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Coronavirus disease 2019: A new pediatric challenge

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ABSTRACT

Coronavirus disease 2019 (COVID 19) is a pandemic disease that is today a global public health problem caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2). COVID-19 is a disease of middle and old age, but clinical expression may also be present in childhood. Asymptomatic and mild clinical forms are most often present in persons aged 0-19, but severe clinical forms such as, among others, acute respiratory distress syndrome and multisystem inflammatory syndrome may occur. In addition to presenting the epidemiology, clinical symptomatology of COVID-19, the authors consider certain specifics of COVID-19, that is, possible reasons for the lower incidence of the disease as well as unusual and rare clinical forms of the disease in children. The current activities of health professionals in the supervision of COVID-19 are mainly focused on early detection, isolation and treatment of patients, isolation of contacts, the regular and thorough practice of respiratory hygiene, hand hygiene, and physical distancing. Future efficient and safe vaccination will solve the biggest global medical challenge caused by the new coronavirus in the best possible manner.

Keywords: COVID-19; children; specificity; epidemiology; protective factors

INTRODUCTION

The first cases of coronavirus disease 2019 (COVID-19) disease appeared in late December 2019 in the Chinese city of Wuhan, where a group of patients with pneumonia of unknown etiology was observed (1). In February 2020, the World Health Organization (WHO) named the new coronavirus SARS-CoV-2, and the disease caused by SARS-CoV-2 was called COVID-19 (2). Given the trend of rapid global expansion and "sustainable transmission around the world," in mid-March 2020, the WHO declared a state of pandemic (3). In approximately 190 countries of the world as of 24.5 in 2020, >5,000,000 cases of COVID-19 were confirmed, the number of deaths was 337,736, in BiH in the mentioned period, there were 2371 confirmed cases and 140 died of COVID-19 (4).

The age distribution of COVID infection is 1.5 months up to 96 years, without a difference in gender distribution, with severe forms are more pronounced in adults of age over 60 years and in patients with comorbidities present (5). A severe clinical picture of COVID-19 may be present from

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an early age, as indicated by the De Biasi et al. study (6) that 32% of infants were hospitalized due to the severity of the disease. With the tendency of increasing pandemic proportions, the number of patients in children with a predominance of mild forms of COVID-19 is increasing. In the previously published studies, the prevalence was: 1.7% of children <18 years of age in the USA, in the Netherlands <1% of children, while according to a large observational study in the UK, 2.0% of children (7). Population studies in Iceland Gudbjartsson et al. found that no child under the age of 10 was infected with the new coronavirus versus ~1% of infected adolescents and adults (8). It is estimated that ≥90% of children have asymptomatic, mild, or moderate forms of COVID-19, but severe forms of the disease are more pronounced in infants versus children 11-15 years and ≥16 years (11% vs. 4% and 3%) (9).

Given that the epidemiological distribution and spectrum of clinical expression of COVID-19 in children are insufficiently known, this article aims to present certain specifics of COVID-19 in children following relevant references – lower disease distribution, milder clinical form, and unusual and rare clinical forms of the disease.

EPIDEMIOLOGY OF COVID-19

Human coronaviruses

Human coronaviruses were discovered in 1960 and HCoVs-229E, HKU1, NL63, and OC43C are the most commonly isolated human strains that cause around 20% of upper respiratory tract infections in children, 13% of children are asymptomatic, and 10-50% of children with symptoms have association of these strains with other respiratory viruses (10).

These strains of coronavirus most commonly affect children <3 years of age with congenital heart disease (10).

Chan et al. (11) found that the SARS-CoV-2 genome isolated from a group of Wuhan patients with atypical pneumonia has 89% identical SARS-CoVZXC21 bat nucleotides and 82% identical SARS-CoV nucleotides, indicating, among other things, that a new primary reserve is a possible reserve. Bat. SARS-COV-2 can be transmitted from bats to an intermediate host (supposedly pangolin) and from them to humans (12).

It is considered that SARS-CoV-2 can be stable ~ 3 hours in the air, ~ 4 hours on copper, ~ 24 hours on cardboard, and ~ 2-3 days on stainless steel and plastic materials ~ 3 days (13). SARS-CoV, presumably SARS-CoV-2, can be efficiently inactivated by lipid solvents, including 75% ether, ethanol, disinfectants containing chloroquine, peracetic acid, and chloroform other than chlorhexidine (14).

