CURRENT UNDERSTANDING OF EPIDEMIOLOGY AND PATHOGENESIS OF MULTISYSTEM INFLAMMATORY SYNDROME ASSOCIATED WITH SARS-COV-2 IN CHILDREN

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The review is dedicated to matters related to epidemiology and pathogenesis of multisystem inflammatory syndrome associated with SARS-CoV-2 in children (MIS-C). The majority of the reviewed reports are focused on immunopathogenesis of the disease. The causes of the syndrome related to the features of the virus are listed in the paper, the association with circulating variants is described. The role of the SARS-CoV-2 surface protein as superantigen is considered. The literature data on the likelihood of MIS-C development according to the antibody-dependent enhancement pattern are discussed. The factors of cellular and humoral immune response contributing to hyperinflammation are addressed. Sporadic papers describing genetic mutations that can play a certain role in the MIS-C pathogenesis are provided. Furthermore, the association of vaccination against novel coronavirus infection with the likelihood of MIS-C in vaccinated individuals is discussed.

Keywords: children, multisystem inflammatory syndrome, pathogenesis, SARS-CoV-2, COVID-19

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СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ ОБ ЭПИДЕМИОЛОГИИ И ПАТОГЕНЕЗЕ МУЛЬТИСИСТЕМНОГО ВОСПАЛИТЕЛЬНОГО СИНДРОМА У ДЕТЕЙ, АССОЦИИРОВАННОГО С SARS-COV-2

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Обзор посвящен вопросам эпидемиологии и патогенеза мультисистемного воспалительного синдрома у детей, ассоциированного с SARS-CoV-2 (МВС-Д). Наибольшее число проанализированных публикаций посвящено иммунопатогенезу заболевания. В статье перечислены возможные причины возникновения синдрома, связанные с особенностями вируса, описана связь с циркулирующими вариантами. Рассмотрена роль поверхностного белка SARS-CoV-2 как суперантигена. Приведено обсуждение литературных данных о возможности развития МВС-Д по механизму антителозависимого усиления инфекции. Разобраны факторы клеточного и гуморального иммунного ответа, способствующие развитию гипервоспалительного ответа. Представлены единичные работы, описывающие генетические мутации, которые могут играть определенную роль в патогенезе МВС-Д. Помимо этого рассмотрена связь между вакцинацией против новой коронавирусной инфекции и вероятностью развития МВС-Д у привитых.

Ключевые слова: дети, мультисистемный воспалительный синдром, патогенез, SARS-CoV-2, COVID-19

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The multisystem inflammatory syndrome associated with SARS-CoV-2 in children (MIS-C) is the condition occurring within 2–6 weeks after novel coronavirus infection caused by SARS-CoV-2 (COVID-19), it is characterized by severe inflammation affecting two or more organs or systems (mostly skin, mucous membranes, cardiovascular system, gastrointestinal tract). According to the data reported by various authors, 36–80% of patients are admitted to intensive care units (ICU), 10–20% of children need mechanical ventilation (MV), about 1% need extracorporeal membrane oxygenation (ECMO) [1–3]. Researchers still have no consensus whether MIS-C is a complication of COVID-19 or a distinct nosological entity.

MIS-C was first reported in school-age children by researchers from the UK in the beginning of the COVID-19 pandemic [4]. To date, the development of this syndrome has been reported in patients of various age cohorts, including newborns and young adults, however, MIS-C is most often found in children and adolescents [5, 6].

Today, criteria issued by the World Health Organization (WHO) [7] also provided in domestic guidelines [8] are used to diagnose MIS-C in most countries of the world, including the Russian Federation. According to these criteria, MIS-C occurs 2–6 weeks after recovery from COVID-19, most often in children and adolescents aged 0–19. It is characterized by pyretic fever (≥ 3 days), involvement of two or more organs or systems, elevated levels of inflammatory markers, and no information about the presence of infectious agents capable of causing such symptoms [7].

As defined by the US Centers for Disease Control and Prevention (CDC), MIS-C is a clinically severe disorder characterized by fever, elevated levels of inflammatory markers, and impaired function of several organs and systems, which requires hospitalization of the patient. It develops against the background of recent confirmed or probable COVID-19, while there is no other possible explanation of the disease clinical manifestations [9].

