

Review Article

Immunological features of the multisystem inflammatory syndrome associated with SARS-CoV-2 in children

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Abstract: A particular group of children developed severe multisystem inflammation associated with current or recent SARS-CoV-2 infection or contact with a COVID-19 patient in the previous few weeks. The condition was defined as multisystem inflammatory syndrome (MIS) in children (MIS-C). As the definition of CDC and WHO is fast widely accepted, the lack of an international consensus on the definition of the syndrome cases, however, leads to some difficulties for clinicians. Additionally, MIS-C shares some immunological, pathological features with the conditions, such as cytokine storm, long COVID and/or post-COVID syndrome. The picture is further complicated by the existence of the syndrome in adults (MIS-A). Therefore, we have compared these conditions from the immunological point of view in our review based on the published case reports, studies, systematic reviews and metaanalyses. This knowledge is essential not only for immunologists. The paediatricians must be familiar with the immunological bases of the syndrome and implement it in on-time recognition and diagnosis and minimize systemic damage of this life-threatening condition at the earliest stage possible. Further investigations still need to be done to find and develop the best effective therapy and prophylactics.

Keywords: Multisystem inflammatory syndrome in children, MIS-C, MIS-A, cytokine storm, cytokines, SARS-CoV-2, COVID-19, long COVID, post-COVID

Introduction

After the first outbreak in Wuhan City, China, SARS-CoV-2 spread fast over the world, and the World Health Organization classified COVID-19 a pandemic in March 2020 [1]. Since then, for almost two years, data on SARS-CoV-2 infection in children have been predominantly controversial. However, it was widely accepted that the SARS-CoV-2 infection in children had a tendency for a milder course than in adult patients [2]. Additionally, diagnostic efforts and outcomes were comparable to adults, with fever and respiratory symptoms most frequent. Moreover, fewer children appear to have had severe pneumonia. In youngsters, elevated inflammatory markers were less prevalent, and lymphocytopenia seemed to be uncommon [3].

Although some newborn babies had COVID-19, evidence of vertical intrauterine transmission was lacking. Treatment options included administering oxygen, inhaling medications, giving nutritional assistance, and preserving fluid and electrolyte balances [3].

Interestingly, multiple studies have focused on the lesser morbidity in children, despite similar or greater virus loads than adults [4]. All of these findings have yet to be completely elucidated. Several aspects of the juvenile immune system may explain disparities between children and adults. According to Carsetti et al., the immune system of children is well prepared to deal with novel pathogens because of high levels of natural IgM antibodies and the ability to rapidly produce natural antibodies

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with broad reactivity, as well as the production of anti-inflammatory interleukin (IL)-10 by neonatal B cells [5]. Variations in T cell subsets in adults due to continuous antigen stimulation and thymic involution, differing levels of ACE-2 expression in children, and the simultaneous presence of other viruses competing with SARS-CoV-2 in the respiratory mucosa of children have all been proposed as explanations [6].

However, a certain group of children developed severe multisystem inflammation associated with current or recent SARS-CoV-2 infection or contact with a COVID-19 patient in the previous few weeks [7]. The occurrence of cases of the unusual pediatric syndrome, called multisystem inflammatory syndrome in children (MIS-C), which is thought to be associated with SARS-CoV2, poses an additional challenge during the current global public health crisis [8].

In our review, we search for original articles, systematic reviews, meta-examinations, case series and recommendations of medical societies and health organizations published by the 10th of January, 2021, PubMed/MEDLINE/WHO COVID-19 databases. We use the keywords “multisystem inflammatory syndrome in children”; “MIS-C”; “cytokine storm”, “cytokines”, “SARS-CoV-2”, “COVID-19”, “long COVID”, “post-COVID”. Manually, other items were searched for the reference lists of the selected items.

What do we know about MIS-C so far?

