

PECULIARITIES OF THE CORONAVIRUS INFECTION CLINICAL COURSE CAUSED BY SARS-COV2 IN CHILDREN POPULATION (LITERARY REVIEW)

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The coronavirus SARS has been known since 2002. In 2019 the rapid spread of the virus SARS-CoV-2 caused a global pandemic. The article provides an analysis of information on the origin and structure of the virus, discusses the epidemiological aspects of coronavirus infection and the main links of pathogenesis, describes data on the main clinical manifestations of SARS-CoV-2 in children and the long-term consequences of the disease, such as multisystem inflammatory syndrome in children and adolescents (MIS-C), focused attention on diagnostic tools, methods of treatment and prevention.

The purpose – to analyze and summarize information about the peculiarities of the course of the coronavirus infection caused by the SARS-CoV-2 virus among children, its epidemiological characteristics and means of prevention.

Conclusions. 1. Knowledge of the epidemiological and clinical features of the novel coronavirus disease COVID-19 in the child population needs constant updating, as many aspects of the clinical course of infection in children remain unclear. 2. CoV-2 affects children less frequently and less aggressively than adults, with very low mortality, which may be due to a rarer exposure to major sources of transmission (e.g. nosocomial) and a predisposition to significantly milder disease symptoms. 3. Laboratory and radiological findings in sick children with symptoms are mostly non-specific, but they can help identify patients in severe conditions. 4. Due to mutations of the virus, scientific studies of the clinical and pathogenetic features of the course and prevention of COVID-19 continue, because the consequences of the transferred disease require further study. 5. Vaccination of children today is one of the important preventive measures to prevent the complicated course of acute respiratory disease associated with SARS-CoV-2.

Key words:

SARS-CoV-2 coronavirus, children, characteristics of the virus, epidemiology, pathogenesis, symptom complex, treatment, vaccination.

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ОСОБЛИВОСТІ КЛІНІЧНОГО ПЕРЕБІГУ КОРОНАВІРУСНОЇ ІНФЕКЦІЇ, СПРИЧИНЕНОЇ SARS-COV2, У ДИТЯЧОГО НАСЕЛЕННЯ

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Коронавірус SARS відомий ще з 2002 року. У 2019 році стрімке поширення вірусу SARS-CoV-2 стало причиною світової пандемії. У статті наведений аналіз інформації щодо походження та будови вірусу, обговорено епідеміологічні аспекти коронавірусної інфекції та основні ланки патогенезу, узагальнено дані щодо основних клінічних проявів SARS-CoV-2 у дітей та віддалених наслідків захворювання, таких як мультисистемний запальний синдром у дітей та підлітків (MIS-C), сфокусовано увагу на засобах діагностики, методах лікування та профілактики.

Мета роботи – проаналізувати та узагальнити інформацію про особливості перебігу коронавірусної інфекції, спричиненої вірусом SARS-CoV-2, серед дитячого населення, її епідеміологічні характеристики та засоби профілактики.

Висновки. 1. Знання епідеміологічних та клінічних особливостей нової коронавірусної хвороби COVID-19 у дитячого населення потребують постійного оновлення, оскільки багато аспектів клінічного перебігу інфекції у дітей залишаються незрозумілими. 2. CoV-2 вражає дітей рідше і менш агресивно, ніж дорослих, із дуже низькою смертністю, що може бути пов'язано з рідшим впливом основних джерел передачі (наприклад, внутрішньолікарняного) і схильністю до значно слабших симптомів захворювання. 3. Лабораторні та рентгенологічні дані у хворих дітей із симптомами переважно неспецифічні, але вони можуть допомогти виявити пацієнтів у тяжких станах. 4. У зв'язку з мутаціями вірусу наукові дослідження клініко-патогенетичних особливостей перебігу та профілактики COVID-19 продовжуються, адже наслідки перенесеного захворювання потребують подальшого вивчення. 5. Вакцинація дітей на сьогодні є одним із важливих профілактичних заходів із запобігання ускладненого перебігу гострого респіраторного захворювання, асоційованого із SARS-CoV-2.

