruses can cause subacute thyroiditis (de Quervain's thyroiditis), and clusters of this disease have been reported during outbreaks of viral infection. De Quervain's thyroiditis is thought to be of viral origin, with possible pathogens including mumps virus, cytomegalovirus, enterovirus, and coxsackie virus" [38]. "Clinically, this condition is characterized by thyrotoxicosis with severe pain in the anterior neck. The possibility of localization of SARS-CoV-2 in the thyroid gland cannot be excluded, given that previous studies have shown the presence of some virus-like particles in the follicular epithelium of patients with subacute thyroiditis. In addition, the thyroid gland is closely adjacent to the structures of the upper respiratory tract, which are primarily affected by this virus. Thyrotoxicosis can worsen the condition of the cardiovascular system, leading in some cases to tachyarrhythmia. In one of the autopsy observations, de Quervain's thyroiditis was observed, with a pronounced predominance of lymphoid elements in the inflammatory infiltrate. It is now known that some COVID-19 patients suffer from ear pain (which may be a symptom of subacute thyroiditis) and one of the most common cardiovascular complications in these patients is tachyarrhythmia. Thus, timely assessment of free thyroid hormones will allow for early diagnosis and appropriate therapy, and will also help avoid more severe complications. Given that subacute thyroiditis often occurs several weeks after a viral upper respiratory tract infection, it should be assumed that it may be a late complication of SARS-CoV-2 infection" [39].

1.3 Features of Laboratory and Biochemical Changes based on the Study of the Disease History in Children Treated for Coronavirus Infection

"In most children, the disease is mild, but it is not known whether those who have suffered from COVID-19 asymptomatically remain healthy or whether they require special rehabilitation. The clinical picture of the new coronavirus infection COVID-19 is characterized by typical signs of acute respiratory viral infections, with predominant damage to the upper respiratory tract, a predominance of mild forms of the disease, which in turn complicates the differential diagnosis with other acute respiratory viral infections and requires mandatory laboratory examination to confirm the etiological significance of SARS-CoV-2 in each individual case". [40]

Zimmermann and N. Curtis [2020] summarized "the epidemiological and clinical features of children infected with SARS-CoV-2, including neonates born to women infected with SARS-CoV-2 during pregnancy. The study included 333 infants (data from 11 centers)". "The incubation period from the moment of contact varied from 2

to 25 days. The virus could be isolated from the nasopharynx for 22 days, and from stool even for 30 days or more after contact with a carrier of SARS-CoV-2. Coinfections were reported in 79% of children. Approximately 35% of infected children had no symptoms. The most common symptoms were cough (48%; minimum and maximum frequency of this symptom was: 19–100%), fever (42%; 11–100%), and pharyngitis (30%; 11–100%). Other symptoms included nasal congestion, rhinorrhea, tachypnea, shortness of breath, diarrhea, vomiting and headaches. Children often complained of fatigue (asthenia) for no apparent reason. Children were more likely than adults to develop symptoms of gastrointestinal tract damage. Radiological findings included unilateral or bilateral infiltrative changes, in some cases ground-glass opacities in the interstitial lung tissue or consolidation with a halo-like surround were observed. At the same time, children rarely required transfer to the intensive care unit (3%)" [41]. "The journal JAMA published an article by Chinese scientists showing the immunological features of mild and moderate COVID-19 in pediatric patients [9] the work was carried out in the Department of Laboratory Medicine, Wuhan Children's Hospital. 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 63-70% of patients with severe disease have lymphopenia and depletion of natural killer (NK) cells, while the level of neutrophils, a major player in the so-called cytokine storm, has been elevated. 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 defined clinical outcome (ie, death or discharge) as of April 18, 2020 is shown. Throat swab and anal swab samples were collected and tested for SARS-CoV-2 with the recommended kit from the Chinese Center for Disease Control and Prevention. All samples were processed in the Laboratory Medicine Department of Wuhan Children's Hospital. Total RNA was extracted for 2 hours using a nucleic acid isolation kit (DAAN Gene). Real-time reverse transcription and polymerase chain reaction analysis was performed using the SARS-CoV-2 Nucleic Acid Detection Kit according to the manufacturer's protocol (BGI Biotechnology)". [40]

