



Features of the Immune Response and Multisystem Inflammatory Syndrome in Children with COVID-19: A Mini-Review

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Abstract

On March 11, 2020, the World Health Organization declared a pandemic of severe acute respiratory syndrome (SARS) caused by coronavirus type 2 (SARS-CoV-2). Despite extensive treatment and preventive measures, COVID-19 remains one of the leading causes of severe morbidity and mortality among viral diseases. However, the disease is typically mild or asymptomatic in young people and children. In this mini-review, we will discuss the immune response and multisystem inflammatory syndrome in children with COVID-19.

Keywords: Children; COVID-19; Immune response; Multisystem inflammatory syndrome; MIS-C

Introduction

On March 11, 2020, the World Health Organization declared a pandemic of severe acute respiratory syndrome (SARS) caused by coronavirus type 2 (SARS-CoV-2), coining the term coronavirus disease 2019 (COVID-19) [1]. Despite the extensive list of therapeutic and preventive measures developed to protect against

this disease, COVID-19 continues to be one of the leading causes of severe illness and mortality among viral diseases. However, it is worth noting that the disease is typically mild or asymptomatic in young people and children. In the Russian Federation, cases of new coronavirus infection are less frequently reported in pediatric

practice compared to adults, with children accounting for only 8.6% of all cases [2]. Of these cases, 80% are mild and only 0.2% are severe, with the latter being more common in children under one year of age [3]. The proportion of pediatric patients requiring inpatient medical care ranges from 5.7% to 20% of children with COVID-19.

Features of the Immune Response to COVID-19 in Children

As research has shown, children have a lower percentage of infection with SARS-CoV-2 compared to adults, and are at a significantly reduced risk of developing severe acute respiratory syndrome (SARS), despite a similar risk of infection. This is reflected in a sharp increase in mortality with increasing age [4-5]. According to literature, children have a higher basal expression of relevant pathogen recognition receptors (PRRs), such as MDA5 (IFIH1) and RIG-I (DDX58), in upper respiratory tract epithelial cells, macrophages, and dendritic cells. This results in stronger innate antiviral responses to SARS-CoV-2 infection compared to adults [6]. In all epithelial cells, particularly ciliated cells, children have significantly higher expression of interferon-stimulated genes (ISGs) at both early and late stages of infection compared to infected adults [6]. Additionally, various subpopulations of immune cells have been described, predominantly found in children, including cytotoxic KLRC1 (NKG2A)+ T cells and populations of CD8+ T cells with a memory phenotype [6]. NKG2A is a lectin-like inhibitory receptor found on cytotoxic T cells that plays a crucial role in limiting overactivation, preventing apoptosis, and maintaining virus-specific CD8+ T cell responses [7]. While the levels of SARS-CoV-2 RNA copies, the number of ACE2 receptors, and TMPRSS2 were similar in both children and adults [8-9], children showed a higher expression of genes associated with the IFN-dependent immune response, the inflammatory inflammasome NLRP3 (a receptor of the PRR system that activates caspase-1 [10]), and other innate mechanisms [10]. Additionally, higher levels of IFN- α 2, IFN- γ , IP-10 protein, IL-8, and IL-1 β were found in upper respiratory tract secretions in children compared to adults [11].

Furthermore, children with COVID-19 showed a decrease in the number of natural killer cells and CD4+ cytotoxic T lymphocytes, but an increase in the number of naïve lymphocytes in the blood. In contrast, adults with COVID-19 had a significant increase in the number of cytotoxic T cells [12].

Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious condition that has been linked to COVID-19

As previously mentioned, the clinical manifestations of New Coronavirus infection in children are typically less severe than in adults. In fact, more than 90% of cases in children are asymptomatic or present with mild to moderate symptoms [13-14]. Hospitalization rates among children are also lower. According to reports from the US Centers for Disease Control and Prevention (CDC), the hospitalization rate for children is almost 2 times lower than that of adults (5.7% versus 10%) and fewer pediatric patients require intensive care unit therapy [15]. However, in April 2020,

reports emerged from the United Kingdom and some European countries of a disease pattern in children resembling incomplete Kawasaki syndrome (KS) or toxic shock syndrome. This clinic was accompanied by a pronounced hyperinflammatory response associated with SARS-CoV-2 infection in previously healthy children [16-18]. Some children also showed signs of myocarditis with cardiogenic shock [13]. This condition is referred to as pediatric inflammatory multisystem syndrome associated with SARS-CoV-2 (PIMS-TS) in Europe, and multisystem inflammatory syndrome in children (MIS-C) in the USA [19].

