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COVID-19 in children: Heterogeneity within the disease and hypothetical pathogenesis

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Abstract

The disease course of coronavirus disease 2019 (COVID-19) is usually mild and self-limiting in previously healthy children, but they may also develop severe disease. Severe COVID-19 infection is especially observed in very young children or those with underlying comorbidities. Moreover, a multisystem inflammatory syndrome that mimics the Kawasaki disease shock syndrome can develop in children that are genetically predisposed to displaying an overactive immune response to SARS-CoV-2 infection. In this review, we describe the clinical phenotypes of mild and severe COVID-19 and multisystem inflammatory syndrome in children (MIS-C). We also discuss the possible immunobiological mechanisms that may be involved in the protection of children against COVID-19 and the development of multisystem inflammatory syndrome.

Key words: SARS-CoV-2; COVID-19; pediatric multisystem inflammatory disease, COVID-19 related; immunity, innate; T-lymphocytes; immunosenescence, immunity.

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Abbreviations:

SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
COVID-19	corona virus disease 2019
ACE2	angiotensin-converting enzyme 2
MIS-C	multisystem inflammatory syndrome in children
KDSS	Kawasaki disease shock syndrome
KD	Kawasaki disease
NK	natural killer

Introduction

Currently, the world is experiencing a coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In adults, the intensity of COVID-19 infection can differ substantially between individuals, ranging from mild to severe disease.[1] Numerous studies have highlighted the low incidence of SARS-CoV-2 infection in children, who account for only 0–7.4% of the COVID-19 cases identified worldwide.[1-5] Approximately 20% of the affected children are asymptomatic.[1,6] A recent systematic review of 11 studies[7] and a multinational, multicenter cohort study in Europe[6] revealed that only 4–8% of children infected with COVID-19 were admitted to the intensive care unit (ICU). These incidences are substantially lower than those observed in adults; ~16% of the adult study population was severely affected.[6] Moreover, the fatality rate of children with COVID-19 is extremely low (0–0.69%)[1,6,7] compared to that of the adult population (8–14.8%).[8]

Clinical disease spectrum of COVID-19 in children

The clinical spectrum of COVID-19 in children is summarized in **Table 1**. As indicated above, most children with COVID-19 experience mild disease. Similar to the clinical spectrum observed in adults, the most common presentations were fever and respiratory symptoms. About 17% of the children suffered from gastrointestinal (GI) symptoms such as abdominal pain, vomiting, or diarrhea. The incidence of GI symptoms was even higher in a recent Chinese study on 14 hospitalized boys and 20 girls, among them nearly 27% had diarrhea and about 25% had nausea or vomiting.[9] Nearly half of the children in this study were also infected with other respiratory pathogens such as influenza A virus, influenza B virus, or *Mycoplasma pneumoniae*. Interestingly, 7% of the patients reported isolated GI symptoms without typical respiratory tract symptoms.[6] There was no predominant male pattern similar to that published for adult populations.[6,7,8]

