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Modern Perspectives on The Impact of Comorbidities on The Course of Covid-19 In Children

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Abstract
This article analyzes contemporary scientific literature regarding the impact of comorbidities on the course of COVID-19 in children. Obesity, diabetes mellitus, cardiovascular diseases, chronic lung diseases, neurological disorders, and immunodeficiency states are examined as independent risk factors for a severe course of COVID-19. Pathogenetic mechanisms, including cytokine storm, increased inflammatory markers, and T-cell immunity dysfunction, are described in detail. The article also highlights the clinical significance of MIS-C syndrome, its diagnostic criteria, modern treatment approaches, and vaccination recommendations.

Keywords: COVID-19, children, comorbidities, obesity, diabetes mellitus, MIS-C, cytokine storm, pediatrics, risk factors, immune response.

Introduction

The COVID-19 pandemic, which began in Wuhan, China, in December 2019, has become the greatest global health crisis of the last century. The World Health Organization (WHO) declared the disease a pandemic on March 11, 2020 [1]. Within a few months, the SARS-CoV-2 virus spread to every country in the world, threatening the lives of millions. To date, according to various sources, more than 700 million confirmed cases of COVID-19 have been registered worldwide [2].

The pediatric population was initially considered less susceptible to COVID-19 than adults. Indeed, the majority of pediatric patients experience a mild to moderate course of the disease. However, clinical observations and large-scale epidemiological studies have shown that certain risk factors - particularly comorbid conditions - significantly increase the likelihood of a severe course, hospitalization, and even admission to an intensive care unit in children [3, 4]. This situation is of particular importance for pediatric practice, as a clear determination of a patient's risk group ensures timely referral and effective treatment.

Studying the impact of comorbid conditions on the course of COVID-19 remains one of the priority areas of pediatric infectiology. This review article systematically presents the scientific evidence accumulated on this topic to date and provides a basis for the development of clinical recommendations.

Epidemiological and Clinical Characteristics of Covid-19 In Children

Spread of the Disease

Children and adolescents account for 10-15% of COVID-19 cases. According to the U.S. Centers for Disease Control and Prevention (CDC), confirmed cases of COVID-19 in children under 18 years of age comprised 12-13% of the total incidence rate during the initial waves

of the pandemic [5]. With the spread of the Delta and Omicron variants, the incidence in children increased sharply, with numerous cluster outbreaks recorded, especially among school-aged children and adolescents [6].

Due to the high infectivity of the Omicron strain, the rate of illness and the total number of cases in children increased in many countries. At the same time, it was found that very young children - particularly those under 2 years old - are relatively more severely affected and may present with croup-like symptoms and a clinical picture similar to bronchiolitis [7].

Clinical Symptoms

The clinical presentation of COVID-19 in children is significantly different from that in adults. In most pediatric patients, the disease is asymptomatic or mild, with common symptoms including fever, cough, sore throat, shortness of breath, muscle pain, and loss of appetite [8]. Loss of smell and taste, which is characteristic of adults, has been noted to be significantly less common in children.

The hospitalization rate in children is several times lower than in adults: approximately 1-3% of patients require hospitalization, and 0.1-0.3% of cases require treatment in the intensive care unit [9]. However, these figures can increase sharply in the presence of comorbidities.

Complications

The most severe complications of COVID-19 in children include acute respiratory distress syndrome (ARDS), pneumonia, myocarditis, thromboembolism, and sepsis-like conditions. Additionally, nervous system complications such as encephalopathy and even encephalitis have been observed in some cases [10]. Long-term complications (long COVID) are not absent in the pediatric population: fatigue, impaired concentration, and headaches can persist for several months after the illness.

MIS-C Syndrome

One of the most specific and dangerous complications of COVID-19 in children is multisystem inflammatory syndrome in children (MIS-C), which occurs following a SARS-CoV-2 infection. This syndrome typically develops 2-6 weeks after having COVID-19 and is characterized by intense inflammation, fever, and damage to multiple organs and systems [11].