Etiology

Regardless of the MIS-C definition used, both options imply that the disease occurs due to prior SARS-CoV-2 infection regardless of the previous COVID-19 severity. The detection of specific immunoglobulins G (IgG) against novel coronavirus in the majority of patients is evident of the association between the disease developed and previous COVID-19. The presence of acute infection markers (IgM against SARS-CoV-2 and extraction of SARS-CoV-2 RNA) was reported only in 5–10% of sick children. These patients were clinically consistent with the MIS-C criteria, and the more thorough questioning showed that children had recently had COVID-19 or were in contact with COVID-19 patients [10].

In the beginning of the pandemic the evidence of contact with the COVID-19 patient within four weeks before developing the symptoms was enough to diagnose MIS-C as one of the criteria due to high incidence of the infection. Meanwhile, additional information is currently required to determine the association between MIS-C and previous COVID-19, which is due to a number of reasons. After three years from the beginning of the pandemic more than 80% of the population have IgG against SARS-CoV-2; IgM fade away within 3–4 weeks since the moment of infection and most often are not detected in the midst of MIS-C, that is why serological tests are not representative in such cases [11].

Second, the number of COVID-19 cases is decreasing, COVID-19 is becoming a seasonal respiratory infection by integrating into the structure of numerous viral infections manifested by respiratory tract involvement. As for daily practice, etiological decoding of uncomplicated acute respiratory tract infections is extremely rare, especially in outpatient practice, which is explained by both economic reasons and the results' negligible impact on the treatment tactics. That is why patients are less frequently tested for SARS-CoV-2.

Third, MIS-C is similar to other disorders characterized by severe inflammatory response (staphylococcal or streptococcal toxic shock syndrome, hemophagocytic syndrome, Kawasaki disease (KD), bacterial sepsis, etc.) in terms of clinical manifestations, which makes it more difficult to diagnose the syndrome [12, 13]. The case reports of viral infection (adenovirus, cytomegalovirus, Epstein–Barr virus) with the course similar to multisystem inflammatory syndrome were found in the literature before the pandemic, however, pathogenesis of this condition was also poorly understood. This resulted in controversy in the scientific community regarding the role of other infectious agents in the MIS-C development [14–16].

The researchers assumed the role of additional infectious agent in the MIS-C realization [17]. The authors of the report considered the probability that additional infectious agent acted as a trigger in patients having the history of COVID-19. Superinfection can trigger an acute inflammatory episode of MIS-C. Furthermore, despite the fact that no signs of the herpesvirus reactivation or persistent viral or bacterial infection have been found in the patients' peripheral blood, this theory also requires further research.

Understanding the causes of MIS-C is essential for development of optimal tactics for therapeutic interventions in patients with this disorder. Despite the symptoms' similarity, the MIS-C treatment is dramatically different from therapy of the number of conditions, such as sepsis, with which it is most often necessary to carry out differential diagnosis. Exclusion of bacterial pathogens that are significant for the syndrome development makes it possible to avoid antibacterial therapy; the symptoms are stopped after administration of high-dose intravenous immunoglobulins, systemic glucocorticoids, and, in rare cases, inhibitors of interleukin-6 (IL6) and interleukin-1 (IL1) receptor antagonists. By analogy with the KD therapy, acetylsalicylic acid is prescribed to prevent thromboembolic complications [8]. Untimely diagnosis results in delayed prescription of essential therapy, thereby adversely affecting the disease outcomes and prognosis.

Epidemiology

Since etiological diagnosis of MIS-C is difficult, and clinically the syndrome has no pathognomonic signs and is similar to other disorders characterized by severe inflammation, true MIS-C incidence in the population is likely to be underestimated. Foreign research has shown that the prevalence of the syndrome is 2 cases per 100,000 population under the age of 21 years [1] or less than 1% of children having a history of COVID-19 [2].

A total of 230 MIS-C cases were reported in Europe and the UK by 15 May 2020 (within a month after the first reported case), among which two (one in the UK and one in France) were fatal (0.87%) [18].