According to the authors (Kuznik B.I., Sturov V.G. 2021), "in contrast to adults, children 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 proinflammatory 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 intense intravascular coagulation. Finally, in children, in most cases, there is no significant increase in CRP, procalcitonin and troponin. In children with a complicated medical history (obesity, diabetes, heart, kidney or liver failure, etc.), the disease can be very severe, in some cases leading to death. The same applies to newborns and infants, in whom innate immunity plays a significant role in fighting infection. In children with COVID-19, in the early stages of the disease, neutrophils play the main role, and in the later stages, Th (CD4+), including Tregs (CD4+CD25+), which synthesize suppressive IL-4 and IL-10, which not only prevent the occurrence of cytokine storms, but also contribute to the synthesis of antibodies that block the action of the SARS-CoV-2 virus. Of course, therapy for children with COVID-19 should be prescribed based on the severity and age of the child". [40] "A significant role in the fight against severe and extremely severe COVID-19 in children is assigned to immunomodulatory drugs (INF-γ, tocilizumab, azithromycin, doxycycline, etc.), as well as antiviral drugs (favipiravir, etc.). 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 was also 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. [22] analyzed laboratory data from 1099 patients with COVID-19 infection. 926 of them had a mild course of the disease, and 173 had a severe course of the disease. In a comparative analysis of clinical blood test indicators, leukocytosis was detected 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 typical for patients of both groups and was observed in 80.4 and 96.1% of cases, respectively. Thrombocytopenia in mild cases of the process was detected in 31.6%, and in severe cases - in 57.7% of patients. When analyzing biochemical parameters in blood serum, the authors found that the level of C-

reactive protein (CRP) >10 mg/l increased in 56.4% of patients with a mild course and 81.5% with a severe course of the process. An increase in the level of procalcitonin was detected in 3.7 and 13.7% of patients, respectively, the activity of lactate dehydrogenase (LDH) - 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 blood 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" [42-44].

Y. Liu et al. [38], "having examined adults and children with COVID-19, found that clinical blood tests most often revealed lymphopenia, which, depending on the course of the process, occurred in 75% of cases; an acceleration of ESR (85%) and a decrease in hemoglobin levels (50%) were also noted". "In a biochemical blood test, the frequency of increased CRP levels was observed in 93%, LDH activity in 92%, and a decrease in serum albumin concentration in 98% of patients. Blood fibrinolytic activity (D-dimer) increased in 43% of patients. The authors concluded that disease severity can be predicted by the presence and severity of lymphopenia, low albumin values, and elevated LDH and CRP values" [38].

1.4 The State of the Level of Thyroid-Stimulating Hormone, Total T3, Total T4 and Cortisol in Children Who Have Had a Coronavirus Infection

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. [36] show that "anxiety and depression are elevated among pregnant women during this infectious pandemic". "Thyroid function changes during stressful experiences, and any abnormality in early pregnancy can significantly affect fetal development and pregnancy outcomes. This study aimed to determine whether the COVID-19 pandemic causes changes in thyroid hormones in early pregnant women" [45]. A cohort study in patients with COVID-19 without pre-existing thyroid disease found a slight decrease in serum thyrotropin (STT) and free thyroxine (FT4), but this was transient and returned to baseline after recovery from COVID-19. In another among Chinese participants, total triiodothyronine (TT3) and STT were significantly lower in patients with COVID-19 than in controls, but the difference disappeared after recovery from COVID-19. Given the greater susceptibility of pregnant women to COVID-19 and the important role of thyroid hormones in pregnancy outcomes, scientists recommended:

Reassess the thyroid status of pregnant women infected with COVID-19 in the 1st trimester of pregnancy, especially those considered at high risk for thyroid dysfunction or with a history of autoimmune thyroid disease.

Chen W, Tian Y, Li Z, Zhu J, Wei T, Lei J. [16] "Chinese scientists review the interaction between SARS-CoV-2 and the thyroid gland. Thyroid dysfunction is common in patients with COVID-19 infection. On the contrary, some thyroid diseases may have a negative impact on the prevention and control of COVID-19. In addition, some anti-COVID-19 medications may cause injury to the thyroid gland or affect its metabolism. COVID-19 and thyroid disease may mutually increase disease burden. Patients with SARS-CoV-2 infection should not ignore the effect on thyroid function, especially if associated symptoms are evident. In addition, patients with thyroid diseases should follow certain management principles during an epidemic".

"Acute and chronic diseases can cause profound modulations and interactions in a number of neuroendocrine systems, including changes within the hypothalamic-pituitary-thyroid axis. Evidence in the literature suggests that SARS-CoV-2 may also affect thyroid tissue and function" [46]. Various mechanisms have been proposed to explain the underlying pathogenic mechanism. The first suggests that high expression of ACE2 in the thyroid gland may facilitate SARS-CoV-2 entry. A second potential explanation is that systemic immune activation in response to SARS-CoV-2 infection may cause damage to the thyroid gland. The third hypothesis is selective transient dysregulation of the pituitary gland, due to both a direct cytotoxic effect of the virus at the level of the pituitary gland and an indirect effect through the activation of proinflammatory cytokines that produce a "cytokine storm" [41].

