JOURNAL OF COMPLEMENTARY MEDICINE RESEARCH
Journal of Complementary Medicine Research, ISSN: 2146-8397 Vol. 13, No. 3, 2022 (pp. 50-53)
RESEARCH ARTICLE
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Coronavirus Disease in Children and Adolescents: Symptoms, Treatment, Consequences

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ABSTRACT

The article examines the causes, symptoms and consequences of the development of coronavirus disease in pediatrics. It has been determined that coronavirus disease is usually easier in children than in adults; symptoms usually include headache, fever and cough. Severe variants of the development of coronavirus disease in children with concomitant diseases are possible.

Multisystem inflammatory syndrome in children is a postinfectious complication of severe acute respiratory syndrome of coronavirus infection with pronounced cardiovascular and gastrointestinal symptoms.

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How to cite this article: Mochalova OI, Emelianova TA, Ramzanovna AS, Agaeva AR, Shaptukaeva MK. Coronavirus Disease in Children and Adolescents: Symptoms, Treatment, Consequences. Journal of Complementary Medicine Research, Vol. 13, No. 3, 2022 (pp. 50-53).

INTRODUCTION

At the end of 2019, a new coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), developed in China. COVID-19 quickly spread around the world and turned into a global pandemic.[1] Most cases of COVID-19 in children were milder than in adults, but in the early spring of 2020, children who had signs of previous SARS-CoV-2 infection developed a new inflammatory syndrome called multisystem inflammatory syndrome in children (MIS-C). Accordingly, it is necessary to say that the course of coronavirus disease in children is no less dangerous than in adults, in this regard, the study of the features of the course of the disease in children and adolescents is extremely relevant. The aim of the study is to consider the causes, symptoms and consequences of the development of coronavirus disease in pediatrics.

KEYWORDS:
Coronavirus disease,
Chronic diseases,
consequences.
features of the course,
Pediatrics,
Symptoms,

ARTICLE HISTORY:
Received : Feb 20, 2022
Accepted: Mar 18, 2022
Published: Jun 03, 2022

DOI:
10.5455/jcmr.2022.13.03.10

MATERIALS AND METHODS

To write the study, articles by a number of authors were analyzed within the framework of the research topic, as well as comparative and analytical research methods were applied.

RESULTS

The wave-like development of coronavirus infection kept the entire medical world in good shape for almost two years. It was noted that most often the disease affected adults, however, as various studies show, in the pediatric population this virus also cannot be discounted.[2]

The severity of the disease in children is usually lower: only 1% to 5% of cases in children qualify as severe compared to 10%-20% in adults. It is believed that this discovery reflects lower levels of expression of angiotensin converting enzyme 2 in alveolar cells, which is the mechanism of penetration of SARS-CoV-2 into cells. Similarly, the mortality rate is estimated at 0.3% (95% confidence interval, 0.1–0.4) in patients under the age of 21, compared with 5.8% for adults.[3] Age over 12 years and high initial C-reactive protein (CRP) are risk factors for admission to the pediatric intensive care unit, and high CRP - leukocytosis and

thrombocytopenia are risk factors for organ dysfunction. Viral load and young age, especially children under the age of 1 year, are other risk factors for more severe disease.[4]

The manifestations of symptoms in pediatric cases of COVID-19 vary. Estimates of asymptomatic infection range from 13% to 50% of cases in children. The average time from exposure to symptoms is 7 days. Among the symptomatic cases, headache occurs in about two–thirds, and fever and cough occur in about half of the cases.

Gastrointestinal symptoms, sore throat and rhinorrhea are rare, although patients with more severe COVID-19 have symptoms from the gastrointestinal tract and upper respiratory tract.[5]

The definition of severe COVID-19 in children varies, but includes the requirement of inpatient treatment and the presence of at least one severe manifestation and a positive reverse transcriptase polymerase chain reaction test for SARS CoV-2 infection.