According to the data posted on the CDC official website (as at 3 July 2023), a total of 9499 MIS-C cases were reported in the USA, 79 children died (0.83%). The syndrome detection rate varied significantly from state to state. The largest number of cases was reported in such states, as California (more than 800) and Texas (600–800). About 46% of patients were children aged 5–11, among them boys prevailed (60%). About 57% of patients were of Hispanic ancestry (2358 children) or were African Americans of non-Hispanic ancestry (2720 individuals) [8].

The Public Health Agency of Canada reported 269 MIS-C cases between 11 March 2020 and 2 October 2021. The association with previous COVID-19 was confirmed by epidemiology data or laboratory tests only in 142 individuals (53%). The average age of patients was 6 years, among them boys prevailed (58%). A total of 36% of patients needed admission to ICU [19].

Following identification of various SARS-CoV-2 variants, there had been emerging evidence of the relationship between certain virus variants and the MIS-C detection rate. According to the data provided by CDC, the largest number of cases in the USA was reported between October 2020 and May 2021 following the rise in COVID-19 incidence caused by the "alpha" variant. The second "wave" of MIS-C took place in September–November 2021 during circulation of the "delta" variant, and the third one occurred between December 2021 and March 2022, immediately after the incidence peak caused by the "omicron" variant. Sporadic MIS-C cases have been reported since February 2023 [8].

The studies conducted in Canada have also revealed several incidence peaks: peak in May 2020 associated with the Wuhan variant and two waves, between November 2020 to March 2021 and in May 2021, caused by "alpha" variant [18].

Comparative analysis of the MIS-C incidence in the UK conducted by the research team [20] showed that number of the disease cases caused by "delta" variant was 56% lower before the start of mass vaccination and 66% lower after the start of mass vaccination relative to the wave caused by "alpha" variant; the number of cases caused by "omicron" variant was 95% lower.

Similar data were obtained in Australia. The Australian Paediatric Active Enhanced Disease Surveillance network (PAEDS) revealed only 95 MIS-C cases between 1 May 2020 and 30 April 2022. In New South Wales, Queensland

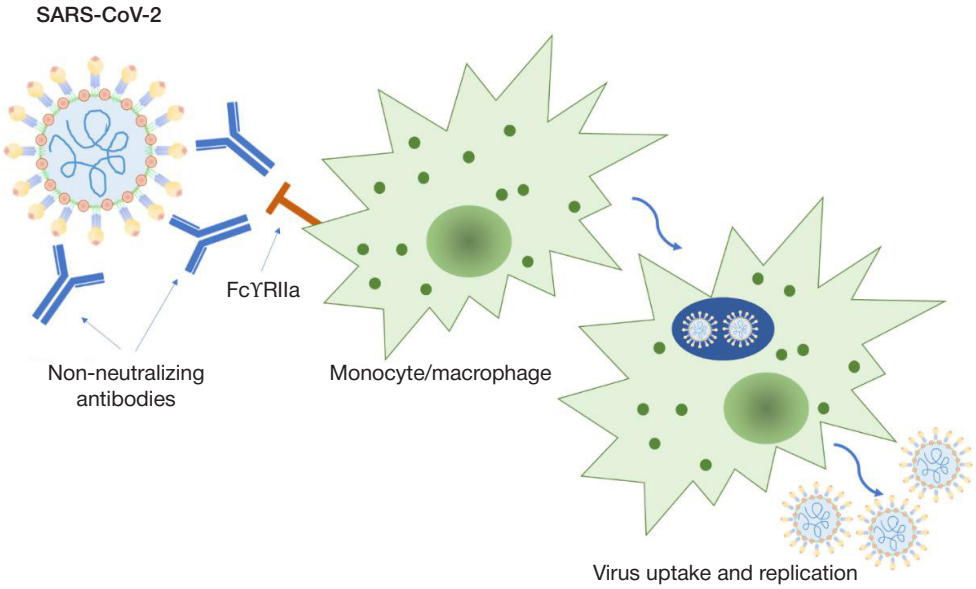

Fig. 1. Schematic representation of antibody-dependent enhancement: binding of SARS-CoV-2 by non-neutralizing antibodies → presentation of the virus to the cell → virus uptake into the monocyte/macrophage → virus replication in the cell → release of SARS-CoV-2 copies. Adapted from [32]