Ключові слова:

коронавірус SARS-CoV-2, діти, характеристика вірусу, епідеміологія, патогенез, симптомокомплекс, лікування, вакцинація

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Introduction

In 2002 the virus of severe acute respiratory syndrome (SARS) occurred in the province of Guangdong, China [1, 2]. Ten years later, in 2012 the Middle East respiratory syndrome coronavirus (MERS-CoV) appeared as a zoonotic infection in the Middle East transmitted from bats to people. According to the literary data MERS-CoV infected the respiratory tract epithelial cells through the receptors of dipeptidyl-peptidase 4 and CD26, causing 806 lethal outcomes [3]. At the end of December 2019 one more extraordinary focus of infection occurred which rapidly became pandemic caused by the new coronavirus – SARS-CoV-2. From the clinical point of view it is characterized by severe acute respiratory syndrome and high mortality [4].

SARS-CoV-2 belongs to *Coronaviridae* family, possessing 50 % and 79 % likelihood of the viruses MERS and SARS respectively, but the new virus SARS-CoV-2 has exceeded severity of SARS and MERS. The pandemic caused by the circulation of SARS-CoV-2 has become a global problem due to a high frequency of genomic mutations in the viral RNA and evolution of spike proteins [5].

SARS-CoV-2 (125 nm in size) is 96,3 % identical with the coronavirus of bats RaTG13. The virus possesses the membrane, non-segmental phosphorylated nucleocapsid covered with single-stranded genomes of RNA 26-32 kb long. Similar to all the coronaviruses in general, the virus consists of several proteins [6]:

- (1) N (nucleocapsid) protein stabilizing RNA;
- (2) glycoprotein S (spike) forming pleplomers and promoting virus attack and fusion with the host cellular membrane;
- (3) membrane (M) protein essential for collecting the virus;
- (4) envelope (E) protein – a component of the membrane;
- (5) hemagglutinin-BE participating in the virus release.

Glycoprotein S in the structure of SARS-CoV-2 consists of two, and S2 are connected together by polybasic amino acid bridge [7]. Glycoprotein S has a property to promote virus penetration through the receptor of the cellular surface presented by angiotensin converting enzyme-2 (ACE2) [8]. Expression and spread of the input receptors in the host body can influence on pathogenicity and tropism of the virus. A specific feature of SARS-CoV2 causative agent is known its much higher affinity to binding with ACE2 receptors than SARS-CoV, and monoclonal antibodies against a binding domain of SARS-CoV receptor are not able to effectively bind S-protein SARS-CoV2 [9], which enables S1 subunit of S protein representing the domain of the receptor binding with ACE2 to function more effectively [10]. Moreover, S-proteins of the coronavirus stimulate evasion of the causative agent from the immune mechanisms protecting its epitopes against neutralization by antibodies [11], though the serum of patients with COVID-19 is able to neutralize SARS-CoV [8].

The viruses can break interferon (IFN) synthesis initiated by identification of pathogenic components by means of pattern recognition receptors (PRR) [12]. Since interferons play a crucial role for the natural immunity and have a deep influence on the adaptive immune response,

disturbance of their synthesis promotes a successful reproduction of viruses. In addition, viral causative agents are able to synthesize proteins that resist interferon protection [13]. Thus, according to the latest information [14] viruses can prevent sounding of its genetic material, deteriorate signal cascade resulting in the induction of IFN-I and/or antagonize activity of transcription factors participating in the expression of IFN-I gene. The viruses are also able to code proteins [15] which help them to survive and avoid identification. Viruses often interfere into various ways of interferonogenesis in order to avoid elimination due to the mechanisms of natural immunity. The importance of IFN system in the host antiviral response is emphasized by the fact that viruses give a part of their genetic material to code IFN antagonists.