Among the severe cases, the majority of sick children (71%) had severe respiratory disease, while less than 3% had severe damage to the cardiovascular system and 9% had severe damage to the cardiovascular system. Of these patients, half needed some form of respiratory support, including 15% on artificial ventilation and 1.4% on extracorporeal membrane oxygenation.[6]

Neurological manifestations were noted in 20% of patients in the same cohort. When considering both patients with severe COVID-19 and MIS-C with neurological manifestations, 12% had potentially life-threatening complications, including encephalopathy, stroke, cerebral edema, demyelination and Guillain-Barre syndrome.

It was noted that, like adults, children are susceptible to severe COVID-19, up to a fatal outcome. However, in most cases of severe disease, concomitant diseases such as asthma, immunosuppression and neurological diseases were present in children.

Prematurity, a history of asthma or diabetes; an immunodeficiency condition; and gastrointestinal diseases have been associated with increased chances of hospitalization in such patients. In addition, children with asthma and gastrointestinal diseases often require respiratory support.[7]

Obesity was also associated with a higher risk of severe COVID-19. Patients with chronic conditions may have concomitant deterioration of the underlying disease, including diabetic ketoacidosis.

Coinfection with other viruses and bacteria is an important factor. Meta-analysis showed that 5.6% of children had coinfection; in this group 58% had Mycoplasma pneumoniae, 11.1% had influenza A or B, 9.7% had respiratory syncytial virus; the rest had other common types of viral and bacterial infections.[8]

Thrombotic complications from COVID-19, such as deep vein thrombosis and pulmonary embolism, were observed in 2.1% of cases in children in a multicenter retrospective cohort study in the USA, sometimes despite thromboprophylaxis.

In a meta-analysis of pediatric cases, the most frequent laboratory data were high levels of ferritin and procalcitonin in about 25% and high levels of CRP in about 20% of patients. The average CRP among children with COVID-19 is estimated at 9.4 mg/l. In contrast to the cases in adults, the number of leukocytes was normal in about 70% of cases, while leukopenia or leukocytosis was observed in 15% of cases.[9]

In the registered pediatric cases, chest X-rays were normal in about one third, and focal consolidations were detected in another third; the rest showed "opaque frosted glass". A systematic review of the results of computed tomography of the chest (CT) in pediatric cases showed that in 61.5% of cases either seals or darkening of the "frosted glass" type were detected; 26.5% were normal.[10]

DISCUSSION

Patients with mild or moderate symptoms of COVID-19 often do well only with supportive therapy. However, treatments such as monoclonal antibodies, antiviral therapy, glucocorticoids and immunosuppression may be indicated.

Monoclonal antibodies, such as bamlanivimab-etesevimab and kazirivimab-imdevimab, are approved for emergency use by the U.S. Food and Drug Administration in pediatric patients with mild to moderate disease severity and with a high risk of disease progression to severe.

High-risk conditions include obesity, chronic respiratory diseases, chronic kidney diseases, and immunocompromised conditions, such as rheumatological diseases receiving immunosuppressive therapy. Antiviral therapy with remdesivir should be considered for patients with a positive polymerase chain reaction test for SARS-CoV-2 and severe or critical manifestations of COVID-19.

GC may be an option for pediatric patients who require respiratory support, but data are not available. GC can also be considered in patients with concomitant acute respiratory distress syndrome, septic shock or adrenal insufficiency.

Convalescent plasma has an emergency use permit for adult patients in critical condition with COVID-19, but its use in pediatric patients with COVID-19 has not been sufficiently studied. If appropriate, it should be prescribed in the early stages of the disease, especially if there is no improvement after remdesivir and GC, as well as in patients with impaired humoral immunity. Finally, it was suggested to consider the possibility of antiplatelet and anticoagulant therapy to prevent thrombotic complications. Experts recommended prophylactic low-molecular-weight heparin to children hospitalized with COVID-19 or MIS-C who are at higher risk of thrombosis, including risk factors for severe disease associated with SARS-CoV-2, or risk factors for venous thromboembolism, such as family history, obesity and chronic inflammatory conditions.[11]

A portion of adult patients develop a high level of inflammation around the second week of COVID-19, called hyperinflammatory syndrome associated with COVID-19. Frequent manifestations include fever, high ferritin levels, liver damage, hematological disorders, coagulopathy, and high levels of inflammatory cytokines, especially CRP and IL-6. Several trials of COVID-19-related hyperinflammatory syndrome have been conducted in

adults, primarily with tocilizumab, with conflicting results. The use of tocilizumab in pediatric patients with COVID-19 has not been formally studied. However, recommendations have been issued for pediatric patients with COVID-19 who develop hyperinflammation; recommendations include anakinra and consideration of other treatments with less evidence, including GC and tociliuzumab.