and Victoria the following number of cases was reported: 10 (3–26) MIS-C cases per 10,000 visits during the period before the emergence of "delta" variant (4 cases), 5 (4–7) cases per 10,000 visits during the period of "delta" variant circulation (30 cases), 0.8 (0–1) cases per 10,000 visits during circulation of "omicron" variant (61 cases) [21, 22].

Dependence of the MIS-C rate on the COVID-10 incidence peaks is an indirect evidence of the SARS-CoV-2 etiologic role in the syndrome pathogenesis, and the risk of the syndrome is likely to be associated with its genetic variant.

There are no official data on the rate of MIS-C in Russia. The majority of domestic publications are represented by case reports and reviews [23–25]. The researchers analyzed the data of 122 children with MIS-C aged 8.9 (5.3; 11.8), among them more than a half were boys (56.6%). A total of 45.1% of patients were admitted to ICU [26].

Pathogenesis

Multiple studies are focused on explaining the mechanisms underlying the MIS-C development. Since MIS-C was similar to KD, macrophage activation syndrome, and cytokine release syndrome in terms of clinical features, it was hypothesized that MIS-C resulted from hyperimmune response to the virus (as in the above conditions) in the beginning of the pandemic. However, most researchers tend to think that the MIS-C development mechanism differs from that of the above conditions [7, 12, 18, 27].

Currently, several theories of the MIS-C pathogenesis are discussed, among which the most popular are as follows: abnormal innate immune response to infection resulting from the cross-reaction between viral antigens and antigens of the host; response to the ongoing virus replication in the unrecognized viral reservoirs; superantigen theory; antibody-dependent enhancement (ADE). Researchers do not rule out the impact of genetic or epigenetic predisposition. Actually, it is more likely that there are concurrent mechanisms underlying the MIS-C development [28–31].

The theory of ADE associated with the SARS-CoV-2 infection was one of the first hypotheses. Since the detection rate of specific antibodies against SARS-CoV-2 was higher than the rate of viral RNA detection by PCR, it was suggested that antibodies against SARS-CoV-2 could be among the disease triggers. The non-neutralizing antibodies (nNAb) are produced after the first exposure to novel coronavirus. Some nNAb target specific region of viral spike protein (S-protein),

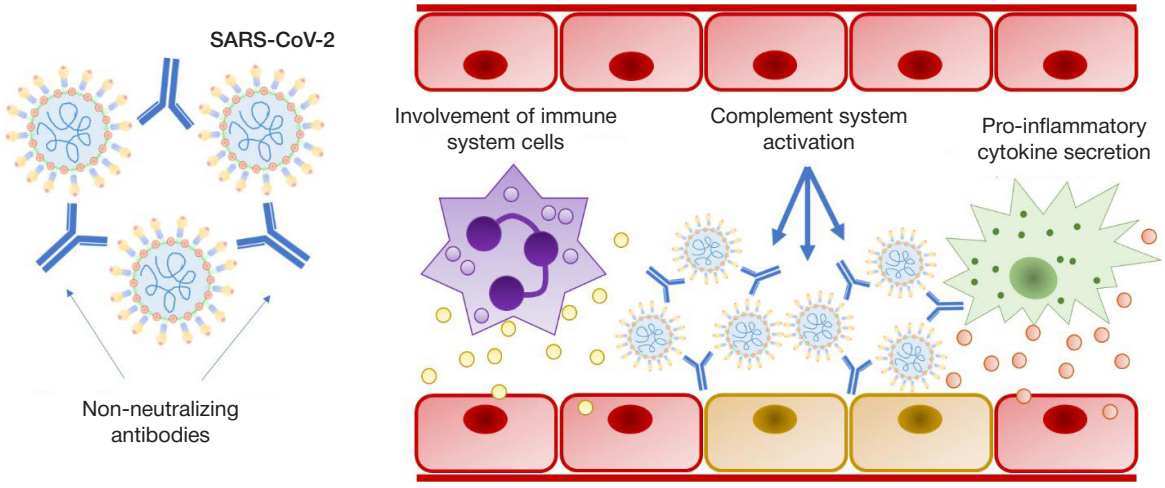

Fig. 2. Schematic representation of antibody-dependent enhancement: binding of SARS-CoV-2 by non-neutralizing antibodies → immune complexes' formation and deposition in the tissues → hyperimmune response. Adapted from [32]