Due to the lack of an internationally accepted uniform definition of MIS-C, there is still a lack of definitive data on the condition's incidence and whether it affects a specific age or race group more frequently. A study in the USA found the highest incidence of MIS-C among younger children and Hispanic or Latino, Black, and Asian or Pacific Islander persons [9]. Despite the accumulation of published data on quite a few cases of MIS-C worldwide, the incidence seems to be relatively low. In the USA, an incidence of 4.9 children per 1,000,000 person-months has been reported for children under five years of age and 6.3 per 1,000,000 person-months for children between 6 and 10 years of age [9]. Pediatricians in the UK stated the first cases of children with a clinical presentation of fever, cardiovascular shock and symp-

toms resembling Kawasaki disease (KD), toxic shock syndrome and cytokine storm [10]. The Royal College of Pediatrics and Child Health (RCPCH) also provides the first definition of the syndrome, namely pediatric inflammatory, multisystem syndrome temporarily associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)”, or pediatric inflammatory, multisystem syndrome (PIMS) [11]. Soon after that, the leading healthcare organizations - the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) gave their definition of a syndrome case, which they called multisystem inflammatory syndrome in children (or MIS-C) [12, 13]. The definition of CDC and WHO is fast and widely accepted.

Speaking of MIS-C, some of the typical clinical signs and symptoms are related to the underlying immunological processes. Fever above 38.0°C for more than 1-3 days, skin or mucosal inflammation, involvement of several organs (heart, kidneys, lungs, gut, liver), hypotension and shock, coagulopathy. Laboratory evidence for systemic inflammation are also crucial criteria for MIS-C. Amongst them parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), as well as D-dimer, procalcitonin, fibrinogen, ferritin, lactic acid dehydrogenase (LDH) are the most commonly elevated, whereas albumin is usually decreased. Additionally, increased levels of cytokines (IL-6), as well as altered hematological parameters (neutrophilia, lymphopenia, etc.) [11-13]. Recently, we demonstrated liver involvement in children with MIS-C as a typical feature of the condition [14].

However, the lack of an international consensus on the definition of the syndrome cases leads to some difficulties for researchers publishing clinical cases and case series and those conducting systematic and multisystem analyses.

Distinguishing MIS-C from KD and other alternative diagnoses, including severe septic conditions, is also a challenge for clinicians and epidemiologists to define disease burdens. Often in children, SARS-CoV-2 infection is asymptomatic [10]. Moreover, outside of lockdown, it is challenging to determine potential contact with a proven or suspected case of COVID-19. On the other hand, with the time and ubiquity of

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SARS-CoV-2 worldwide, the detection of positive anti-SARS antibodies cannot be evidence of a recent infection or a verification of the link between the development of symptoms and SARS-CoV-2 [15, 16].

As we mentioned above, the symptoms of MIS-C are similar to those of myocarditis, toxic shock syndrome, and KD. According to current research, MIS-C is caused by increased innate and adaptive immune responses, defined by a cytokine storm [17]. All these immunological processes are induced by past SARS-CoV-2 infection. However, MIS-C can be distinguished from KD by epidemiological, clinical, and immunological characteristics. Patients' ages, as well as their geographical and ethnic distribution, differ as well. In addition, MIS-C is associated with substantial gastrointestinal and cardiovascular system involvement and the need for intensive care unit (ICU) hospitalization [17]. From the laboratory tests, prominent are neutrophilia, lymphopenia, high IFN levels, and low numbers of naïve CD4+ T cells, with a high proportion of activated memory T cells. Further research on MIS-C will help us better comprehend the disorders associated with an immunological dysregulation and cytokine storm [17].

In addition, the forthcoming universal opening of schools and childcare centers will significantly expand children's social contacts [18]. The last, combined with a high incidence of mild or asymptomatic childhood illness, would make it difficult to prove a causal link with the virus, which is one of the critical features of the syndrome. A characteristic feature of MIS-C is the involvement mainly of older children - at and over five years, the pronounced multiorgan involvement with a preference of the gastrointestinal and cardiovascular systems [11, 12].