Table 1. Clinical spectrum of COVID-19 infection in children

Characteristic	Mild to moderate COVID-19 infection[7]	Severe COVID-19 infection[11]	COVID-19 infection related to MIS-C[21]
Numbers of patients	211	48	21
Age, median (IQR), year	6.5 (0–12)	13 (4.2–16.6)	7.9 (3.7–16.6)
Ethnicity, no (%)	not mentioned	not mentioned	24 (57) were from Sub-Saharan, African origin
Health conditions	all were previously healthy	83% with pre-existing comorbidities	all were previously healthy, none had underlying cardiac disease
Presenting symptoms, no (%)	122 (49) cough, 118 (47) fever	respiratory symptoms 35 (73)	all had high fever, mucous membrane involvement, rash, lymphadenopathy, fits with criteria of Kawasaki diseases
Male gender, no (%)	147 (59)	25 (52)	9 (43)
Respiratory symptoms, no (%)	151 (60) had mild pneumonia	35 (73)	mild or absent respiratory symptoms (numbers did not show)
Gastrointestinal symptoms, no (%)	42 (17)	1 (2)	21 (100)
Cardiovascular symptoms, no (%)	not mentioned	2 (4)	16 (76) myocarditis, 5 (24) moderate coronary artery dilations
Skin	not mentioned	not mentioned	16 (76) had polymorphous skin rash and changes of the lips and oral cavity; 17 (81) had bilateral bulbar conjunctival injection
Neurological symptoms	1 (0.5) had encephalopathy	2 (4)	6 (29) had headache, confusion, meningeal irritation
Signs of inflammation & inflammatory markers	22 (28) had high CRP and procalcitonin	not mentioned	12 (57) had serous effusion, all had high CRP/procalcitonin/serum IL-6, 19 (95) had high D-dimers
Obesity, no (%)	not mentioned	7 (15)	16 (76)
SARS-CoV-2 detection	100% RT-PCR positive from nasopharyngeal/ throat swabs	100% RT-PCR positive from nasopharyngeal/throat swabs	90% had evidence of recent SARS-CoV-2 infection (positive RT-PCR result in 38%, positive IgG antibody detection in 90%)
Treatment, no (%)	not mentioned	28 (61) receiving specific drugs (hydroxychloroquine, azithromycin, remdesivir, tocilizumab); 12 (25) required vasoactive drugs; 18 (38) on ventilator	All received intravenous immunoglobulin and low dose aspirin; 10 (48%) also received corticosteroids; 11 (52) on ventilator
Fatality rate, no (%)	0	2 (4.2)	0

MIS-C: multisystem inflammatory syndrome in children; CRP: C-reactive protein (CRP); SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RT-PCR: Reverse transcription polymerase chain reaction; Ig: immunoglobulin; IL: interleukin

Symptomatic treatment alone could resolve the symptoms of most children.[10]

Recently, in a study on a small group of children with severe or even fatal COVID-19, the most common initial presentations were respiratory symptoms requiring respiratory support (81%), with 13% requiring extracorporeal supportive therapies. Eighty-seven percent of the subjects had at least one organ failure. Interestingly, in this group, only 2% showed gastrointestinal symptoms, and this value was significantly lower than that of children with mild diseases.[11] Sixty-one percent of the children received COVID-19 related pharmacotherapies such as hydroxychloroquine, azithromycin, remdesivir, and tocilizumab, either as a single agent or in combination. The fatality rate in this study was 4.2%.[11] So far, two factors have been consistently associated with severe COVID-19 in children: preexisting medical conditions and a very young age. Eighty percent of the children admitted to the ICU due to COVID-19 had preexisting or therapy-related comorbidities that compromised their defenses, such as long-term ventilation support due to developmental delay (e.g., prolonged tracheostomy), malignancies, or immunosuppressive drug therapy (**Table 1**).[11] These comorbidities were also observed in a recent large multinational study.[6] As already mentioned, very young age is a contributing factor to severe COVID-19.[6] Approximately 10% of infants less than 1-year-old have suffered from severe COVID-19 disease as compared to 7.3% and 3.7% children in the age groups of 1–5 years and > 5 years old, respectively.[12] Another study showed that an age of less than 1 month increased the risk of severe COVID-19 by 2.5-fold.[6] These observations emphasize the need for close

follow-up and prompt treatment of children with comorbidities and very young infants that are suspected to be infected with SARS-CoV-2. A recent National Health System study in the UK revealed data for the comparison of the primary care records of 17,278,392 adults who were pseudonymously linked to 10,926 COVID-19-related deaths. These data revealed various determinants related to COVID-19 mortality, including age.[13] Conditions that contribute to the development of severe COVID-19 in adults include diabetes, chronic renal and liver disease, previous malignancies, dementia and chronic use of immunosuppressive drugs are rare or absent in pediatric populations.