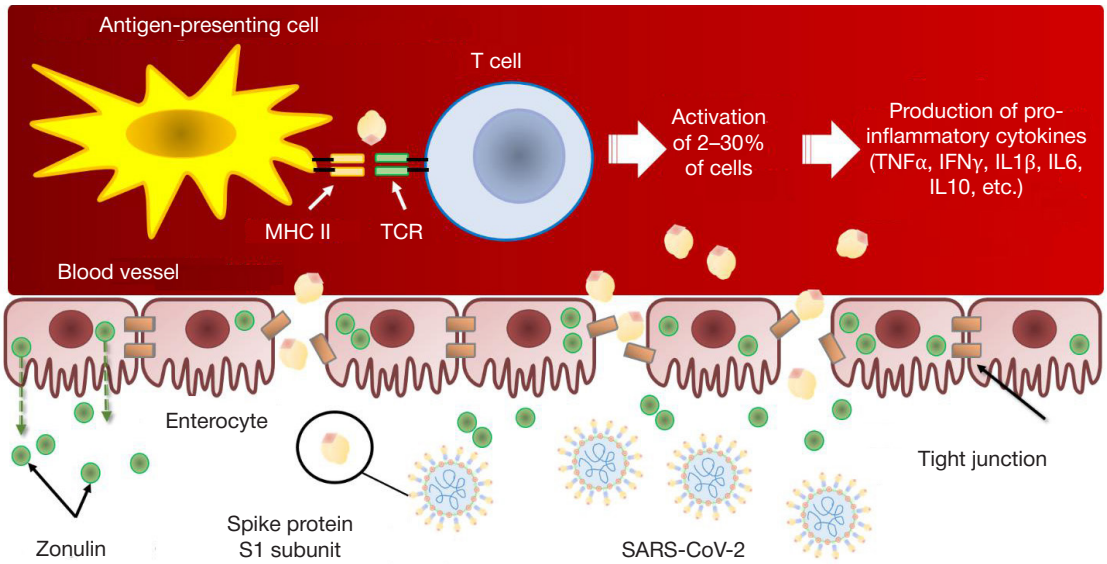

Fig. 3. Schematic representation of superantigen theory as MIS-C pathogenesis: SARS-CoV-2 persistence in the gut → zonulin release → disruption of intercellular contacts and increased intestinal permeability → viral S-protein S1 subunit entry in the bloodstream (as superantigen) → bonding of MHC II molecules found on the antigen-presenting cells with S1 subunit of the virus and T cell activation via TCR → hyperimmune response. Modified and adapted from [35, 37]

that is why MIS-C can develop according to the scenario of the ADE syndrome leading to viral replication in macrophages and disruption of numerous human cells (Fig. 1).

After binding to the macrophage Fc receptors, the virus-antibody complexes settle in tissues and lead to abnormal immune response regulation and enhanced cytokine secretion after the complement activation. Active production of inflammatory mediators contributes to the increased blood vessel permeability, fever, shock, and severe multiple organ damage (Fig. 2).

Meanwhile, as data on SARS-CoV-2 accumulated, it was found that the virus did not infect macrophages, that is why the ADE type involving Fc receptors was unlikely, and low affinity nNAb were produced in small amounts, hardly recognized the virus and did not bind to it [28, 33–34].