There is also data in the literature on the delayed effects of COVID-19 in children. In a small series of cases from China, repeated computed tomography about 30 days after discharge showed that half of the children had imaging abnormalities, but all indicators of shortness of breath were light, the condition of the children subsequently constantly improved, and not a single patient needed oxygen.

Prolonged COVID has been described in adults with symptoms of headache, fatigue, shortness of breath and anosmia lasting from several weeks to months after infection.

The full spectrum of prolonged COVID or post-acute consequences of SARS-CoV-2 infection in children has not yet been fully analyzed, but work in this direction continues [12].

Currently, matrix RNA vaccines against SARS-CoV-2 are approved for patients aged 12 years and older; large pediatric trials are being conducted, the results of which are expected by the summer of 2021. Vaccination is recommended for suitable individuals who have had COVID-19, but it is recommended to postpone vaccination for 90 days after acute illness.

It must be said that pediatric patients with chronic rheumatological diseases do not always seem to be at a higher risk of contracting COVID-19. In adults, the probability of death is higher if the patient suffers from moderate or high activity of rheumatological disease and takes certain medications, including GC, rituximab and sulfasalazine. Similar data on rheumatic diseases in children have not been reported, but they are being collected. To date, no specific recommendations have been issued regarding vaccination against SARS-CoV-2 in children suffering from rheumatology, but the ACR recommends certain immunosuppressants for adults with rheumatic diseases in connection with vaccination.

Multisystem inflammatory syndrome in children (MIS-C) is a potentially life-threatening condition that can have acute, severe cardiovascular symptoms. Presumably, this is a post-infectious phenomenon after SARS-CoV-2 infection, and is considered in the spectrum of post-acute consequences of the manifestation of SARS-CoV-2 infection. This syndrome was first described in a group of children with hyperinflammatory shock in London in mid-April 2020.

Shortly thereafter, the number of cases increased worldwide, prompting the Centers for Disease Control and Prevention (CDC) to identify MIS-C in May.

The time of onset of symptoms is usually 3 to 6 weeks after contact with SARS-CoV-2. Most patients with MIS-C did not have serious illnesses at the time of SARS-CoV infection.

It was determined that MIS-C is more common in boys (59%) than in girls. The average age ranges from 7.3 to 10.0 years; accordingly, such a disease is rare in adults. Patients with MIS-C aged 6 to 12 and 13 to 20 years more often than patients aged 0 to 5 years needed intensive care.[13]

The incidence is higher among patients who identify themselves as racial or ethnic minorities, especially among people of African, Afro-Caribbean and Latin American descent. Obesity is common in patients with MIS-C, with about half of the patients being overweight or obese based on body mass index.

Patients with MIS-C have fever and damage to at least 2 organ systems. The most common symptoms are gastrointestinal, skin-mucous and cardiovascular. Skin-mucosal features and rash in MIS-C cause comparisons with Kawasaki disease.

The rash is variable, skin-mucous symptoms appear quickly, on average 2.7 days after the onset of fever. Approximately a quarter to half of the patients with MIS-C also met the criteria for Kawasaki disease, most often with incomplete manifestation. Almost a quarter of patients have myocarditis, which makes hypotension and shock common symptoms. Other cardiac complications include arrhythmia, left ventricular (LV) dysfunction, and coronary artery ectasia or aneurysm. Neurological symptoms occur in 22% of cases, including headache, change in mental state and aseptic meningitis. Unlike patients with acute COVID-19, rhinorrhea and cough are observed only in 13% and 7% of patients, respectively.

Hospitalization is recommended for patients with potential MIS-C, because patients are at risk of rapid development of severe disease. Hypotension may require urgent intervention.