The pathophysiology of both subclinical and severe COVID-19 in children remains unclear. Critically ill adult patients have been reported to demonstrate impaired or delayed anti-viral interferon (IFN) responses against SARS-CoV-2 infection.[14,15] On the contrary, the consequences of an uncontrolled overwhelming viral load include the overproduction of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), inducing a so-called cytokine storm. Impaired anti-viral responses were also observed in immunocompromised patients and infants under the age of 6 months.[16] An age-associated increase in the capacity to produce IFN-γ and TNF-α after the first year of life was recently reported. This may explain, in part, the severity of COVID-19 infection at an age of less than one year.[17] Immunological reactions that activate the clotting system may result in thrombosis. This is actually a major risk factor for mortality in adults, and is not taking place in children in whom thrombosis has a low prevalence in general. A genetic factor was also found to contribute to severity of COVID-19. Recently, rare putative *loss-of-function* variants of *TLR7* were identified in 4 young male patients who suffered from severe COVID-19.[18] These variants were functionally associated with impaired type I and II IFN responses.[18] However, all these factors are probably not the only ones contributing to the severity of COVID-19 in children and hence need further exploration.

The "multisystem inflammatory syndrome in children" (MIS-C) or "pediatric inflammatory multisystemic syndrome" has recently been reported. The term is used to refer to the development of severe inflammation involving multiple organs in healthy children, probably due to SARS-CoV-2 infection. Although there is a strong association between MIS-C and SARS-CoV-2, it is unclear whether it is a post-viral complication or a primary effect of SARS-CoV-2 infection. Clinical reports of MIS-C have recently been published in various countries, including China,[9] the United States,[19] Italy,[20] the United Kingdom,[21] France,[22] and Switzerland.[23] The median duration between symptoms of COVID-19 and the onset of MIS-C was 42 days (range 18–79 days). In some of the affected children, the symptoms started at the earliest 48 hours after the acute infection period (16), indicating that MIS-C might even occur during the late phase of infection. RT-PCR results for SARS-CoV-2 were positive for 38% of children with MIS-C, although almost nobody showed any symptoms of acute SARS-CoV-2 infection. IgG antibodies against SARS-CoV-2, on the other hand, were detected in 90% of the patients.

The presentation of MIS-C was similar to Kawasaki disease shock syndrome (KDSS), including myocarditis with a shock-like state combined with typical signs of Kawasaki disease (KD).[24] From previous literature, KDSS was reported in older children compared to classic KD.[24] KDSS was suspected to be related to viral triggers, including seasonal coronaviruses in some studies.[24] All patients with MIS-C also had cardiovascular involvement. Many of them suffered from impaired myocardial function, which is not commonly seen in typical KD whom the pathophysiology mainly involves the coronary arteries. This feature is the major difference between MIS-C and severe acute COVID-19 infection, in which only 4% of cases showed cardiovascular symptoms.[11] Additionally, in MIS-C, significant gastrointestinal symptoms were present, while only mild respiratory symptoms were reported. Skin rash, red eyes, and oral mucous membrane involvement were observed in about 76-81% cases. MIS-C was more prevalent in older individuals and in non-Asian children unlike that seen in typical KD. Obesity, an important risk factor for severity and mortality in adult patients with COVID-19, was also prominent in some MIS-C cohorts, as found in a recent French study.[22,25]

Mechanisms protecting children from SARS-CoV -2 infection and severe COVID-19

The mechanisms underlying the relative resistance of children to SARS-CoV-2 infection and clinical disease are still unclear and probably have a multifactorial background. The lining of the respiratory and gastro-intestinal system, including the local environment and secretions, is the first defense against viral entrance, followed by the innate immune response. However, the innate immune response to COVID-19 is not well understood. Binding of the virus to pattern recognition receptors (PRRs)/ toll-like receptors (TLRs) can activate downstream pathways, resulting in the secretion of various cytokines, particularly type I and III IFNs and the pro-inflammatory cytokines, interleukin (IL)-1, IL-6, IL-8, IL-18, and TNF-α.[26] SARS-CoV-2 proteins, however, could inhibit type-1 IFN responses, resulting in incomplete type-1 IFN signatures.[26] Various immune cell types are involved in early immune defense, including myeloid cells such as granulocytes and innate lymphoid cells, including natural killer cells (NK), which can produce cytokines or are cytotoxic (excellent review by Vabret N. et al., 2020). [26] These immune cells are part of the defense system but are also associated with severe complications including the acute respiratory distress syndrome (ARDS), when they are over-activated. Local tissue damage exaggerates this initial immune process. The innate antiviral response activates and potentiates the subsequent adaptive immune responses against the virus, particularly CD8 responses.