The hypothesis about the role of superantigens is based on the MIS-C clinical similarity to toxic shock syndrome caused by bacterial exo- and endotoxins. Superantigen can cause nonspecific activation of the large number of T cells, which, in turn, also produce pro-inflammatory cytokines and chemokines, thereby initiating autoimmune inflammation. High similarity of the SARS-CoV-2 spike protein subunit 1, S1 (responsible for binding of the virus to the host cell receptor), and the fragment of staphylococcal enterotoxin B, the superantigen, was revealed (Fig. 3). Assessment of peripheral blood samples from patients with MIS-C by immunosequencing revealed the *TRBV11-2* gene expansion that was correlated to the MIS-C severity and the serum levels of cytokines, which was consistent with the features of immune response caused by superantigen. The long-term persistence of SARS-CoV-2 in the gut of patients with MIS-C and circulation of the viral protein S1 subunits support this theory [35, 36].

The reports show that prolonged SARS-CoV-2 persistence in the gastrointestinal tract of children with MIS-C resulted in the release of zonulin (intestinal permeability marker) followed by the SARS-CoV-2 antigens entry in bloodstream and the development of hyperinflammation [37]. The data obtained by the authors are consistent with the other study results: genetic factors (expansion and activation of the *TRBV11-2*+ gene) alters the diversity of the T cell receptors in children with MIS-C, which, in turn, can be induced by superantigen [38, 39].

Genetic analysis showed that enrichment of rare pathological variants affecting inflammatory and autoimmune pathways, such as dominant-negative mutations in the Notch1 NUMB and NUMBL regulators resulting in the Notch1 regulation enhancement, was observed in patients with MIS-C [40]. The Notch1 signal transmission to Tregs induced CD22, thereby causing their mTORC1-dependent destabilization and systemic inflammation enhancement.

It has been proven that in individuals with KD the virus can play a role of trigger by binding to antibodies and forming the immune complexes that settle on the blood vessel walls and cause inflammatory response through binding to Fc receptors or complement system activation. The genes involved in antigen production (*FCGR2A*, the gene encoding lymphoid tyrosine kinase, and the gene encoding the CD40 ligand) are responsible for this process. The gene encoding inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) regulating cell activation is responsible for cellular response associated with KD. Similar mechanisms can underly the MIS-C pathogenesis [41]. The research team [42] analyzed three groups of patients (a total of 20 individuals) in order to reveal the differences and clarify the disease pathogenetic features: individuals with MIS-C ($n = 6$), mild and severe COVID-19 ($n = 5$ and $n = 9$, respectively). The authors determined the cytokine profiles (IFNγ, IL10, IL6, IL8, and TNFα) and the levels of soluble complement complex C5b-9, they also assessed the abundance of schizocytes in peripheral blood smears considering clinical data. The analysis showed that the total of TNFα and IL10 levels was significantly higher in patients with MIS-C than in patients with severe COVID-19. The elevated levels of these cytokines are indirect evidence of impaired innate immunity. In the discussion section the authors note that moderate increase in the levels of IL1, IL2, and IL6 is observed in individuals with KD. However, TNFα levels are likely to play a key role in pathogenesis of both MIS-C and KD. The levels of soluble complement complex C5b-9 were significantly higher in children with severe COVID-19, slightly lower in patients with MIS-C, and within normal range in patients with mild COVID-19. Schizocytes were found in peripheral blood smears in 67% of individuals with mild COVID-19, 80% of patients with severe COVID-19, and 100% of patients with MIS-C. Elevated levels of soluble complement complex C5b-9 are indicative of the presence of blood vessel damage in the MIS-C pathogenesis [42].

Cytokines and chemokines play a vitally important role in initiation, prolongation and suppression of immune response to any infection, including COVID-19. Studies have revealed elevated blood levels of IL6 in patients with severe MIS-C, however, the values did not exceed that observed in children with sepsis. In addition to IL1 and IL8, the levels of which are slightly elevated in MIS-C relative to KD, a significantly increased production of TNFα, IFNγ, and IL10 relative to KD is observed in individuals with MIS-C. The IL17 inflammatory mediator plays a more prominent role in pathogenesis of KD than that of MIS-C. It is important to note that the cytokine and chemokine levels can vary considerably between the studies involving various ratios of age cohorts, sample collection terms and diagnostic methods [43–47].