MIS-C is a rare complication that can occur 1-6 weeks after a new coronavirus infection [20]. A common characteristic among patients with MIS-C is contact with an infected individual 2-6 weeks before the onset of symptoms or the presence of specific antibodies [21]. Most children admitted to the intensive care unit had acute COVID-19 with minimal symptoms, and at the time of hospitalization, their nasopharyngeal swab tests for SARS-CoV-2 by polymerase chain reaction (PCR) were negative [21-22]. Some studies have shown that children with MIS-C have tested positive for IgG antibodies to SARS-CoV-2, and in a few cases, IgM antibodies were also detected [13, 23]. Unlike Kawasaki disease, the multisystem inflammatory syndrome associated with COVID-19 in children is more commonly seen in older age groups and adolescents, and is typically mild, although there have been rare cases of severe illness [24].

At present, the pathogenesis of MIS-C is a controversial issue. One theory suggests that the delayed production of interferon at the onset of COVID-19 may be a key factor. This delay is known to lead to a more severe course of the disease in adult patients, with significant damage to lung tissue in the second week. However, in children, this damage may occur even when the virus is not detected in the mucous membranes of the nasopharynx and oropharynx [13, 25]. Additionally, there is a proposed mechanism in which the virus's own replication is increased through phagocytosis, leading to the death of immune cells and ultimately resulting in shock and multiple organ failure [26]. In some cases, the presence of the virus has been detected in myocardial tissue, suggesting the possibility of virus-mediated tissue damage as a contributing factor [27-28]. A similar pathogenesis is observed in macrophage activation syndrome, which is more common in children with juvenile arthritis and reactive hemophagocytic lymphohistiocytosis associated with a virus [29-33]. A potential role for autoantibodies in the pathogenesis of MIS-C, as in Kawasaki disease, has also been suggested. The levels of several autoantibodies identified in children with MIS-C were found to be higher than those in the healthy control group, as well as in groups of children with acute COVID-19 and Kawasaki disease [34]. Overexpression of autoantibodies involved in the activation of lymphocytes and intracellular signaling pathways has been revealed [19]. Autoantibodies specific to MIS-C have been discovered, targeting various subtypes of casein kinase [32, 35]. The multisystem nature of the lesions in MIS-C may be associated with the prevalence of potential targets for these autoantibodies [19]. New data indicate increased levels of interleukins IL18 and IL6 in patients with MIS-C, as well as increased lymphocyte

and myeloid chemotaxis and immune dysregulation of mucous membranes [20, 22]. Immunophenotyping of peripheral blood cells in patients with MIS-C showed characteristic changes in the proportions and functions of immune cells. The number of naïve CD4+ and CD8+ cytotoxic T cells was significantly reduced, as was the ratio of monocytes to natural killer (NK) cells [36]. Additionally, signs of activation were found in neutrophils and CD16+ monocytes (FcγR1), as well as increased expression of migratory proteins (ICAM-1), indicating an increased influx of NK and myeloid cells to the periphery [19, 34]. Abnormally low numbers of NK cells and CD8+ cytotoxic lymphocytes in the blood, combined with increased cytotoxic activation of these cells (as indicated by increased expression of perforin and granzyme genes), contribute to the maintenance of inflammation and development of autoreactivity [37-38]. The hyperinflammatory syndrome in MIS-C differs from that in Kawasaki disease, where IL17A is mainly involved, and also differs from acute COVID-19 in children and cytokine storm in adult patients [16, 19, 30, 32, 35, 39].

According to laboratory diagnostics, MIS-C is characterized by a significant increase in pro-inflammatory markers such as C-reactive protein, procalcitonin, ferritin, erythrocyte sedimentation rate, IL6, and fibrinogen. Additionally, markers of myocardial damage, including brain natriuretic propeptide, N-terminal precursor of brain natriuretic peptide, and troponin, are elevated. Most patients also exhibit increased D-dimer levels, neutrophilia, lymphocytopenia, and decreased albumin levels. Unlike classical Kawasaki disease, children with MIS-C often present with thrombocytopenia. Electrocardiography may reveal repolarization disturbances, focal ischemic changes, and conduction and rhythm disturbances. Echocardiography imaging may show signs of myocarditis, a decrease in left ventricular ejection fraction to 50% or less, pericardial effusion, and dilatation of the coronary arteries [40]. Ultrasound of the abdominal organs may detect hepatosplenomegaly, lymphadenopathy, ascites, colitis, and ileitis [21, 39, 41]. Chest radiography or computed tomography may reveal ground-glass changes in the lungs and interstitial changes in some patients, which are likely associated with circulatory failure, acute respiratory distress syndrome, and hemocoagulation disorders [21]. The main symptoms of MIS-C in children include fever lasting more than 24 hours, systemic involvement of multiple organs (such as the heart, kidneys, central nervous system, respiratory tract, and gastrointestinal system), and possible development of acute respiratory distress syndrome. Other common manifestations include hematological disorders, skin rashes, myalgia, arthralgia, and associated symptoms such as hypercoagulation, disseminated intravascular coagulation (DIC), and possible thromboembolic complications [24]. It is important to note that children with MIS-C may also experience lethargy, confusion, and other neurological symptoms.

