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Review

A Novel and Severe Clinical Picture Related to COVID-19: Multi-Inflammatory Syndrome in Children

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ABSTRACT

Preliminary data have suggested that children have milder COVID-19 disease course compared to adults. However, pediatric cases with severe clinical findings caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) are being reported since April 2020. These children have been presented with significant hyperinflammatory states resembling Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome. However, they had several distinct features, as well. Therefore, this novel condition was considered a unique disease and named Multi-inflammatory syndrome in children (MIS-C). Thus, new concerns have been raised regarding the vulnerability of the children. However, it has been realized that this condition is extremely rare. Nonetheless, considering that it is a life-threatening disease and may cause devastating consequences, clinicians should be aware of MIS-C while evaluating children with persistent fever and history of COVID-19 contact or active infection.

INTRODUCTION

In December 2019, a cluster of pneumonia cases with atypical and severe symptoms emerged in Wuhan Province of China. Due to the distinct clinical features of these patients, advanced laboratory investigations were performed, and a novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was isolated for the first time. The disease caused by the virus was also novel and named coronavirus disease 2019 (COVID-19). Then, the virus spread worldwide, and due to the rapidly increasing number of patients, World Health Organization declared this outbreak as a global pandemic on March 11, 2020.[1]

The clinical findings of COVID-19 range in a large scale between an asymptomatic carriage and severe presentations such as acute respiratory syndrome (ARDS) and multiorgan dysfunction.[2,3] Fortunately, early data revealed that children have a milder disease course and better prognosis compared to adults.[4,5] Thus, the idea of the children is almost not affected by the pandemic was prevalent. Families did not sufficiently insist on their children wearing a mask or keeping the social distance, and several

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governments loosened the school attendance restrictions.

However, this positive discrimination in favor of children provided by the virus did not last so long. In April 2020, SARS-CoV-2 was isolated from eight children with suggestive symptoms of Kawasaki disease (KD), such as fever, conjunctivitis, and peripheral edema. In addition to KD- resembling features, those children had gastrointestinal symptoms such as vomiting and diarrhea and developed refractory shock.[6] Subsequently, it has been shown that SARS-CoV-2 may also induce a hyperinflammatory state in children resembling toxic shock syndrome (TSS) and macrophage activation syndrome (MAS) rather than KD.[7,8] Therefore, the Centers for Disease Control and Prevention (CDC) recognized this SARS-CoV-2-induced hyperinflammatory condition as a novel disease and named it as multisystem inflammatory syndrome in children (MIS-C).[9]

Recent findings regarding MIS-C suggest that children are not thought to have host advantages against SARS-CoV-2 as much as previously considered. Therefore, in this review article, we aimed to contribute to a better understanding of this novel disease.

Epidemiology

A male dominance among the patients was shown in several studies.[10-12] A systematic review evaluating 917 MIS-C patients showed that the median age of the patients was 9.3 years, and 56.8% of the cases were males.[13] Similarly, male/female ratio was 1.37:1, and the median age was 7.5 years in another systematic review including 992 MIS-C patients.[14] It is well known that the current pandemic was originated from East Asia. Besides, KD is in the differential diagnosis of MIS-C mostly seen in Asian children.[15] On the contrary, there is an Afro-Caribbean and Hispanic ethnic predominance among the MIS-C patients.[16] These intriguing findings make us consider that a genetic predisposition or environmental circumstances may play a pivotal role in the pathogenesis of MIS-C.

Pathogenesis

Although it has not been precisely elucidated yet, there are several suggested mechanisms for explaining the pathogenesis of MIS-C. Children diagnosed as MIS-C usually have contracted SARS-CoV-2 infection two to four weeks before the onset of MIS-C symptoms.[17] There is an overall four-week interval between the date of the peak incidence of the outbreak and the date of the observation of MIS-C patients for the first time.[18-21] Besides, it has been demonstrated in several studies that positive antibody testing is much more common than polymerase-chain reaction (PCR) test positivity among MIS-C patients.[22-24] These findings strongly suggest that a post-infectious process rather than a direct viral invasion is responsible for the pathogenesis of the disease.

There are also conflicting hypotheses. For instance, a decreased SARS-CoV-2 antibody activity in patients with MIS-C compared to COVID-19 patients has been recently shown. Therefore, a persistent infection was speculated to be the main pathogenic mechanism instead of a post-infectious syndrome.[25] Consistently, Colmenero et al.[26] demonstrated viroid particles of SARS-CoV-2 in the skin biopsies of seven children who presented with chilblain four weeks after the peak incidence of the outbreak in their geographical region, similar to the MIS-C patients.