The diagnostic criteria for MIS-C include the following: a body temperature above 38°C lasting up to 21 days; laboratory signs of multi-organ damage; a PCR or antibody test result confirming SARS-CoV-2; and the exclusion of other infectious etiologies. The clinical presentation may include features similar to Kawasaki disease, including aneurysmal dilation of the coronary arteries. Cardiac pathology was detected in 50-80% of affected children, gastrointestinal symptoms in 30-50%, and neurological manifestations in 25-40% [12].

The Influence of Comorbidities on The Course of Covid-19

Obesity

Obesity is one of the strongest and most well-studied independent risk factors for a severe course of COVID-19 in children. Several large studies show that the likelihood of hospitalization in obese children is 2-3 times higher than in their non-obese peers [13]. According to the US CDC, obesity was present in 42% of COVID-19-related hospitalizations among children [5].

Pathogenetically, obesity aggravates the course of COVID-19 through the following mechanisms: first, visceral adipose tissue expresses large quantities of ACE2 receptors, serving as a secondary reservoir for viral dissemination; second, a chronic increase in adipokines and pro-inflammatory cytokines disrupts the immune response; third, mechanical pressure on the diaphragm reduces respiratory reserve and increases the risk of hypoventilation [14].

Diabetes Mellitus

Diabetes mellitus (DM) is well-established as a major risk factor for severe COVID-19 in adults. This association is also confirmed in children, although the mechanism of comorbidity is somewhat different. In children with type 1 DM, the risk of developing ketoacidosis during COVID-19 increases sharply, especially in a state of decompensation [15]. A meta-analysis published in The Lancet found that children with T1D had a 2.1-fold higher risk of hospitalization and a 3.0-fold higher risk of admission to intensive care due to COVID-19 [16].

Hyperglycemia exacerbates the disease by reducing the phagocytic activity of immune cells, impairing neutrophil chemotaxis, and suppressing T-lymphocyte function. Additionally, studies have shown that the SARS-CoV-2 virus can directly damage beta cells in the pancreas [17].

Cardiovascular Diseases

Children with congenital heart defects, cardiomyopathies, and arrhythmias have been found to have a statistically significant higher risk of severe COVID-19 and the development of MIS-C. According to data from the USA and European countries, the mortality rate due to COVID-19 in children with congenital heart disease was four times higher than in the general pediatric population [18].

Pulmonary hypertension, single ventricle syndrome, and cyanotic congenital heart defects constitute a particularly high-risk group. The systemic inflammation and hypercoagulation caused by COVID-19 become an additional stress factor for a heart that is already working at the limit of its compensation.

Chronic Lung Diseases

Initially, there was conflicting data regarding the impact of bronchial asthma - the most common chronic lung disease in children - on the course of COVID-19. Subsequent large-scale studies have shown that controlled bronchial asthma is not an independent risk factor for a severe course of COVID-19; however, in cases of uncontrolled or severe asthma, the risk of lung damage increases significantly [4].

For children with cystic fibrosis, chronic lung disease, and bronchopulmonary dysplasia, the risk of severe COVID-19 and pulmonary complications is considerably higher. In this category of patients, respiratory failure can develop rapidly, and the need for prompt artificial ventilation may arise [3].

Neurological Diseases

Children with epilepsy, cerebral palsy, neuromuscular diseases, and other neurological pathologies constitute a particularly vulnerable group with respect to COVID-19. Studies have shown that among children with neurological diseases, the hospitalization rate due to COVID-19 is 3.1 times higher, and the rate of admission to intensive care is 5.2 times higher [10].

In these patients, there is a risk of worsening epileptic seizures, a sharp deterioration in neurological status, and weakening of the respiratory muscles due to the effects of COVID-19. Limited activity and exposure to immunosuppressive factors in children with disabling neurological diseases increase their susceptibility to COVID-19.

Immunodeficiency

COVID-19 is particularly dangerous in children with oncological diseases, those on post-transplant immunosuppressive therapy, and those with congenital immunodeficiency or HIV/AIDS. In this group, an atypical course of the disease, prolonged viral shedding, and a poor response to standard antiviral therapy are observed [19].

In children with hematological malignancies (acute leukemia, lymphoma) and those who have undergone bone marrow transplantation, the risk of death from COVID-19 can be tens of times higher than in the general pediatric population. Among immunosuppressive drugs, rituximab and steroids have been identified as the drugs that most significantly suppress the antiviral immune response.