On the other hand, it is unclear whether and what the spectrum of clinical severity of MIS-C is, given that most severe cases are examined and diagnosed in hospitalized children. Cases of children with MIS-C have been reported presenting with classic symptoms of the acute surgical abdomen. Whether and how many children with prolonged high fever, abdominal pain, mild gastrointestinal symptoms, with or without mesenteric lymphadenitis, actually have viral gastroenteritis or a more favorable spectrum of MIS-C with predominantly gastrointestinal

involvement is difficult to be proven. In children with such symptoms, especially self-limiting, conducting more in-depth laboratory and imaging studies to confirm the syndrome is not indicated [19]. At the moment, there are no risk and prognostic factors for MIS-C. The syndrome often develops in previously healthy children without concomitant diseases [20].

Although SARS-CoV-2 appears to be more gentle in childhood and the current incidence of MIS-C is not high, it is necessary to raise awareness of the syndrome among health professionals and politicians, parents, teachers, and school administrators.

MIS-C - is it long COVID-19 or post-COVID-19?

The appearance of the SARS CoV-2 was followed by the emergence of conditions such as MIS-C and the so-called Long COVID and/or Post-COVID syndrome).

As stated above, it was broadly accepted that children and adolescents were mostly protected from the severe disease at the beginning of the global pandemic [21]. While this is still being considered true, the occurrence of possibly life-threatening conditions such as MIS-C has raised some concerns about the possible implications of this novel coronavirus on children and young individuals [21]. This syndrome might occur 4-6 weeks after infection with SARS-CoV 2, which could be asymptomatic, mild, or more severe symptoms. The clinical manifestations of the disease are set as fever and multiorgan damage: gastrointestinal, cardiovascular, cutaneous, neurological, respiratory, nephrological, and hepatologic implications [21]. It is estimated that 80% of the patients with this complication would require treatment in an intensive care unit with a fatality rate of 2% [21]. The pathophysiology and the most effective treatment plan are still debatable [21]. However, the majority of children have good outcomes with the application of anti-inflammatory drugs such as steroids, immunoglobulins, other biologics and supportive therapy. The treatment could also include broad-spectrum antibiotics, remdesivir, aspirin and tocilizumab [22]. The condition of children and adolescents with this diagnosis may become extremely severe rapidly, so they should be looked at with caution [22]. It is yet to be determined whether MIS-C is a post-infectious

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complication of the infection with SARS-CoV 2 or a predominant complication of the acute infection with the virus. Nevertheless, there is strong epidemiological evidence of a connection between the two conditions [22].

Immunological features of long/post-COVID-19 in children are among the reasons why it is challenging to distinguish MIS-C from the former conditions [23]. Antibody responses to spike protein were strong in children, along with increased seroconversion responses to seasonal beta-coronaviruses via S2 domain cross-recognition. The ability of children and adults to neutralize viral variations was also demonstrated as comparable [23]. Spike-specific T cell responses were more than twice as robust in children, also found in many seronegative youngsters, indicating pre-existing cross-reactive responses to seasonal coronaviruses. Importantly, children sustained antibody and cellular responses 6 months following infection, but adults had a relative decrease in immune responses [23].

Furthermore, spike-specific responses in children were rather consistent after a year. As a result, children develop powerful, cross-reactive, and long-lasting immune responses to SARS-CoV-2, emphasizing the spike protein. These findings provide light on the relative clinical protection that most children experience and may assist in influencing the design of future interventions regarding pediatric vaccination regimens [23].

However, children can experience SARS-CoV-2 post-infection symptoms. Still, it is unclear how these individuals are affected by long COVID [24]. Although evidence is predominantly limited to select populations without control groups, which does not allow estimating the overall prevalence and burden in a general pediatric population, even though protracted COVID exists in children, estimates of the incidence of persistent symptoms based on little evidence range from 0% to 27% [24].

Ludvigsson et al. described five youngsters who expressed weariness and dyspnea [25]. However, joint discomfort and chest pain were also prevalent. Other symptoms included neurological issues, skin rashes, sleep difficulties, depression, muscular soreness, and recurrent fever. However, weariness appears to be the

most common symptom, and it lasted at the end of the study in all five children. However, these symptoms may resemble MIS-C without a dramatic clinical picture of systemic inflammation and organ failure [3]. However, the cited systematic review of Ludvigsson was more inconsistent in providing information, although they reviewed 179 publications on long COVID-19 in children [3].