Besides the above mechanisms, we will discuss additional hypothesis that fill the knowledge gap of SARS-CoV-2 defense in the pathobiology of COVID-19 in children, specifically involving age-related angiotensin-converting enzyme 2 (ACE2) receptor expression, trained immunity, immunosenescence and exhaustion.

Angiotensin-converting enzyme 2 receptor

Several studies indicate that the expression of the ACE2 receptor, which is recognized as a receptor by SARS-CoV-2 for host entry,[27] differs between children and adults. The nasal epithelium is the first interaction site between SARS-CoV-2 and the host. Recently, Bunyavanich et al.[28] demonstrated age-dependent ACE2 receptor gene expression in the nasal epithelium, with significantly lower ACE2 receptor gene expression in young children than in older children, adolescents, and adults. Therefore, it is likely that the relatively low nasal epithelial ACE2 receptor expression confers protection against SARS-CoV-2 infection in children. In contrast, the ACE2 receptor is expressed at a higher level in the lower respiratory tract of children aged < 10 years compared to older subjects (19–71 years).[29] Under physiological conditions, ACE2 acts as a protease for the conversion of angiotensin II to its anti-inflammatory metabolites, angiotensin-1 to 7.[30] In the lower respiratory tract, decreased ACE2 expression can be a sign of severe acute respiratory distress and lung injury, suggesting a protective role of ACE2 in severe lung injury by limiting angiotensin 2-mediated pulmonary capillary leak and inflammation.[31] This information highlights the dual role of ACE2 as a viral receptor and a protective agent in acute lung injury. Although future in-depth studies exploring the regulation of ACE2-ACE-2 receptor-angiotensin-II system are required, anatomical and regulatory differences of this system between children and adults may represent one of the mechanisms providing relative protection to children against infection with SARS-CoV-2.

Trained immunity

The innate immune system is crucially important in young children, as adaptive immunity has not yet been fully developed. In other words, young children (< 2 years of age) are highly dependent on a rapid innate immune response to control disturbances in homeostasis, including infections. Trained immunity is the long-term epigenetic reprogramming of innate immune cells, such as myeloid cells and natural killer (NK) cells, and occurs upon exposure to homeostasis perturbance by exogenous or endogenous molecules