Pathogenesis and Immunological Mechanisms

Cytokines and Inflammatory Markers

The cytokine storm - the uncontrolled overproduction of inflammatory cytokines - plays a central pathogenetic role in the course of COVID-19. In children with severe COVID-19 and MIS-C, plasma concentrations of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-10, TNF-α, and IFN-γ have been observed to be tens of times higher than normal [20].

Chronic diseases, particularly obesity and diabetes mellitus, create a state of basal inflammation (metabolic inflammation) in the body. This, in turn, creates a "fertile ground" for the development of a cytokine storm when SARS-CoV-2 infection is introduced. Initially high concentrations of leptin, resistin, and TNF-α produced by adipocytes increase the immune system's predisposition to hyperactivation.

Laboratory Biomarkers: Ferritin, D-dimer, CRP

Ferritin, as an acute-phase protein, is significantly elevated in severe COVID-19 and MIS-C, and a blood level exceeding 500 mcg/l is considered a prognostic sign of a severe course. In MIS-C, hyperferritinemia can exceed 10,000 mcg/l in some patients [11].

The D-dimer level is an important biomarker for assessing the risk of hypercoagulation and thromboembolic complications. In severe forms of COVID-19, a D-dimer level above 1000 ng/ml is recognized as an independent prognostic factor for ICU admission and mortality risk [9]. An increase in C-reactive protein (CRP) is observed more rapidly and sharply in children with comorbidities, reflecting the intensity of the inflammatory process.

Characteristics of the Immune Response

The immune system in children responds to the virus differently than in adults. The often milder course of COVID-19 in children is explained by the relatively high activity of the thymus gland, cross-reactive T-cell immunity formed from past coronavirus infections (HCoV-OC43, HCoV-229E), and a stronger innate immune response [21].

However, in children with immunodeficiency or autoimmune diseases, these defense mechanisms are compromised. Furthermore, it is hypothesized that the pathogenesis of MIS-C may involve an autoimmune reaction of IgG antibodies against damaged tissues, which supports the theory that this syndrome is characterized by hyperactivation of the mononuclear phagocyte system [12].

Clinical Prognosis and Risk Factors

Likelihood of a severe course and hospitalization

Numerous multicenter studies have been conducted to assess the specific risk increase associated with comorbidities. According to the HEROES-RECOVER cohort study, the risk of hospitalization is 1.5-2.1 times higher in children with one comorbidity and 3.5-4.8 times higher in those with two or more comorbidities, compared to children with no comorbidities [22].

The highest-risk group includes the following: infants under 2 years of age; children with obesity and metabolic syndrome; and patients with congenital heart defects, neuromuscular diseases, or an immunosuppressed state. In these groups, immediate hospitalization and monitoring of the patient's condition are clinically justified upon receiving a positive PCR result [5, 23].

Need for intensive care

The need for ICU (Intensive Care Unit) admission is generally rare in children, but this probability increases sharply in the presence of the above-mentioned risk factors. It has been established that in children with more than one comorbidity, the risk of ICU admission is 6.3 times higher than in the general pediatric COVID-19 population [3]. ICU treatment is required in 50-65% of children with MIS-C.

Diagnostics and Monitoring

Laboratory Markers

An expanded laboratory workup is necessary for children with COVID-19 and comorbidities. The standard approach includes: PCR confirmation of SARS-CoV-2; CBC (complete blood count); biochemical blood analysis - liver enzymes, renal function indicators; inflammatory markers - CRP, ferritin, IL-6, procalcitonin; coagulogram - D-dimer, fibrinogen; lactate dehydrogenase [8, 9].

If MIS-C is suspected, it is recommended to determine NT-proBNP and troponin I levels, test for antinuclear antibodies with a highly sensitive test, perform a urinalysis, and conduct a bacteriological culture to rule out co-infections [11, 12].

Instrumental Examinations

ECG and echocardiography (EchoCG) are mandatory examination methods for suspected cardiac pathology and for MIS-C diagnoses. Computed tomography (CT) or chest X-ray is used to assess lung damage. Lung ultrasound (LUS) is becoming increasingly widely used due to the absence of a radiation burden and its ease of use in young children [3].