The reasons for continuing symptoms after infection with SARS-CoV 2 or the so-called Long COVID are still considered quite a mystery. However, a case report of five Swedish children suggests that they could also suffer from symptoms suggestive of Long COVID (similarly to adults) and that it is more common in female individuals [3]. According to their caregivers, the children had symptoms 6-8 months after the initial infection with the novel coronavirus, such as fatigue, dyspnea, heart palpitations or chest pain, headaches, difficulty concentrating, muscle weakness, dizziness and sore throats [3]. It was further clarified that not even one of the children had yet fully returned to school [3]. Limited evidence regarding the pathophysiology, risk factors or treatment of Long COVID exist [25]. As a whole, Long covid could result from continuous tissue damage, pathological inflammation, immune dysregulation and autoimmunity [25]. In adults, there is a suggestion that after vaccination against SARS CoV-2, the symptoms of Long COVID tend to get milder or disappear completely. In children, this is yet to be determined.

The determination between these two diagnoses could be a challenge in clinical practice because of the close timing of their occurrence. However, MIS-C often begins with a very high fever accompanied by other typical symptoms of the condition mentioned above. The incidence of hospitalization of children with this condition is high, and intensive care is required in the most extreme cases. Long COVID is characterized by much slower but longer disease progression, sometimes even more than 8 months [25]. Both conditions are associated with the contraction of the novel coronavirus and possible continuous tissue damage and hyper inflammation in the affected children. The severity of the initial infection in both cases does not seem to correlate with the occurrence of either condition. Both are possible in even

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asymptomatic individuals, those with milder or severe disease. A lot is yet to be determined for these diagnoses, and clinicians will face quite a challenge with the implications of SARS-CoV-2 in children's health. The youngest individuals (less than 5 years old) still could not be offered vaccine protection against SARS-CoV-2.

MIS in children and adults (MIS-A)

According to CDC, MIS can be presented in children and adults, although its occurrence in the latter is rare [11]. For patients older than 21 years of age, the criteria are focused mainly on the previous encounter with SARS-CoV-2 and subjective feeling of fever and measurement of temperature 38.0°C or above for at least 24 hours before and 3 days after hospitalization. However, there are primary and secondary criteria [10-12]. The first ones emphasize mainly on cardiovascular pathologies, as well as cutaneous manifestation and conjunctivitis. The secondary focus is on neurological symptoms regarding the central and peripheral nervous system and gastrointestinal and laboratory findings concerning platelet count and refractory to treat shock [26].

Johns Hopkins University researchers documented a sudden increase in cases among young adults, especially in Barcelona [27]. In England, the age group of 12-24 was affected more than ever, with recorded infections marking a rise as well. In addition, the delta variant of SARS-CoV-2 is affecting more and more children, and unvaccinated young adults as the virus evolves. Information from CDC again showed an almost 30% rise in the ages between 0-17 years in only 7 days between July and August [28].

In the spring of 2020, there were many case reports regarding the pediatric population suffering from similar toxic-shock syndrome and KD [2]. Myocarditis, rash and even shock were the most common presentations of those possibly life-threatening conditions. The hyperinflammatory state was common SARS-CoV-2 positive serology, 2-4 week asymptomatic period from the acute infection and skyrocketing inflammation markers found in laboratory testing. Now we define it as MIS-C [2]. A similar syndrome is presented later in adults. The survival rate was estimated higher. The symptoms of MIS-A were equivalent to those who have

COVID-19 [29]. The main difference in the patients of different age groups was that children were thought to be spared from the virus at the beginning of the pandemic. Most cases of COVID-19 were asymptomatic or mild.