Conclusion

Children have particularities in the course of COVID-19, as well as immune response and multisystem inflammatory syndrome. Understanding the pathogenesis of COVID-19 in children will help prevent the development of severe complications and long-term

consequences in the form of somatic or neurological deficits.

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Conflicts of Interest

None.

References

- Kogan EA, Berezovskii YuS, Protsenko DD, Bagdasaryan TR, et al. (2020) Pathological anatomy of infection caused by SARS-CoV-2. *Russian Journal of Forensic Medicine* 6(2): 8-30.
- Ivanov DO, Petrenko YuV, Reznik VA, Nasyrov RA, et al. (2022) New infection coronavirus in a child at the age of 2 years 4 months with acute lymphoblastic leukemia (fatal case). *Pediatrician (St. Petersburg)* 13(3): 73-82.
- Ivanov DO, Petrenko YuV, Reznik VA, Nasyrov RA, et al. (2021) Characteristics of new coronavirus infection in patients with acute myeloid leukemia. *Vopr prakt pediatrician (Clinical Practice in Pediatrics)* 16(3): 121-129.
- Castagnoli R, et al. (2020) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr.* 174: 882-889.
- Goldstein E, Lipsitch M, Cevik M (2021) On the effect of age on the transmission of SARS-CoV-2 in households, schools, and the community. *J Infect Dis* 223: 362-369.
- Loske J, Röhmel J, Lukassen S, et al. (2022) Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children. *Nat Biotechnol* 40: 319-324.
- Rapaport AS, et al. (2015) The inhibitory receptor NKG2A sustains virus-specific CD8+ T cells in response to a lethal poxvirus infection. *Immunity* 43: 1112-1124.
- Heald-Sargent T, et al. (2020) Age-related differences in nasopharyngeal severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) levels in patients with mild to moderate Coronavirus disease 2019 (COVID-19). *JAMA Pediatr* 174(9):902-903.
- Koch CM, et al. (2021) Age-related differences in the nasal mucosal immune response to SARS-CoV-2. *American Journal of Respiratory Cell and Molecular Biology* 66(2).
- Fu J, Wu H (2023) Structural Mechanisms of NLRP3 Inflammasome Assembly and Activation. *Annu Rev Immunol* 41: 301-316.
- Pierce CA, Sy S, Galen B (2021) Goldstein DY, Orner E, Keller MJ, Herold KC, Herold BC. Natural mucosal barriers and COVID-19 in children. *JCI Insight* 6(9): e148694.
- Yoshida M, Worlock KB, Huang N, et al. (2022) Local and systemic responses to SARS-CoV-2 infection in children and adults. *Nature* 602: 321-327.
- Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, et al. (2020) An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 395(10239): 1771-1778.
- Namazova-Baranova LS, Baranov AA (2020) Coronaviral Infection (COVID-19) in Children (Situation on June 2020). *Pediatric pharmacology* 17(3): 162-178.
- CDC COVID-19 Response Team. Coronavirus disease 2019 in children. United States, February 12—April 2, 2020. *MMWR Morb. Mortal Wkly Rep.* 2020 Apr 6.
- Paediatric Intensive Care Society (PICS) Statement: Increased number of reported cases of novel presentation of multi system inflammatory disease. Available at <https://picsociety.uk/wpcontent/uploads/2020/04/>