Since there are several clinical similarities between TSS and MIS-C, studies focused on investigating the molecular proof of this similarity have been also performed.[27] It is already known that staphylococcal enterotoxin B (SEB) has a superantigen (SAg) motif, and this motif causes host-cell damage via inducing a massive release of inflammatory cytokines.[28] Similar to SEB, SARS-CoV-2 has also been shown to encode a protein that shares remarkable sequential and structural similarities with SAgs.[29,30]

A study evaluating 58 MIS-C patients reported that while the PCR test was negative in most of their patients, SARS-CoV-2 antibody test results were positive. Besides, majority of them had significantly elevated inflammatory markers, and anakinra (anti-IL-1 agent) and achieved a prominent clinical improvement. Therefore, they suggested that the possible mechanism of action of the disease is an exacerbated post-infectious hyperinflammatory response.[31]

Similarly, most of the patients presented with cardiac signs and increased inflammatory markers, and as reported by Kaushik et al.[32] they had antibody positivity against SARS-CoV-2. Given that there is no strong evidence for the cardiac tropism of the virus, they proposed that an antibody-induced cytokine storm may be responsible for the tissue damage.

Clinical features

The first cases with SARS-CoV-2- induced hyperinflammation were reported by Riphagen et al.[6] from the United Kingdom (UK). As it was mentioned before, the patients all had KD- like symptoms such as fever, conjunctivitis, peripheral edema, and extremity pain. Moreover, they had gastrointestinal features such as diarrhea, vomiting, and abdominal pain. However, none of them had significant respiratory involvement. One of the patients who developed cardiac dysrhythmia and received extracorporeal membrane oxygenation (ECMO) therapy unfortunately died. An unclear linkage between KD and SARS-CoV-2 was emerged.

Following this study from the UK , Chiotos et al.[33] described six patients with MIS-C. Similarly, they had KD-like features, gastrointestinal symptoms, and shock. Among ten MIS-C patients reported from Italy, in addition to KD-like symptoms such as fever, rashes, conjunctivitis, mucositis, and lymphadenopathy, the patients had diarrhea (n:6), hypotension (n:5), pneumonia (n:5), and meningeal signs (n:4).[22]

However, subsequently reported cases with SARS-CoV-2- induced hyperinflammation had distinct aspects from the KD. Rather than the KD, given the clinical and laboratory similarities such as fever, refractory shock, organ damage signs, and complete blood count, cytokine, inflammatory markers, and lipid profiles, TSS and MAS were also emphasized in the differential diagnosis of MIS-C, as well.[17,34,35]

In the study which reported the first MIS-C cases from New York City, although all the patients were seropositive, only seven of fifteen cases had a positive PCR result. While all the patients had fever, the patients also had severe cardiac involvement (n:13), gastrointestinal features (n:13), skin changes (n:7), respiratory involvement (n:7), conjunctivitis (n:4), peripheral edema (n:4), and 9 cases required treatment with inotropic or vasopressor agents. Levels of acute phase reactants increased in most of them, whereas platelets, lymphocytes, and serum albumin levels decreased.[36]

It was shown in a retrospective study that following the fever, the most common symptoms among MIS-C patients were gastrointestinal involvement, conjunctivitis, erythematous rash, and oral changes.[37] A study from Turkey, including 36 MIS-C patients, reported that the most common symptoms were fever, mucocutaneous rashes, and gastrointestinal symptoms, respectively.[38] Fever and abdominal pain were the most common symptoms in a study of Tolunay et al.[39] The first report regarding the MIS-C from East Mediterranean Region compared COVID-19 and MIS-C and revealed that the patients with MIS-C had a higher duration of fever and higher rates of rashes and conjunctivitis.[40]

According to a systematic review article, the most common clinical findings out of fever were as follows: gastrointestinal (87%), muco-cutaneous (73%), cardiovascular (71%), respiratory (47%), neurological (22%), and musculoskeletal (21%) symptoms.[16] Similarly, it has been revealed in a more current systematic review that the two most common symptoms of MIS-C patients were fever and gastrointestinal symptoms.[16]

It was previously mentioned that MIS-C mainly occurs in school-age children and adolescents. However, there is a recent paper describing ten infants with MIS-C. Unlike seen in older ones, the most common finding other than fever was rashes. Five patients had respiratory distress, and one had febrile convulsion. Unfortunately, two with congenital heart diseases died.[41]