When considering MIS-C, a wide differentiation should be taken into account, including infection and malignancy, since many signs are nonspecific and coincide with sepsis. Patients with MIS-C may have superimposed bacterial infections and should be empirically covered with antibiotics if clinically indicated.

The presentation of MIS-C has similarities to other inflammatory conditions, including Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome. Among patients with symptoms similar to Kawasaki, 26% experienced shock, which is much higher than the 5% commonly seen in patients in the United States with Kawasaki disease shock syndrome.

A British study compared pediatric patients with MIS-C with patients with Kawasaki disease with or without shock and toxic shock syndrome. Patients with MIS-C were older (mean age 9.0 years versus 2.7 years), had more hematological abnormalities and higher levels of troponin and fibrinogen compared to patients with Kawasaki disease. Compared to patients with toxic shock syndrome, patients with MIS-C were older, had deeper anemia and higher levels of CRP and alanine aminotransferase.[14]

Reports of lung imaging abnormalities varied: a meta-analysis showed that 13.7% of patients with MIS-C had X-rays or computed tomography, which is less than in acute COVID-19. A recent study comparing severe acute COVID-19 with MIS-C in one large cohort (n = 1116) revealed a similarity in the incidence of infiltrates on a chest X-ray: 37% of acute severe COVID-19 compared with 38% of patients with MIS-C.

Echocardiography can reveal a decrease in the LV ejection fraction and coronary artery ectasia or aneurysm. Arrhythmias have been reported, usually during acute illness, and ACR

guidelines recommend receiving electrocardiograms every 48 hours during hospitalization and subsequent visits, escalating to telemetry and possible outpatient Holter monitoring for patients with conduction disorders. Echocardiograms are also recommended at diagnosis and during follow-up, including at least 1-2 weeks and 4-6 weeks after admission to the hospital.

Recommendations for the treatment of MIS-C include the administration of intravenous immunoglobulins (IVIG, 2 g/ kg per ideal body weight), which may need to be administered slowly to people with impaired cardiac function. For patients with moderate and severe symptoms, IVIG with GC is a first-level therapy. GC can also be prescribed for refractory disease in low and medium doses from 1 to 2 mg / kg / day with a gradual dose reduction over 2-3 weeks.

Antiplatelet therapy and anticoagulants may be indicated for patients with MIS-C. Low doses of aspirin from 3 to 5 mg/ kg/day to a maximum dose of 81 mg are also recommended in patients with signs of Kawasaki disease, coronary artery aneurysm or thrombocytosis. Anticoagulant therapy should be initiated in patients with a coronary artery aneurysm with a z-index of more than 10 and considered in patients with a LV ejection fraction of less than 35%. If vasopressors are required, epinephrine is recommended, followed by norepinephrine; dobutamine may also be effective for patients with severe myocardial dysfunction.

A study conducted at the beginning of the pandemic showed that 80% of patients needed hospitalization in the intensive care unit. The cardiovascular load in MIS-C is significant. In the European cohort study, the most frequent findings in MIS-C were shock, arrhythmias, pericardial effusion and coronary artery aneurysm. Studies have also shown that elevated levels of CRP, ferritin, d-dimer, and markers of cardiac damage (troponin, B-type natriuretic peptide, and pro-B-type natriuretic peptide) were associated with decreased cardiac function in a cohort of more than 1,000 people. There are also reports of venous thromboembolism in 6.5% of patients with MIS-C compared with 2.1% in symptomatic and 0.7% in asymptomatic cases of COVID-19.[15]

CONCLUSION

The manifestations of COVID-19 in children are usually milder than in adults, although severe cases can occur in healthy children and more often in children with concomitant diseases. MIS-C is a post-infectious hyperinflammatory syndrome that occurs a few weeks after exposure to SARS-CoV-2, which has distinct clinical signs, including gastrointestinal, skin-mucosal and cardiac symptoms, and is characterized by a high level of inflammation. Further research is needed to determine the optimal treatment methods for COVID-19 and MIS-C in children.

AUTHOR CONTRIBUTIONS

All authors contributed in reviewing the final version of this paper.

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