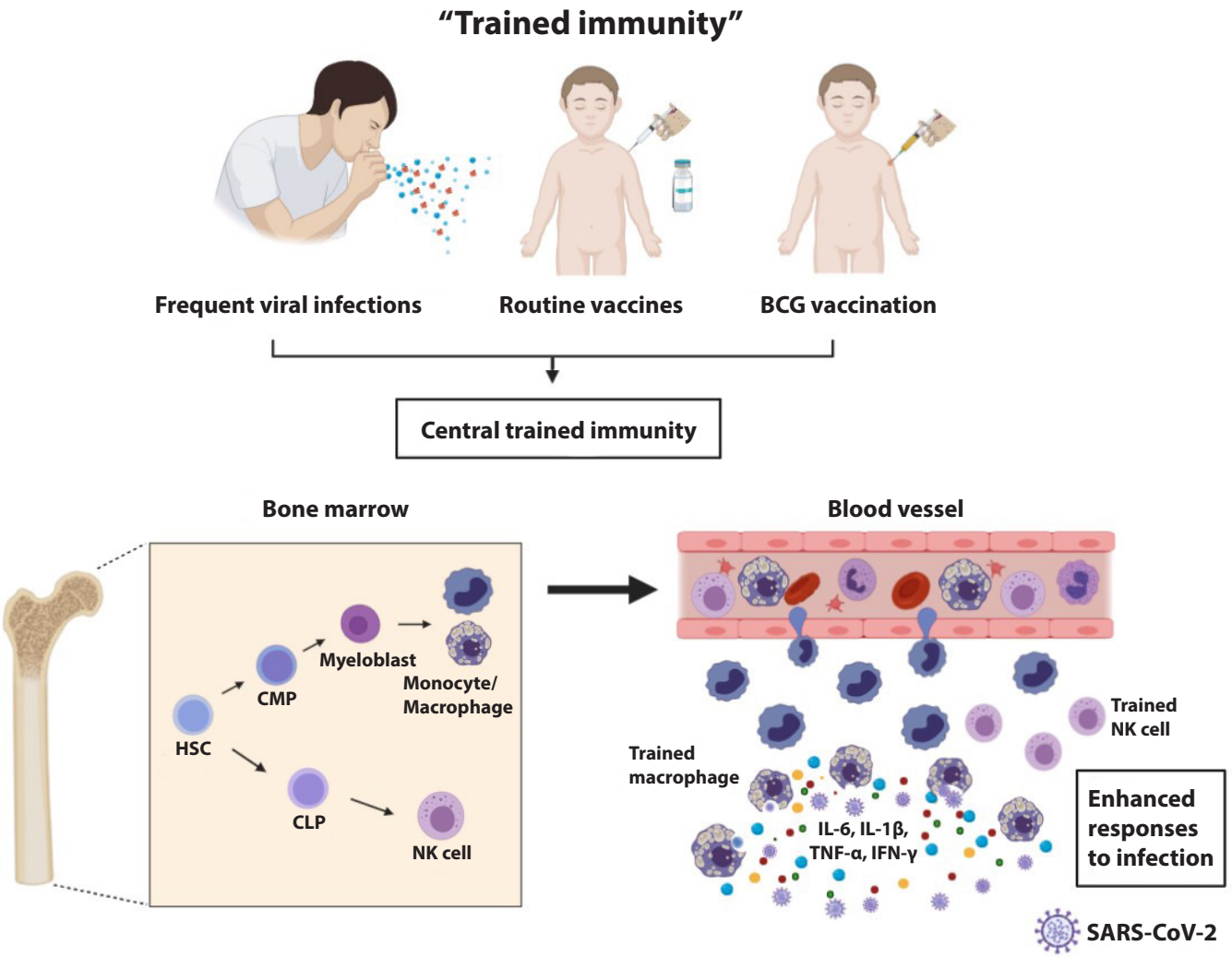

Figure 1. Trained immunity. Trained immunity resulting from frequent viral respiratory tract infections, routine vaccinations, and BCG vaccination shapes and enhances the innate immune response to SARS-CoV-2 in children at the level of myeloid progenitors in the bone marrow, and is called "central trained immunity". BCG, Bacillus Calmette-Guérin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; HSC, hematopoietic stem cell; CMP, common myeloid progenitor; CLP, common lymphoid progenitor; IL, interleukin; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma; NK, natural killer.

(e.g., pathogens) (**Figure 1**). Trained immunity leads to increased immune response upon secondary stimulation with, for instance, the same or even unrelated pathogens.[32] Such secondary stimulation is typically associated with increased production of cytokines such as IFN-γ, IL-1β, IL-6, and TNF-α, which are key cytokines in the immune response to many pathogens.[32,33] From *in vitro* and *in vivo* studies, Bacillus Calmette- Guérin (BCG) vaccination, live vaccines (against measles, mumps, rubella, influenza, smallpox, and oral polio)[34,35] and frequent viral infections were found to induce trained immunity. This defense mechanism cross-protects against infection with *Candida albicans*, *Schistosoma mansoni*, *Mycobacterium tuberculosis*, and various respiratory viruses such as respiratory syncytial virus, Influenza A, and Influenza B viruses. Trained immunity, thus, represents a very important protective mechanism against (re)infection, and likely is of great importance especially in early life. Although the protective effect of trained immunity is unlikely to last beyond 1–2 years, it may very well be that it contributes to the relative protection of children against SARS-CoV-2 infection. It might be worth evaluating the impact of trained immunity as a therapeutic target to protect against SARS-CoV-2 infection in the future.