It is well-known that the increase in the levels of autoantibodies is typical for various autoimmune and inflammatory disorders, it also occurs in response to some viral infections. Studies revealed elevated levels of autoantibodies in patients with MIS-C [48]. Three autoantigens were identified as ones associated with MIS-C: UBE3A, ECE1, and RBM38. Another eight autoantigens were earlier reported in individuals with other disorders (ATP4A, TROVE2 of two types, KLHL12, FAM84A, HK1, MAOA, and CTDP1). The authors have found tissue-specific autoantigens in such organs, as the gut, heart, endothelium, and skeletal muscles, which explains clinical symptoms from these organs in MIS-C.

Cardiovascular system is a major target organ in MIS-C. Heart disorders in the form of valvulitis, coronary artery dilation and aneurysms, myocardial dysfunction, and fulminant myocarditis are observed in patients. The researchers make various assumptions to explain the rate of cardiac disorders. Thus, myocardial damage is most likely to result from binding of the virus to the ACE-2 receptors found on endothelial cells of arteries and veins and direct infection of cardiomyocytes by the virus [49–51]. Furthermore, the release of inflammatory cytokines also contributes to the vascular matrix disruption and loss of blood vessel structural integrity, thereby leading to coronary artery dilation and aneurysm formation [43]. Pathological examination of autopsy samples from patients with MIS-C confirms the presence of inflammatory infiltration in the myocardium and demonstrates high viral load in the patients' cardiac muscle [52, 53]. The research team assessed the results of heart MRI in four patients with MIS-C and revealed diffuse myocardial edema with no signs of replacement fibrosis or focal necrosis [54].

Vaccination against COVID-19 and MIS-C

Great attention is paid to the probability of developing MIS-C after vaccination against COVID-19 due to the emergence of sporadic reports of the syndrome development following vaccination against novel coronavirus infection. The paper [55] reports two cases of MIS-C following administration of the BNT162b2 vaccine (based on mRNA encoding the SARS-CoV-2 spike protein) in Virginia state (USA). A 15-year-old girl developed clinical symptoms of the disease six days after vaccination, however, it was later confirmed that she had a history of COVID-19 (the virus was not extracted by PCR, however, specific antibodies (IgG) against the SARS-CoV-2 nucleocapsid protein were detected along with no antibodies against S-protein). A 17-year-old girl was the second patient, who developed clinical symptoms of MIS-C seven days after vaccination. Novel coronavirus was also not extracted from nasopharyngeal discharge by PCR. There were specific antibodies (IgG) against S-protein and no antibodies against nucleocapsid protein, that is why it was impossible to confirm or disprove the likelihood of previous COVID-19. Both teenagers received therapy with normal human immunoglobulin for intravenous administration and systemic glucocorticoids, they were discharged from hospital when healthy.

A total of 52 MIS-C cases in children aged 0–17 for the period between 1 August 2021 and 1 February 2022 were assessed in Denmark. Among them one case occurred in a fully vaccinated adolescent. A 17-year-old girl developed MIS-C four months after administration of the second dose of BNT162b2 vaccine and five weeks after the confirmed breakthrough infection caused by SARS-CoV-2. The rate of MIS-C was 1 case per 3400 unvaccinated children (95% CI: 2600–4600) and 1 case per 9900 vaccinated individuals (95% CI: 1800–390,000) [56].

Ambiguity of the mechanisms underlying the development of MIS-C and the risk of this syndrome in vaccinated children led to the debate regarding the development of tactics for vaccination of patients having a history of MIS-C against SARS-CoV-2. In this context an international study involving 273 children having a history of MIS-C from 32 countries was performed. There were no reports of recurrent MIS-C or any other serious side effects of vaccination against SARS-CoV-2 in this group of children [57].

CONCLUSION

While etiological role of SARS-CoV-2 in the development of MIS-C is almost beyond doubt, there are still many unresolved issues related to the syndrome pathogenesis. Today, work continues on defining the role of immune mechanisms in the MIS-C development and course, various aspects related to innate and adaptive immunity are clarified. Further research on the MIS-C pathogenesis is essential for optimization of diagnostic and therapeutic measures contributing to prevention of severe effects of this disorder.

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