Considering the underlying pathogenic mechanism of MIS-C, in addition to TSS, MAS, and KD- like symptoms, a variety of organ damage or inflammation signs are already expected. For instance, several MIS-C patients initially presented with acute abdomen- like signs such as acute appendicitis.[42,43] Furthermore, it is well known that MIS-C patients may have severe cardiac compromise at high rates that can be considered life-threatening events.[44]

Therefore, to prevent unnecessary surgical operations during the pandemic, it has been suggested that pediatric surgeons perform a myocardial evaluation and rule out the MIS-C in children who presented with acute abdomen.[45]

Although any segment of the gastrointestinal tract can be compromised, there is a predominance of ileal and colonic inflammation among the patients. Progressive bowel obstruction which mainly recovers with medical treatment may occur. However, a minority of the cases may require surgical resections.[46]

In a retrospective study, acute kidney injury (AKI) was seen in ten of fifty-five MIS-C patients. AKI developed at admission in most of them which were associated with lower serum albumin levels and higher white blood cell counts.[47]

Two out of 9 MIS-C patients recently reported from Germany had unusual findings. One developed encephalomyelitis. The other had been newly diagnosed with acute leukemia, just a few weeks after the onset of SARS-CoV-2 infection. Two days after the chemotherapy, this male patient had a sudden respiratory failure and was diagnosed as MIS-C in the intensive care unit. However, it remains unclear whether chemotherapy or the virus triggered leukemia.[48]

Thirty-five patients admitted to the pediatric intensive care unit due to acute heart failure and hyperinflammatory condition were evaluated in a multicenter study, and SARS-CoV-2 infection was proven in thirty-one of them.[49] Furthermore, Stevens et al.[50] reported a MIS-C patient who initially presented with acute pancreatitis, and Kashyap et al.[51] reported a seven-month-old patient with MIS-C-related status epilepticus.

We also encountered children with MIS-C in our daily practice. There was a slight male predominance, and cases were mostly school-age children and adolescents, similar to the current literature.[13,14] While the PCR tests were negative in most of them, they were seropositive against SARS-CoV-2. Fever and gastrointestinal symptoms were the most common symptoms. Although not pointed out before, rashes of our patients were mostly well-demarcated and round shaped. We presented rashes of some of our patients below (Figure 1). Thrombocytopenia, lymphopenia, abnormal cardiac enzymes, and elevated acute phase reactants were the most common laboratory findings. Overall, one third of the patients required intensive care due to respiratory failure or other severe organ damages. All but one recovered completely. Unfortunately, one patient who previously received the diagnosis of acute lymphoblastic leukemia died.

Diagnosis

Considering the similarities and differences between the hyperinflammatory conditions caused by SARS-CoV-2, and KD, TSS, and MAS, this novel entity was considered to be a unique disease by CDC, and its diagnostic criteria were established (Table 1).[9,52]

Table 1. Diagnostic criteria of MIS-C

Case Definition for MIS-C (48)

- An individual aged <21 years presenting with fevera, laboratory evidence of inflammationb, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurological); **AND**
- No alternative plausible diagnoses; **AND**
- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test or COVID-19 exposure within the four weeks before the onset of symptoms.

COVID-19, coronavirus disease 2019; IL, interleukin; MIS-C, multisystem inflammatory syndrome in children; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a] *Fever ≥38.0°C for ≥24 hours or report of subjective fever lasting ≥24 hours.*

[b] *Including, but not limited to, one or more of the following: an elevated C-reactive protein, erythrocyte sedimentation rate, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin.*



Figure 1. The rashes seen in some of our MIS-C patients

Treatment

Since highly suggestive symptoms for KD are seen in patients with MIS-C, early cases were treated with intravenous immunoglobulin (IVIG) and acetylsalicylic acid similar to the patients with KD, and favorable outcomes have been achieved.[6,49,53] Moreover, immunomodulatory treatment options such as anakinra and tocilizumab were given to IVIG and steroid non-responders which were found to be highly effective.[31,32,53]

Given that the MIS-C is a hyperinflammatory condition, steroids were widely used based on their well-known strong anti-inflammatory effects although their safety and efficacy remain unclear.[17] In a study from Istanbul, seven of twenty MIS-C patients required intensive care. While IVIG responses of the patients were inadequate, steroids were observed to have a dramatic effect.[54]

In our daily practice, all patients with MIS-C are initially given IVIG at a dose of 2 gr/kg as the first-line treatment. If there is shock or organ threatening event, methylprednisolone (1-2 mg/kg/day) is added. To the refractory cases, methylprednisolone (10-30 mg/kg/day) or high dose anakinra is given as the second-line treatment. Moreover, all of the MIS-C patients receive acetylsalicylic acid unless active bleeding or platelet count is lower than 80 000/ mm^3.[55] Plasmapheresis is performed in patients with resistance to medical treatment options in our center, and most of our refractory cases clinically have improved so far. We tried to summarize schematically our therapeutic approach (Figure 2).