Immunosenescence and exhaustion

T-lymphocytes are central in defense during viral infections. $CD4^+$ T-lymphocytes are potent cytokine producers that further activate the immune response and help B-lymphocyte in antibody production and Ig class switching; whereas, cytotoxic $CD8^+$ T cells destroy virus-infected cells in order to reduce the viral load and inhibit further the spread of the virus. SARS-CoV-2 infection causes peripheral blood ($CD4^+$ and $CD8^+$) lymphopenia, a process which is probably driven by the induction of homing factors and extensive apoptosis/cell death through the effects of IL-6 and Fas-FasL interactions. $CD8^+$ T lymphocytes are predominantly affected more than $CD4^+$ T lymphocytes, as their peripheral blood levels correlated well with disease activity and mortality.[36] In contrast, patients with mild disease, however, have normal or slightly higher T lymphocyte counts.[37,38] T lymphocytes in severe COVID-19 are more activated and may exhibit a trend toward exhaustion as measured by the expression of programmed cell death protein 1 (PD-1) and T-cell immunoglobulin mucin-3 (TIM-3), indicating an impaired function.[39]

Another contributing risk factor for severity and mortality in COVID-19 in adult compared to children may relate to the process called immunosenescence. This term refers to a gradual deterioration of the immune system as a result of aging. The adaptive immune system is more affected than the innate immune system.[40] One of the most characteristic of immunosenescence is the loss of a functional thymus from a subsequent decline in naïve T lymphocyte production (excellent review by van den Broek T. et al., 2018).[41,42] The progressive decline in thymus output has been deduced from an output of ~16 million T lymphocytes per day in young adults to < 1 million T lymphocytes per day in adults older than 65 years of age.[42] The frequencies of naïve CD4 T lymphocytes only moderately decline with age, while the naïve CD8 T lymphocytes compartment clearly shrinks. Although the repertoire diversity (i.e., the number of different T lymphocyte clones) remains very high for both naïve CD4 and CD8 T lymphocytes subsets, infant and older adult T lymphocytes undergo differential changes in their DNA, including changes in telomere length, amount of DNA damage, and epigenetic modifications.[43] These processes may lead to functional impairments resulting in defective immune responses to infections and impaired vaccination responses in the elderly. The immune system of an older individual has a reduced response to both known antigens and neo-antigens. Older adults also have a significant higher risk of mortality from vaccine-preventable diseases than children.[44] For example, despite annual vaccination, influenza infections continue to be associated with high morbidity and mortality rates. The first vaccinations with live viruses, such as yellow fever virus, are associated with increased morbidity and even mortality in older adults.[43] Therefore, impaired immune response to neo-antigens may contribute significantly to the course of COVID-19 in adults.

Remarkably, obesity, another risk factor for severe disease and mortality in COVID-19 patients, is associated with low-grade chronic inflammation and accelerated immunosenescence. Epigenetic changes and aberrant numbers of T lymphocytes were found in patients with morbid obesity (BMI > 40).[46] Obesity affects antiviral defense and are at risk to generate a poor vaccine-induced immune response.[45] Moreover, obesity has been identified as a risk factor for increased disease severity and mortality in individuals infected with influenza. Obese hosts have delayed and impaired antiviral responses to influenza virus infection, and they experience also a poor recovery from the disease.[47] The combination of aging and obesity can result in a severely impaired immune response to SARS-COV-2. While the prevalence of obesity is rapidly increasing in children, it has not reached the prevalence of obesity in adults. This explanation may be another influencing factor for the difference of COVID-19 disease course in children and adults.