Scientists of Uzbekistan (Tozhieva I.M., Khaidarova F.A., Alieva A.V. 2021) consider "the types of complications of coronavirus infection and highlight complications of the thyroid gland. Clinically, some patients with COVID-19 may

experience neck pain, which may be a sign of subacute thyroiditis. Studies have shown that subacute thyroiditis may develop within a few weeks of upper respiratory tract involvement, which may be a late complication in patients with COVID-19. Therefore, thyroid function should be checked after discharge in patients with COVID-19".

Additionally, a study [7] demonstrates that "messenger RNA (mRNA) encoding the ACE2 receptor is expressed in thyroid follicular cells, making the thyroid a potential target for entry of SARS-CoV- 2". "SARS-CoV-2 infection may worsen initial diseases in endocrine organs or cause new abnormalities. In turn, these endocrine diseases may worsen the poor prognosis of COVID-19. Previous studies have shown that COVID-19 mortality rates from different regions of the world vary widely, but have consistently shown that comorbidities such as hypertension, chronic kidney disease, and 2 type of diabetes significantly increase mortality in patients with SARS-CoV-2" [47].

1.5 Prevention and Rehabilitation of Children after Coronavirus Infection

Studying of the mechanisms of the pathogenesis of COVID-19, including laboratory markers, contributes to the accumulation of new knowledge and makes it possible to develop approaches to complex treatment and prevention of life-threatening complications. The experience of monitoring children who have suffered a new coronavirus infection has shown that all patients need medical rehabilitation, including those who have suffered from an asymptomatic or mild form of the disease. Data on the possibility of disruption of the functional state of not only the respiratory organs, but also other body systems determine the need for staged medical rehabilitation of such children. "The article defines the basic principles and stages of medical rehabilitation of these patients, and substantiates the indications for various stages. Medical rehabilitation of children after suffering a new coronavirus infection at all stages is carried out by specialists from a multidisciplinary rehabilitation team, which includes: a pediatrician, a physiotherapist, an exercise therapy doctor, a medical rehabilitation doctor, a reflexologist, a medical psychologist, a speech therapist, an instructor-methodologist, etc. This article presents a wide range of modern technologies of hardware physiotherapy and kinesiotherapy, indicated for children who have suffered from COVID-19, with a description of the main therapeutic effects and the mechanism of the therapeutic effect of physical factors. Psychological rehabilitation is important in the complex of rehabilitation measures for children with COVID-19. Particular attention is paid to the issues of sanatorium-resort treatment of children after suffering a new coronavirus infection. A range of non-drug technologies has been identified for inclusion in the individual program of sanatorium-resort treatment of such patients using natural healing resources (mineral waters, therapeutic mud, healing climate, other natural conditions used for the treatment and prevention of diseases); non-drug therapy, exercise therapy, massage, physiotherapy, hydrotherapy, reflexology, psychotherapy. The article presents criteria for assessing the effectiveness of rehabilitation measures" [48].

An article by Moscow authors (Petrova M.S., Khan M.A. 2021) is devoted to "the issues of medical rehabilitation of children who have suffered coronavirus infection COVID-19, which is an acute infectious disease caused by a new strain of a virus from the SARS CoV-2 genus of coronaviruses". "The authors present current data on the epidemiology and clinical course of this disease in children. It is known that in children, complications and adverse outcomes of COVID-19 are observed much less frequently than in adults; however, experience in monitoring children who have suffered a new coronavirus infection has shown that all patients need medical rehabilitation, including those who have suffered the disease in asymptomatic or mild form. Data on the possibility of disruption of the functional state of not only the respiratory organs, but also other body systems determine the need for staged medical rehabilitation of such children. The article defines the basic principles and stages of medical rehabilitation of these patients, and substantiates the indications for various stages" [49].

Medical rehabilitation of children after suffering a new coronavirus infection at all stages is carried out by specialists from a multidisciplinary rehabilitation team, which includes: a pediatrician, a physiotherapist, an exercise therapy doctor, a medical rehabilitation doctor, a reflexologist, a medical psychologist, a speech therapist, an instructor-methodologist, etc. This article presents a wide range of modern technologies of hardware physiotherapy and kinesiotherapy, indicated for children who have suffered from COVID-19, with a description of the

main therapeutic effects and the mechanism of the therapeutic effect of physical factors. Psychological rehabilitation is important in the complex of rehabilitation measures for children with COVID-19. Particular attention is paid to the issues of sanatorium-resort treatment of children after suffering a new coronavirus infection. A range of non-drug technologies has been identified for inclusion in the individual program of sanatorium-resort treatment of such patients using natural healing resources (mineral waters, therapeutic mud, healing climate, other natural conditions used for the treatment and prevention of diseases); non-drug therapy, exercise therapy, massage, physiotherapy, hydrotherapy, reflexology, psychotherapy. The article presents criteria for assessing the effectiveness of rehabilitation measures. Specialists of the multidisciplinary rehabilitation team draw up an individual program of medical rehabilitation, determine the goals and objectives of the rehabilitation course, decide on admission to physical activity taking into account the functional state of the child's body, designate the range of medicinal and non-medicinal technologies and the scope of rehabilitation measures. In the rehabilitation process, methods of physiotherapy, balneo-peloid therapy, physical therapy, reflexology, manual therapy, psychotherapy, etc. are widely used.