In suspected cases of neurological complications, a brain MRI or CT scan, EEG, and lumbar puncture are performed as indicated. Additionally, regular monitoring of pulse oximetry and respiratory rate helps in the early detection of signs of a severe course of the disease.

Modern Approaches to Treatment and Prevention

Management of COVID-19 in Children

The approach to treating COVID-19 in children depends on the severity of the illness and the presence of comorbidities. In most cases, symptomatic treatment - such as rest, drinking plenty of fluids, and antipyretics (paracetamol) - is sufficient [8]. However, accelerated treatment algorithms are applied to children in high-risk groups.

Antiviral Therapy

Remdesivir - approved by the U.S. FDA for children aged 12 and older and weighing over 40 kg, and also initially authorized for newborns up to 28 days old - is used for hospitalized children who require oxygen [23]. The efficacy of molnupiravir and the nirmatrelvir/ritonavir combination in the pediatric population is still under investigation and is not yet officially recommended for children.

Immunomodulators

For the treatment of MIS-C, glucocorticoids (methylprednisolone 1-2 mg/kg/day) and intravenous immunoglobulin (IVIG, 2 g/kg) are considered first-line drugs. IL-1 blockers (anakinra) and the IL-6 antagonist (tocilizumab) are used in severe MIS-C cases that do not respond to IVIG [12].

The RECOVERY trial has shown that dexamethasone (0.15 mg/kg/day, for up to 10 days) can reduce mortality in older children who require oxygen or are on mechanical ventilation [24]. Corticosteroids are not recommended for younger children or for those with mild cases of the disease.

Vaccination

The COVID-19 vaccine is the most effective method for protecting children with comorbidities from a severe course of the disease. The WHO and CDC primarily recommend that children and adolescents in high-risk groups receive the vaccine [1, 5]. While the vaccine's effectiveness may be reduced in children receiving immunosuppressive therapy, immunization is still recommended for them, unless they have a life-threatening immunodeficiency condition.

mRNA vaccines (Pfizer-BioNTech) are authorized for use in infants from 6 months of age and have been shown in clinical trials to provide 70-90% protection against severe illness in children at risk [6]. Post-vaccination myocarditis is very rare in children and typically resolves on its own.

Discussion

An analysis of the available scientific literature strongly supports the hypothesis that comorbidities significantly worsen the course of COVID-19 in children. However, there are several methodological challenges when comparing studies in this field: the age range of patients varies (0-18 years), the classification of comorbidities and the criteria for their severity are not standardized, and since some studies are retrospective in nature, selection bias cannot be ruled out [22].

The intricate connection between hereditary and social factors with comorbidities - such as the socioeconomic determinants of obesity and the relatively higher severity of COVID-19 in ethnic minorities - complicates the isolation of independent risk factors. It is advisable that future research focus on a more precise stratification of comorbidities, uncovering their interaction mechanisms, and developing personalized recommendations that account for immunogenetic characteristics.

The pathogenesis of MIS-C and the role of comorbidities in it remain poorly understood. Some studies suggest that the development of MIS-C is more dependent on population group, immunogenetic characteristics, and the viral variant than on the presence of comorbidities [11, 20]. This issue requires further large-scale, multicenter research.

Conclusion

This review article demonstrated that comorbidities play a crucial pathogenetic and clinical role in the course of COVID-19 in children. Obesity, diabetes mellitus, congenital heart defects, chronic lung diseases, neurological pathologies, and immunodeficiency states have been identified as independent risk factors for a severe course of COVID-19, hospitalization, and the need

for intensive care.

From the perspective of clinical recommendations, the following are necessary: (1) conduct rapid risk stratification for all children with comorbidities upon diagnosis of COVID-19; (2) immediately initiate extended laboratory and instrumental examinations and dynamic monitoring of patients in the at-risk group; (3) immediately transition to intensive care upon the appearance of MIS-C symptoms; (4) prioritize and ensure complete immunization of at-risk children and adolescents with the COVID-19 vaccine; (5) timely detection of comorbidities, bringing them to a state of compensation, and managing chronic diseases under the supervision of specialized physicians.

Even after the pandemic has ended, it is necessary to continue the comprehensive study of the long-term consequences of COVID-19 in children (long COVID, prior damage from MIS-C) and their interaction with comorbidities.

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