To conclude, current evidence suggests that several factors, including differences in ACE2 receptor expression, trained innate immunity, and a young and fit immune system contribute to the protection of children from severe SARS-CoV -2 infections. The magnitude of the contribution of each of the indicated mechanisms should be further investigated.

Hypothetical pathogenesis of MIS-C

The pathophysiology of MIS-C is currently not well understood and is under active investigation. It is suggested that this syndrome results from an abnormal immune response to the virus, with some similarities/overlaps with KD, macrophage activation syndrome/hemophagocytic lymphohistiocytosis, and cytokine release syndrome. Although causality has not been established, the temporal relationship between the MIS-C and the COVID-19 pandemic raised the suggestion that the mechanism of molecular mimicry, where a foreign antigen shares sequence or structural similarities with self-antigens, might be involved.[49]

Autoimmunity related to molecular mimicry can occur both at the cellular and humoral immune levels and has been described following vaccination or infection, as previously

reported in Guillain-Barré syndrome, multiple sclerosis, and KD, but does require a susceptible genetic background to occur.[48] So far, studies exploring the contribution of molecular mimicry between SARS-CoV-2 antigens and self-antigens, specifically in relation to MIS-C, have not been conducted. However, *in vitro* experiments confirmed homology between the spike and nuclear proteins of SARS-CoV-2 and human tissue antigens; cross-reactions between SARS-CoV-2 IgM/IgG might occur with transglutaminase 3 (tTG3), transglutaminase 2 (tTG2), extractable nuclear antigens (ENA), myelin basic protein, mitochondria, myosin, thyroid peroxidase, collagen, Claudin 5+6, and S100B.[49] Antigen-autoantibody complexes can precipitate inside tissues and, in particular, in blood vessels, and induce an inflammatory reaction through the activation of the complement system, in which complement anaphylatoxins (C3a and C5a) recruit neutrophils, leading to inflammation, including vasculitis, in the affected organ.[50]

Moreover, autoreactive T helper 1 (Th1) and Th17 lymphocytes release proinflammatory cytokines that contribute to the cytokine storm, recruiting more (cytokine-producing) macrophages, neutrophils, and monocytes, and resulting in progressive tissue damage. The clinical spectrum of disease depends on the affected organs, which may include; neurological symptoms (headache, irritability, and encephalopathy), impaired cardiac ventricular function, gastrointestinal symptoms (vomiting, abdominal pain, and/or diarrhea), mucocutaneous symptoms mimicking KD (conjunctivitis, rash), and acute kidney injury. Hematologic abnormalities, including lymphopenia and low platelets, were also reported. The hypothetical pathogenesis of MIS-C is demonstrated in **Figure 2**.