- PICS-statementre-novel-KD-C19-presentation-v2-27042020.pdf (september, 2020) 669-676 p.
17. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. (2020) Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 395(10237): 1607-1608.
 18. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. (2020) COVID-19 and Kawasaki Disease: Novel Virus and Novel Case. *Hosp Pediatr* 10(6): 537-540.
 19. Consiglio C, Cotugno N, Sardh F, et al. (2020) The immunology of multisystem inflammatory syndrome in children with COVID-19. *Cell press*183(4): 968-981.
 20. Kantemirova MG, Novikova YuYu, Ovsyannikov DYu, Kurbanova SKh, et al. (2020) Children's Multisystem Inflammatory Syndrome, Associated With a New Coronavirus Infection (COVID-19): Relevant Information and Clinical Observation. *Pediatric pharmacology* 17(3):219-229.
 21. Lobzin YuV, Vilnits AA, Kostik MM, Bekhtereva MK, et al. (2021) Pediatric multisystem inflammatory syndrome associated with a new coronavirus infection: unresolved issues. *Journal Infectology*. 13(1): 13-20.
 22. Feldstein LR, Rose EB, Horwitz SM, et al. (2020) Multisystem inflammatory syndrome in U.S. children and adolescents. *New Engl J Med* 383: 334-346.
 23. Vella LA, Giles JR, Baxter AE, et al. (2021) Deep immune profiling of MIS-C demonstrates marked but transient immune activation compared to adult and pediatric COVID-19. *Sci Immunol* 6(57): 1-15.
 24. Konstantinova YE, Vilnits AA, Bekhtereva MK, Alekseeva LA, et al. (2023) Current understanding of epidemiology and pathogenesis of multisystem inflammatory syndrome associated with SARS-CoV-2 in children. *Extreme Medicine*. 2023; (3): 13-21.
 25. Rowley AH (2020) Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat Rev Immunol* 20 (8): 453-454.
 26. Evans C, Davies P (2021) SARS-CoV-2 paediatric inflammatory syndrome. *Paediatr Child Health (Oxford)* 31(3): 110-115.
 27. Belhadjer Z, Méot M, Bajolle F, et al. (2020) Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. *Circulation*142(5): 77-84.
 28. Dolhnikoff M, Ferreira Ferranti J, de Almeida Monteiro RA, Duarte Neto AN, Soares Gomes-Gouvêa M, et al. (2020) SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome. *Lancet Child Adolesc Health* 4 (10): 790-794.
 29. Bregel LV, Kostik MM, Fell LZ, Efremova OS, et al. (2020) Kawasaki disease and multisystem inflammatory syndrome in children with COVID-19 infection. *Pediatrics n.a. G.N. Speransky*. 99 (6): 209-219.
 30. Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A, et al. (2016) 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College of Rheumatology/ Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Ann Rheum Dis* 75(3): 481-489.
 31. Toubiana J, Poirault C, Corsia A, Bajolle F, Fourgeaud J, Angoulvant F, et al. (2020) Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ* 369: m2094.
 32. Hennon TR, Penque MD, Abdul-Aziz R, et al. (2020) COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C) guidelines; a Western New York approach. *Progress in Pediatric Cardiology* 57(2): 1-5.
 33. Rodriguez-Smith JJ, Verweyen EL, Clay GM, et al. (2021) Inflammatory biomarkers in COVID-19-associated multisystem inflammatory syndrome in children, Kawasaki disease, and macrophage activation syndrome: a cohort study. *Lancet Rheumatology* 3:e574–e584.
 34. Gruber CN, Patel RS, Trachtman R, et al. (2020) Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). *Cell* 183: 982-995.
 35. Kanegaye JT, Wilder MS, Molkara D, et al. (2009) Recognition of a Kawasaki disease shock syndrome. *Pediatrics* 123(5): 783-789.
 36. Mathew D, Giles JR, Baxter AE, et al. (2020) Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science* 369: pp8511.
 37. Beckmann ND, Comella PH, Cheng E, et al. (2021) Downregulation of exhausted cytotoxic T cells in gene expression networks of multisystem inflammatory syndrome in children. *Nat Commun* 12: 4854.
 38. Ramaswamy A, Brodsky NN, Sumida TS, et al. (2021) Immune dysregulation and autoreactivity correlate with disease severity in SARS-CoV-2-associated multisystem inflammatory syndrome in children. *Immunity* 54:1083-1095.
 39. Constantin T, Pék T, Horváth Z, et al. (2023) Multisystem inflammatory syndrome in children (MIS-C): Implications for long COVID. *Inflammopharmacol* 31: 2221–2236.
 40. Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T (2021) COVID-19 and multisystem inflammatory syndrome in children: A systematic review and meta-analysis. *Pediatr Pulmonol* 56(5): 837-848.
 41. Patel JM (2022) Multisystem Inflammatory Syndrome in Children (MIS-C). *Curr Allergy Asthma Rep* 22: 53-60.