The mechanism of infection by SARS-CoV-2 has not been studied completely yet, but coronavirus S-glycoprotein (S1 and S2 subunits) is known to bind with the cellular receptors (ACE2), resulting in the penetration inside of the cell which initiates taking the virus nucleocapsid into pieces to release the genome of the virus RNA [16]. Receptors ACE2 located in the wall of the respiratory organs and intestine appeared to be the most potential receptors for invasion of SARS-CoV-2. Expression of ACE2 is the highest on the apical surface of well differentiated epithelial cells lining the respiratory tract, and especially the alveoli of the lungs – the main target of SARS-CoV-2. Recently a pronounced expression has been found in the mucous membrane of the mouth and tongue as well which is indicative of the fact that the oral cavity is a potential way of infection [17].

After damage of the epithelial cells induced by the virus the enzymatic activity of ACE2 decreases considerably [18], which is manifested by the reduction of its protective function, and concerning the control over pronounced inflammatory reaction in particular, which is especially important with maturation and aging of the host organism.

Other viral proteins help to pack new viral particles. Three-dimensional S-protein consisting of 1160-1400 amino acids transformed into trans-membrane glycoproteins of S1 and S2 types by means of the viral protease enzyme.

The purpose

To analyze and summarize information about the peculiarities of the course of the coronavirus infection caused by the SARS-CoV-2 virus among children, its epidemiological characteristics and means of prevention.

Main part

The incubation period of SARS-CoV-2 is from 2 to 11 days (on an average it lasts during five days till the clinical manifestation of the disease), and recovery of the infected individuals takes from 12 to 32 days. Elderly people, individuals with diabetes mellitus are at a higher risk of infection by SARS-CoV-2 and unfavorable consequences of the disease.

Viral RNA in the ground of recovery and lack of the symptoms of COVID-19 can circulate in the blood up to 29 days.

The main attack of SARS-CoV-2, initiated by the use of angiotensin converting enzyme-2 (ACE2) and TMPRSS2 receptors [4], is directed to the respiratory tract through the affliction of the ciliated epithelium cells. The virus produces a powerful pathogenic effect on the respiratory passages and digestive tract associated with a number of specific symptoms and symptom complexes, in particular: dry cough, signs of cold, pneumonia, headache, fever, pain in the throat, dyspnea, pulmonary edema, renal dysfunction, weakness, diarrhea, hemorrhages, multiple and various neurologic disorders, anosmia, lack of taste etc. Computed tomography of the chest finds interstitial infiltrates, and multiple spotted opacities in the lung fields. Laboratory examination finds the signs of disorders from the side of humoral and adaptive immunity. Numerous complications of COVID-19 result in the development of multiple organ failure that might have lethal outcomes [19]. Thus, the rate and severity of kidney damage in this infection is compared by certain researchers with one in case of sepsis by the parameters of severity and lethality [20].

In spite of a global interest and worries concerning COVID-19, clinical manifestation of the diseases among the children population still remains not completely understood by pediatricians. Though the clinical course of COVID-19 in children is more favorable and the indices of sickness and severity are lower than in the adult population, especially among elderly group of people, it does not mean that children are less susceptible to the infection. The number of infected and sick children in future may increase, and first of all children with specific needs or chronic diseases. Relevance of the children population concerning the spread of infection is not determined completely and is not investigated more than in adults [21].

Certain literary sources admit that children suffer from the infection equally with the adults [22]. The latest information is indicative of the possibility to develop multiple organ dysfunctions with SARS-CoV-2 among all the groups of population including children as well [23]. Still a thought dominates that COVID-19 among children has milder clinical course and is associated with much more favorable prognosis concerning recovery [21]. Thus, according to Chinese researchers, among more than two thousand children infected by SARS-CoV-2 13 % were asymptomatic [24].