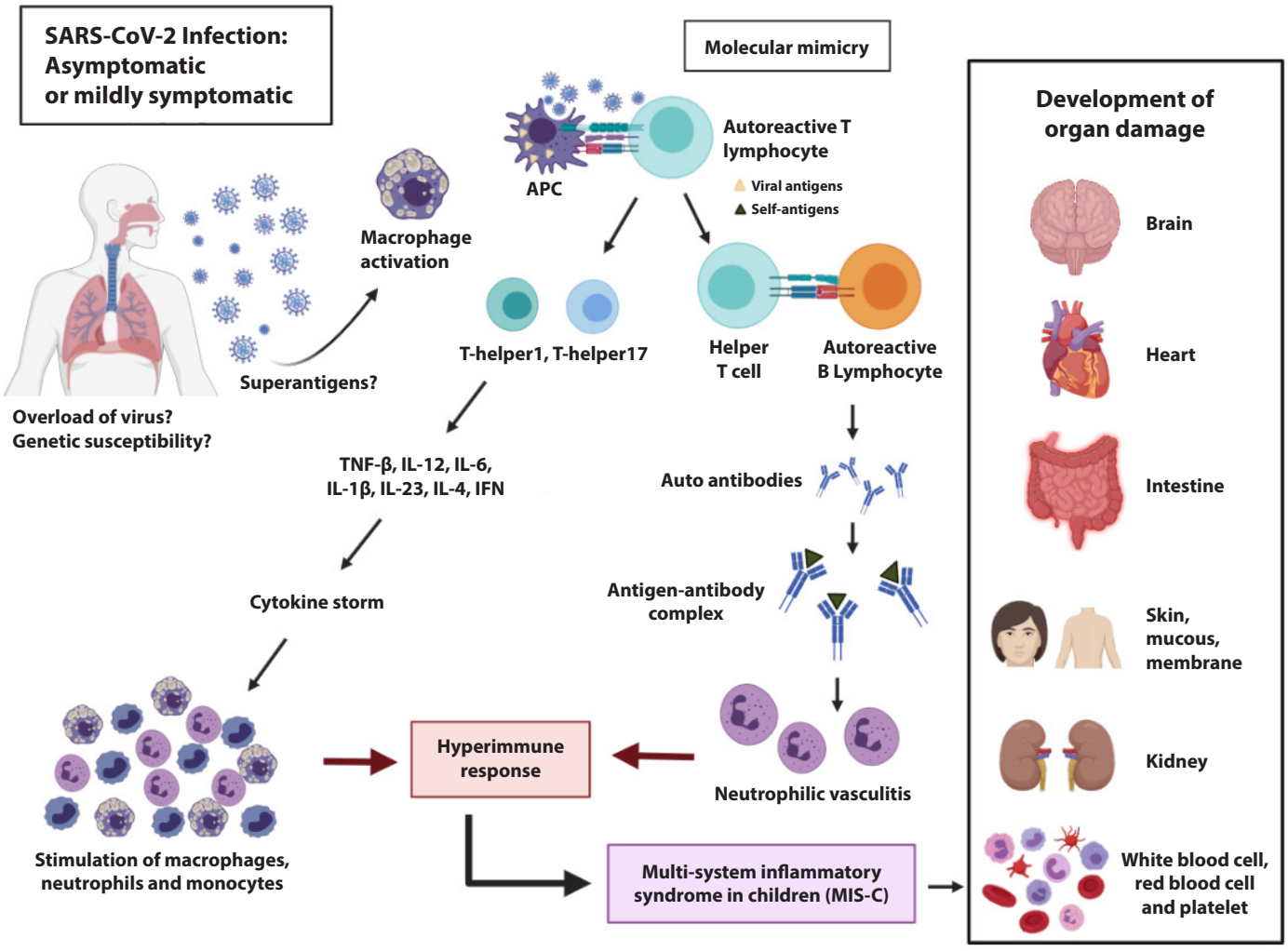

Figure 2. Hypothetical pathogenesis of MIS-C. Early infection with SARS-CoV-2 is likely to be asymptomatic or mildly symptomatic in children. The early infection appears to trigger macrophage activation. SARS-CoV-2, where some antigens are similar to self-antigens, is captured by antigen presenting cells and stimulates autoreactive T lymphocytes. This in turn leads to cytokine release and stimulation of macrophages, neutrophils, and monocytes, along with B lymphocyte activation and subsequent production of autoreactive antibodies, leading to a hyperimmune response. This results in the damage of tissues such as the brain, heart, intestines, skin, mucous membranes, kidneys, and blood cells and presents as the clinical manifestation of MIS-C. MIS-C, multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; APC, antigen presenting cell; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

Conclusion

SARS-CoV-2 infection in children has a more benign disease course compared to that in adults. The potential causality of mild SARS-CoV-2 infection in healthy children is based on many factors, including the lack of preexisting comorbidities, low obesity prevalence, low thrombosis rate, different ACE-2 receptor expression, trained immunity, and general immune fitness. Prognostic factors to identify children who may develop the new hyperinflammatory condition, MIS-C, need to be determined. It has been speculated that autoreactive B- and T- lymphocytes generating from the cross-reactivity between viral and host antigens, together with macrophage activation play a role in generating a cytokine storm which leads to specific organ tissue inflammation.

Conflict of interests

The authors declare no conflicts of interest.

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