COVID-19 transmission

The transmission of SARS-COV-2 follows the usual pattern of transmission of respiratory infections. The main source of infection is a patient infected with SARS-COV2, but it is thought that asymptomatic individuals may also play a significant role in the spread of COVID-19 (10,15). According to Cruz and Zeichner (16), in children infected with COVID-19, the upper respiratory tract versus lower respiratory tract and also SARS-CoV-2 may be present in the stool for several weeks after the detection of COVID-19. This implies the possibility of fecal-oral transmission of COVID-19 which may play a role in disease transmission this way in homes, kindergartens, and schools (10,15,16).

It is thought that 1-2 days before the onset of COVID-19 symptomatology, the transmission of COVID-19 is possible, indicating the importance of detecting asymptomatic and symptomatic individuals at an early stage to prevent or reduce the spread of COVID-19 (17,18).

Approximately ~ 80% of children are infected with SARS-CoV-2 in contact with household members, children most often have clinically visible symptoms before family contact which may indicate that asymptomatic children are not a significant source of SARS-CoV-2 infection (10).

Previous research has not indicated vertical transmission of SARS-COV-2, nor the possibility of spreading through breast milk (9,15), which future extensive research will confirm or rule out, nor the hypothetical possibility of spreading this disease through blood and consuming thermally inadequately processed foods of animal origin.

COVID-19 CLINICAL FORMS IN CHILDREN

Analyzing the symptoms in children, it was found that, among other things, fever is present in 40-60% of children, cough occurs in 40-50% of children, and headache, myalgia, and sore throat are more common than shortness of breath (10,19). Usually, after 7-10 days (10), children recover, and more severe forms are characterized by dyspnea, hypoxia, cyanosis, dehydration with signs of respiratory distress syndrome, shock, myocardial lesions, or multiorgan failure (20,21).

Cai et al. (5) described five cases of COVID-19 disease in children with initial nonrespiratory symptoms, that is, blood in the stool such as raspberry jelly, abdominal pain, convulsions, vomiting and diarrhea, drowsiness, and decreased appetite.

The research of Wu et al. (22) indicates that conjunctivitis and eyelid dermatitis may indicate COVID-19, as confirmed by molecular testing, real-time polymerase chain reaction (RT-PCR) on SARS-CoV-2.

Collona et al. in Italy, it describes frost-like changes in four children aged 5-11 years with mild symptoms of COVID infection, which they explained by a vaso-occlusive phenomenon due to elevated d-dimers (23).

Andina et al. (24) reported identical changes in Madrid in 22 children aged 6-17 years with moderate symptoms of COVID-19 disease. These atypical manifestations of COVID-19 disease did not require treatment and had a good prognosis (23,24).

Most children with a proven COVID infection are asymptomatic or have mild symptoms. However, a small number of children have been identified in the past 2 months with a developed multisystem inflammatory response to SARS-COV-2, which has featured in common with Kawasaki disease, staphylococcal and streptococcal toxic shock syndrome, bacterial sepsis, and macrophage activation syndrome (25). Kawasaki disease is a generalized febrile illness in children <5 years characterized by fever, skin rash, lymphadenopathy, and conjunctivitis. In severe cases of Kawasaki disease, inflammation of the coronary arteries occurs, which spreads, causing a coronary artery aneurysm with the possibility of myocardial infarction in children, which is verified by ultrasound Color Doppler examination of the heart (7,26-28). Kawasaki is not an infectious but a reactive disease, which is treated with immunoglobulins, corticosteroids, and aspirin (27,28).

Licciardi et al. (29) described in two children (7 year and 2-year-old boys) Kawasaki-like hyperinflammatory syndrome as a delayed response to SARS-COV2- infection, which manifested itself, among other things, mucocutaneous changes, elevated markers of inflammation, lymphopenia, thrombocytopenia, and complement consumption with myocarditis. PCR test for SARS-CoV-2 was negative, while had high titers of IgG and IgM on the SARS-CoV-2 virus. They were successfully treated with intravenous corticosteroids and immunoglobulin (29).

Multisystemic inflammatory syndrome (MIS-C) should be considered in children with COVID-19 if age <21 years, have persistent fever, positive inflammatory markers (elevated CRP, accelerated erythrocyte sedimentation rate, elevated fibrinogen, ferritin, LDH or IL-6, neutrophilia, lymphopenia, and hypoalbuminemia), present clinically severe disease requiring hospitalization involving ≥ two organ systems (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological, or neurological) but without any other probable cause with a positive epidemiological survey on COVID-19 or positive molecular or serological test for SARS-COV-2 (30). In cases of death of a child with a proven SARS-COV-2 infection, the possibility of a multisystem inflammatory syndrome (30) should be considered.

This indicates that in some children we can expect an unusual and rare response to etiological factors, including SARS-COV-2, and in the supervision of children with COVID-19, it is necessary to know and timely apply recent diagnostic and therapeutic guidelines, detailed multidisciplinary approach to the sick child and parents and the practice of recommended anti-epidemic measures in the control of COVID-19 infection.