In a study from the United States, infliximab (an anti-tumor necrosis factor-alpha agent) was given to 12 of 13 IVIG and steroid non-responder MIS-C patients, and all of them recovered.[56] Consistently, as recently

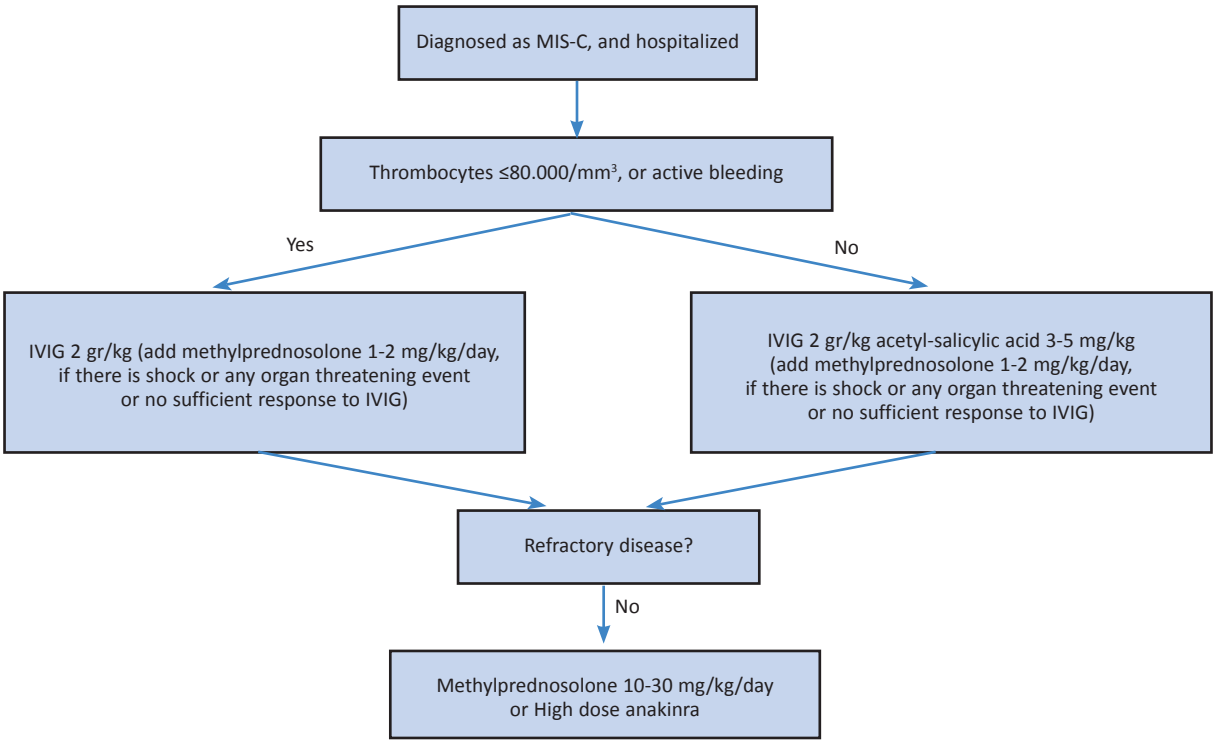


Figure 2. Our therapeutic approach for the MIS-C

reported by Alkan et al.[57] the authors had given infliximab to a MIS-C patient with underlying inflammatory bowel disease, and they achieved clinical recovery.

Although there is insufficient data regarding the safety and effectiveness of highly invasive procedures such as ECMO, they may be performed in medically intractable MIS-C patients.[58]

CONCLUSION

In conclusion, MIS-C is a less understood, rare, and highly fatal complication of COVID-19. Given the recent data regarding MIS-C, children are not thought to be in a favorable position during the pandemic as was presumed previously. Clinicians should be aware of this novel disease while evaluating children with persistent fever and history of COVID-19 contact or active infection. Since the clinical signs may rapidly deteriorate in these patients, medical treatment should be promptly started if there is a diagnostic suspicion. Besides, it has been recently seen that these patients could present with many distinct clinical pictures such as acute appendicitis or pancreatitis. Therefore, particularly in these extraordinary days, MIS-C should always be kept in mind for children with unusual signs and symptoms.

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