"According to an analysis of pediatric patients in China, pneumonia in combination with fever or cough was noted in 30% of children, and in 22% pneumonia was the only manifestation of infection. The phenomena of hypoxia were observed less frequently, but in a number of cases there was a decrease in saturation below 93% or 94%" [45]. "According to the methodological recommendations "Features of clinical manifestations and treatment of the disease caused by a new coronavirus infection (COVID-19) in children, version 1, clinical manifestations of lung damage in the form of shortness of breath during physical exertion (screaming/crying), as well as a decrease in blood saturation (SpO2≤ 95%) occur even with moderate severity of the disease. Severe COVID-19 may include dyspnea (shortness of breath, chest tightness, shortness of breath, or tachypnea), cyanosis/acrocyanosis, SpO2 ≤ 93%" [50].

"Rehabilitation measures are recommended to begin already at the first stage of medical rehabilitation in the inpatient infectious diseases department, where children with COVID 19 are sent" [39]. "The goal of rehabilitation of patients who survived COVID-19 is to restore the function of external respiration, transport and utilization of oxygen by working tissues/organs, reduce the severity of shortness of breath, maintain the cardiovascular system and reduce the risk of cardiovascular complications, restore muscle strength, physical performance and daily activity, improve quality of life and psychological status of the patient, his return to society (society). There are several aspects of rehabilitation of patients with COVID-19: medical, physical, educational and psychological. The medical aspect consists of examination, assessment of the patient's clinical condition, identification and correction of traditional cardiovascular risk factors, and appropriate drug therapy. The psychological aspect of rehabilitation is associated with the need for the patient's psychological adaptation to the illness, increasing his resistance to stressful situations, and, if necessary, treating anxiety and depressive disorders. Psychological assistance is provided to all patients with coronavirus infection starting from the first stage of rehabilitation. Patients with high levels of anxiety and anxiety disorders need to be identified early" [51].

As part of physical rehabilitation, breathing exercises are distinguished (static, dynamic breathing exercises, starting from stage II - inspiratory training using breathing simulators), general strengthening exercises involving small/medium muscle groups, muscle relaxation exercises, resistive/strength and dynamic exercises/trainings . Positional therapy is used (including prone positioning - lying on the stomach in patients and severe respiratory failure to optimize oxygenation), postural correction, early mobilization of the patient (passive, partially passive and active movements in all joints) and verticalization [52]. Initially, emphasis is placed on training the muscles that are the most weakened and functionally significant to ensure the patient's vertical position and locomotion.

Children and adolescents are vulnerable to developing post-traumatic stress syndrome. Psychopathological changes in children with pneumonia associated with a new coronavirus infection are represented by psychogenic neurotic reactions to the very fact of somatic suffering, as well as neurosis-like disorders, mainly in the form of asthenic conditions and depressive spectrum disorders, including anxiety, anxiety-depressive, anxiety- hypochondriacal,

hysterical depressive. condition. Psychological counseling is necessary for a speedy recovery. For older children, especially those with manifestations of phobias, anxiety, and psychological disorders, active psychological support and treatment are indicated. Methods of complex cognitive-oriented psychotherapy are used using parallel-sequential components: psychoeducational; cognitive-causal-oriented, hypno-therapeutic.

“A decrease in the physical activity of children in a hospital, including in an intensive care unit, as well as catabolic changes, especially in skeletal muscles, and a decrease in food consumption subsequently reduce the effectiveness of rehabilitation measures. Nutritional support is an independent factor that improves treatment outcomes, short- and long-term prognosis, and reduces the incidence of complications. The European Society for Clinical Nutrition and Metabolism (ESCNM) recommends an algorithm for assessing nutritional levels with subsequent determination of the degree of nutritional status disorders in adult patients with COVID-19, including screening for malnutrition, optimization of nutritional status, use of vitamin and mineral supplements, regular physical activity, supplemental oral nutrition (supplementation), enteral nutrition” [53].

2. CONCLUSION

The course of COVID-19 in children has a number of specific features, in particular, the disease is often asymptomatic or with a mild clinical picture. Disease outcomes in children are usually favorable. The lack of means for etiotropic treatment and prevention of COVID-19 is of concern. Doctors have access to only symptomatic therapy and tools for managing patients with severe manifestations of this disease. At the same time, the development and implementation of new test systems has been intensified, new antiviral pharmacological agents and vaccines are being studied. The development of effective means of preventing COVID-19 in children remains the main hope of the medical community in the fight against the new coronavirus infection.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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