Generalized data [25] obtained in the course of 49 examinations involving 1780 children aged from 1 month to 18 years showed that a part of severely sick children was about 2 %, very severe – 0,6 % from general sampling. The most frequent symptoms in childhood were fever (51,6 %), cough (47,3 %) and pain in the throat (17,9 %). Sometimes children suffered from dyspnea (7,7 %) and required oxygen support with saturation (SpO₂) lower 92 % (3,3 %). In addition to respiratory symptoms there were diarrhea (9,7 %), vomiting (7,2 %) and weakness (10,6 %). The family epidemiologic anamnesis of a positive contact with sick relatives was found in 73,3 % of cases.

RNA concentration and virus replication are known to be the highest during the first seven days of COVID-19 [26]. Later viral load decreases gradually, transmissibility

reduces, and the virus cannot be isolated from the samples a week later after the symptoms appear [26].

As a rule, children are infected from adults within their families, though they have milder clinical course of the disease. As to the importance of pediatric population as a transmitter of infection it should be noted that infected children having symptoms of the disease or asymptomatic ones potentially can spread the infection, though what a real role of children in transmitting infection SARS-CoV-2 is not clear yet, and the majority of children with verified infection were a part of a family focus [27].

The causes of a relative resistance of children to certain infections remain unknown. Although the mechanisms of this phenomenon are not completely established yet, there are a number of suggestions that are now considered as possible directions to find therapeutic methods to fight infection in case of lack of pediatric effective and safe vaccine.

In this respect it can be explained by a specific role of the natural immunity which (under conditions of imperfect adaptive immune defense) prevails in childhood^[44], and its mechanisms weaken considerably with age and maturation. Therefore, adult response to viral attack is excessive with development of uncontrolled inflammatory cascade which has got the name of «cytokine storm». Acute lung dysfunction occurs due to the changes in oxidation processes resulting in further damage of both tissue and pulmonary function and capacity [28].

Respiratory viruses attacking the lungs cause oxidative stress and activation of inflammation triggering a number of cytokines, for example, IL-1 β and IL-18, playing a critical role. Thus, learning the mechanisms of prooxidant-antioxidant balance with COVID-19 in children should provide additional information concerning the mechanisms of the effect on the formation of acute lung damage with this infection.

The role of co-infection with other viral causative agents is discussed in the scientific literature as well, since children are especially prone to many viral infections with a strong stress on the respiratory system, especially the upper respiratory tract [29]. Thus, contrary to adult patients who did not have any case of a viral co-infection found by a profound virological examination [29], more than two coexisting viruses are identified in the upper respiratory tract of children by means of molecular methods. Under conditions of co-infection there are evidences of synergism or antagonism between coexisting viruses that can play a key role in acute respiratory infection caused by SARS-CoV2. A virus that was the first to colonize the respiratory epithelium of the nasal pharynx is suggested to play a dominant role. It is able to block or decrease invasion of another viral causative agent [30].

The scientific sources available indicate that melatonin inhibits the death of cells caused by the coronavirus; it possesses antioxidant and inhibiting action on the cytokine complex, and prevents formation of secondary pulmonary fibrosis[31]. The night level of melatonin in the blood is known to be considerably higher in children at the age of 1-3 years till 15 years in comparison with

that of adults. A considerable drop of melatonin level occurs after the age of 70. There is a certain negative correlation between the age and melatonin secretion [31]. In fact, children usually demonstrate much higher secretion and activity of melatonin than elderly people, and the latter, contrary to children, have more frequent and more severe form of COVID-19.