Both MIS-A and MIS-C are uncommon. There seems to be dissimilarity in the rate of symptoms in MIS-C among the age groups; small children tend to be suffering more from the skin and mucous membrane involvement [29]. At the same time, older children tend to have more cardiovascular and gastrointestinal symptoms. Another common presentation in around 80% of MIS-A patients was the GI tract complications [29]. In previously healthy children, MIS-C presents in a high-temperature state accompanied by diarrhea and pain in the abdominal area, mucocutaneous inflammation, polymorphic rash conjunctivitis, low lymphocyte number, and raised typical inflammatory markers such as ESR, CRP, ferritin, procalcitonin, IL-6 and fibrinogen. Shock, cardiac involvement and severely low blood pressure are common as well. The future health risks are soon to be researched and documented. The same syndrome can be seen in adults after SARS-CoV-2 infection with no pulmonary findings and higher thrombosis rates [30]. A case series showed that symptoms at the beginning of MIS-A were mainly fever >38.0°C prolonged more than 24 hours and commonly seen cardiac signs such as chest pain. All patients had ECG findings pointing toward heart involvement; most had diarrhea, pain in the abdomen or other symptoms regarding the GI tract. Few presented with mucocutaneous manifestation [11, 12]. A PCR test was performed, and most were still positive; fewer had antibodies [31].

MIS-C and cytokine storm

The etiology of MIS-C is unknown, although it seems to result from an increased host immunological reaction or maladaptive reaction. The primary defense against infection should be a fast and well-coordinated immunological reaction once the infectious agent penetrates human cells. However, hyperinflammation might arise if this process is uncontrolled and overwhelming [32].

SARS-CoV-2 infection is associated with increased inflammatory cytokines (tumor necrosis factor [TNF], IL-1, IL-6 and IFN- α), etc. [33].

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The activation of clotting and the complement cascade release of inflammatory cytokines, notably IL-6, are critical immunological processes during COVID-19 infection [34, 35]. Furthermore, the increased IL-6, IL-10 and TNF production are negatively linked to many lymphocytes that impair innate and acquired immunity [34].

The significant release of inflammatory mediators with excessive immune activation is comparable to the disease recognized in a group of diseases, such as the cytokine storm, which has the exact pathogenic mechanism and distinct causative causes [32]. The neutrophil, the principal player in the cytokine storm, can secrete ferritin, explaining the high levels of this biomarker during many inflammatory disorders [33]. Consequently, ferritin has an immunosuppressive effect that inhibits myeloid cells and T and B cell differentiation, which aggravates the host's response. Thus, MIS-C seems to be a clinical illness with an inflammatory element that causes a vast number of the cytokines to malfunction, including KD, sepsis, macrophage activation, etc. Several impactful studies showed that MIS-C and severe COVID-19 infection may be similar in the documented immunological processes. Both conditions present with lymphopenia, thrombocytopenia and high blood concentrations in IFN- τ , IL-1 β , IL-6, IL-10 and IL-17, although not to the same extent as the more severe cytokine storm syndromes. High levels of IL-10 associated with decreased viral load, and its presence and high levels of TNF α were the most significant indicators for distinguishing MIS-C from severe COVID-19 [33].

MIS-C is not linked with pre-existing comorbidities, occasionally with asthma, as opposed to severe COVID-19. Identified treatment options for both conditions include immunomodulatory medications, such as intravenous immunoglobulin infusions, glucocorticoids, anakinra (IL-1 receptor antagonist) and infliximab (TNF monoclonal antibody); antimicrobials, including remdesivir and broad-spectrum antibiotics; as the American College of Rheumatology recommends [36].

Conclusion

MIS-C is a novel pediatric illness linked to SARS-CoV-2; it is beyond doubt hazardous and

possibly fatal. However, most children will survive, but the long-term effects of this multi-inflammatory system state are not known. Still, timely identification and medical care are needed. COVID-19 is a severe, uncommon MIS-C. The pediatrician must detect and deal with immunomodulatory methods to minimize systemic damage of this life-threatening condition at the earliest stage possible. There is also a need for further investigations to find and develop the best effective therapy.

Disclosure of conflict of interest

None.

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