WHY COVID-19 IS MOST COMMONLY MANIFESTED AS MILD DISEASE IN CHILDREN, WITHOUT FREQUENCY CLINICAL EXPRESSION?

One of the hypothetical questions is why children have a lower incidence of clinically manifested

disease, or why is COVID-19 a mild disease in children?

It is believed that children have a qualitatively different response to SARS-CoV-2 compared to adults, which may be related to the characteristics of their immune system to better control and localize COVID infection to the upper respiratory tract resulting in milder cold-like infections (31-33). It is likely that the simultaneous presence of common strains of coronavirus and other respiratory viruses in the lung and airway mucosa, which are common in children, may limit the growth of SARS-CoV-2 due to direct interaction, competition, and cross-immune protection (33,34), future research will likely be able to provide a more accurate response to the distribution and course of COVID-19 infection in neonates and young children, who have not been exposed to common coronaviruses and other respiratory viruses, and some viral infections are known to result in more severe respiratory infections (RSV) and respiratory failure.

The lower incidence of disease and presentation of mild forms of COVID-19 in children may be related to differences in the expression of angiotensin-converting enzyme-2 (ACE-2), a receptor required for the binding and entry of SARS-CoV-2 into human cells (31,32). A hypothetically insufficient number of ACE-2 receptors in the lungs of children in addition to the above allows limiting COVID-19 to milder acute upper respiratory tract infections versus lower respiratory tract infections in adults which future research will confirm or rule out (31,32,35).

Liu et al. (36) stated a link between the number of viral copies and the severity of COVID-19 expression, which should be taken into consideration in disease severity in children and adults.

In this context, Brodin (32) believes that some tragic deaths of healthcare workers may be caused by exposure to large amounts of SARS-CoV-2 virus.

Possible protection factors (31), which can lead to lower incidence, mostly mild forms, COVID-19 in children, are also a strong innate immune response, immune training, which may be associated with previously given BCG and MMR vaccines, as well as previous exposure to respiratory viruses.

With aging, there are changes in innate and adaptive immunity, and adults are more susceptible to severe infections and even severe forms of COVID-19 due to the large release of cytokines (cytokine storm) from macrophages, monocytes, and lymphocytes, leading to lung tissue damage and multiorgan failure (31,37). In addition, alveolar epithelial cells in children have great regenerative potential, and most children do not have certain risk factors (smoking and obesity) and comorbidities versus adults which may play a role in the greater expression of more severe clinical forms of COVID-19 in adults (31,35).

Present symptomatology, as well as clear or suspicious epidemiological survey, indicates the use of RT-PCR from nasopharyngeal or throat swabs, and in suspected cases with initial negative findings of RT-PCR from nasopharyngeal swabs, lower airway aspirate (10) may be used. Given that most children are asymptomatic or have mild symptoms, and no RT-PCR is performed, this may play a role in assessing the prevalence of COVID-19 infection in children. We believe that future more extensive serological tests, enzyme-linked immunosorbent assay, and neutralization assay, of adequate reliability and accuracy, will answer many hypothetical questions about COVID-19 infection, for example, distribution of infected children as well as other populations; duration of specific protection; the role of asymptomatic children in disease transmission and tests may be predictors of pandemic duration and potential reinfection.

Since SARS-CoV-2 is a new virus and we have never been in contact with it, the body has no antibodies to neutralize the virus. SARS-CoV-2 will spread until an effective vaccine is detected or until a sufficient number of individuals are infected to create adequate collective immunity for further effective surveillance of COVID-19. Current activities are focused on early detection, isolation and treatment of patients, isolation of contacts, the practice of physical distance, regular and thorough respiratory hygiene, hand hygiene and disinfection of space, and work surfaces that have reduced that COVID-19 disease does not spread exponentially, that is, that the basic reproductive number (RO) for SARS-CoV-2 be <1 so that the mass occurrence of the disease gradually disappears.

CONCLUSION

COVID-19 is a new infectious disease with insufficiently known epidemiological characteristics

and spectrum of clinical expression in childhood. Current findings indicate that children have a lower incidence of the disease with a predominance of mild forms of the disease. Practitioners should consider the possibility of COVID-19 in children with atypical symptomatology with a positive or suspicious epidemiological survey. We believe that massive serological testing for SARS-CoV-2 will enable timely and more accurate diagnosis of COVID-19, assess the importance of protective antibodies, more realistically assess the distribution of COVID-19, and the role of asymptomatic children in disease transmission. We are confident that COVID-19 vaccine will successfully address the biggest global challenge we face.

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