The mechanisms of susceptibility to infection of children during their neonatal period of life remain uncertain, since the cases of infection caused by SARS-CoV-2 in neonates are rather rare. To date there is no convincing evidence concerning intrauterine infection of the fetus due to the vertical transmission of the virus from the mother [32]. Certain works showed on a series of cases that amniotic fluid, umbilical blood, throat swabs and colostrum samples collected from infected mothers were negative to COVID-19 [33]. Contrary to the above, other researchers showed the presence of antibodies IgM against SARS-CoV-2 in neonates born from mother with COVID-19. Gradually the evidence of correlation of neonatal pneumonia with SARS-CoV-2 infection has been collected [34]. Thus, in China all the newborns in order to prevent infection and development of pneumonia are isolated from their infected mothers at least for 14 days [35]. Other reports contain the information that similar to the children of an older age the majority of neonates were either asymptomatic (20%), or had mild (48%) and moderate (20%) signs of clinical infection COVID-19. Though severe clinical course of the disease was registered among 12% of neonates with the most frequently found shortness of breath (40%), fever (32%) and disorders of tolerance to food (24%). Laboratory findings determined leukocytosis in the blood in 20% of cases, an elevated level of C-reactive protein and/or procalcitonin – in 12% of observations, a high activity of kreatine-phosphokinase – in 20% of neonates and liver enzymes – in 16% of children [23].

Current studies show that only 2% of patients in childhood were hospitalized to intensive care units or required mechanical ventilation [36]. In general, mortality was 0,08%: the majority of patients developed complications [37], including preterm neonates who died of sepsis [38]. Several clinical trials of drugs for experimental treatment of COVID-19 in children [39] were mainly based on the administration of symptomatic therapy only, and neonates in particular [40]. The therapeutic recommendation concerning treatment of children with COVID-19 still remains the only one:

- administration of nebulizer interferons and oral antiviral means (for example, Lopinavir/Ritonavir) in case of complications (acute respiratory distress syndrome, encephalitis, hemophagocytic syndrome or septic shock);
- administration of intravenous immunoglobulins (IV Ig) in severe clinical cases [41].

Meanwhile, due to a low effect of these therapeutic recommendations in the treatment of SARS-CoV-2, the WHO and CDC today do not recommend any specific treatment of the infection in children [42].

Due to the fact that a number of researchers have accumulated certain experience of SARS-CoV-2 pandemic, it enables to draw a conclusion about

topicality and prospects in the use of interferons as a field of further scientific studies [43], since inhibition of the immune response mechanisms simulated by interferon I under the effect of SARS-CoV-2 have been obtained [44]. A reduced amount of IFN- α/β та IFN- λ in patients with COVID-19 and SARS-CoV-2 is indicated in particular [45], and positive results by means of type I interferons including interferon- β -1a, are obtained in several clinical trials [46]. The results of the studies concerning interferon therapy with COVID-19 were presented in certain publications [47] and systematic examinations [48].

Currently, according to CDC recommendations, starting from 1 November 2023, for the treatment of mild to moderate severity of COVID-19 in non-hospitalised adolescents aged 12 to 17 years, ≥ 40 kg of nirmatrelvir-enhanced ritonavir may be used.

To prevent the complicated course of acute respiratory disease, associated with the SARS-CoV2 virus, starting from 2021, vaccines that have passed quality control by the CDC and the US Food and Drug Administration (FDA) are recommended. As of September 12, 2023, the CDC recommends updated COVID-19 vaccines for 2023-2024: Pfizer-BioNTech, Moderna or Novavax.

Conclusions

1. Knowledge of the epidemiological and clinical features of the novel coronavirus disease COVID-19 in the child population needs constant updating, as many aspects of the clinical course of infection in children remain unclear.

2. CoV-2 affects children less frequently and less aggressively than adults, with very low mortality, which may be due to a rarer exposure to major sources of transmission (e.g. nosocomial) and a predisposition to significantly milder disease symptoms.

3. Laboratory and radiological findings in sick children with symptoms are mostly non-specific, but they can help identify patients in severe conditions.

4. Due to mutations of the virus, scientific studies of the clinical and pathogenetic features of the course and prevention of COVID-19 continue, because the consequences of the transferred disease require further study.

5. Vaccination of children today is one of the important preventive measures to prevent the complicated course of acute respiratory disease associated with SARS-CoV-2.

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