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Review Article

Multisystem Inflammatory Syndrome in Children: An Overview

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Abstract

Introduction: The first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first seen in China in late 2019 and has rapidly spread across the world. As per the previous reports of SARS-CoV-2 infection, it was not seen very commonly in young children. The reason for such a low number of cases could be either asymptomatic cases or mild forms of the disease in this age group. A new syndrome termed "multisystem inflammatory syndrome in children" (MIS-C) was first described in April 2020, with a probable relation to SARS-CoV-2 infection.

Aim of Work: This review aims at highlighting an overview of, and an update on, the multisystem inflammatory syndrome in children.

Methodology: The review is a comprehensive research of WHO official page, Google Scholar, and PUBMED from the year 2005 to 2021.

Conclusion: A lot of knowledge has been gained about MIS-C temporally associated with COVID-19 in a very short span of time; nevertheless, there are still many uncertainties that exist. It is an unusual disease with varying severity and symptoms. The course of the disease is usually turbulent, leading to multiple organ failure and may require hospitalization in intensive care. Although an association does exist between SARS-CoV-2 and COVID-19, more serological tests and viral research need to be conducted to establish definitive evidence of COVID-19 being caused by SARS-CoV-2.

Keywords: *Multisystem Inflammatory Syndrome in Children; Kawasaki Disease; Anticoagulants; Toxic Shock Syndrome; Immunoglobulins*

Introduction

The first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was first reported in China in late 2019 and has quickly spread across the world [1].

Looking at the rapid spread of the disease into different parts of the world, an international public health emergency was declared by the World Health Organization (WHO) on January 30, 2020, and a pandemic on March 1, 2020. As per the previous reports of SARS-CoV-2 infection, it was not seen very commonly in young children. The reason for such a low number of cases could be either asymptomatic cases or mild forms of the disease in this age group [1].

A new syndrome termed "multisystem inflammatory syndrome in children" (MIS-C) was first described in April 2020, with a probable relation to SARS-CoV-2 infection. The initial cases were reported in the U.K, and Italy followed by the U.S. Conditions like Kawasaki Disease

(KD), toxic shock syndrome (TSS), and secondary hemophagocytic lymphohistiocytosis (SHLH)/macrophage activation syndrome (MAS) share some common features with this syndrome [2].

Definition of MIS-C

In May, a health advisory was issued by CDC, and a definition for a case of MIS-C was given (Box 1) [3].

1. An individual aged < 21 years with:
2. Clinical criteria:
   - A minimum 24-h history of subjective or objective fever ≥ 38.0 °C AND
   - Severe illness requiring hospitalization AND
   - Two or more organ systems affected (i.e., renal, cardiac, respiratory, hematologic, neurological, gastrointestinal, dermatological)
3. Laboratory evidence of inflammation
   - One or more of the following: an elevated ESR, CRP, fibrinogen, procalcitonin, D-dimer, LDH, ferritin, or IL-6; elevated neutrophils or reduced lymphocytes; low albumin
4. Laboratory or epidemiologic evidence of SARS-CoV-2 infection
   - Positive SARS-CoV-2 testing by RT-PCR, serology, or antigen OR
   - COVID-19 exposure within 4 weeks prior to onset of symptoms
5. No alternative diagnosis

Abbreviations: CDC, Centers for Disease Control; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; RT-PCR, reverse transcriptase polymerase chain reaction; SARS_C0V-2, severe acute respiratory syndrome coronavirus-2.

Box 1: *CDC case definition for multisystem inflammatory syndrome in children (MIS-C) [3].*

Pathophysiology of MIS-C

The pathophysiology of MIS-C is still unclear. Although, an intensified immune system or maladaptive patient response could be the cause. Hyperinflammation occurs whenever the virus entering the human cells initiates an exaggerated and unregulated immune response [4].

Cytokine storm is a clinical syndrome caused by the overproduction of cytokines. During infections, these cytokines provoke immunity and immunopathology. One of the commonest causes of mortality in infected patients is the inflammatory response triggered by SARS-CoV-2 [5]. SARS- CoV-2 induced infection of dendritic cells or macrophages stimulates the production of inflammatory cytokines such as IL-6, interleukin [IL]-1, tumor necrosis factor [TNF], and interferon-γ [6]. The role of IL-6 and other such inflammatory cytokines is the expression of tissue factors, resulting in the release of inflammatory kinins and activation of coagulation and the complement cascade. Both innate and acquired immunity are affected due to the excessive production of IL-10, IL-6, and TNF, as it is inversely proportional to the total lymphocyte count [7].

Just like in cytokine storms, whenever there is a production of excessive mediators of inflammation, it leads to exaggerated immune system activation. This occurs in a variety of conditions sharing the same pathogenic mechanism but with different triggering factors [4]. The high levels of ferritin in inflammatory syndromes are due to the neutrophils that play a key role in the cytokine storm. The ferritin prevents the differentiation of myeloid cells and B and T lymphocytes, causing a deteriorated response. The severity of inflammation is related to the level of ferritin and hemophagocytosis and is seen in numerous diseases with diverse etiologies: sepsis, macrophage activation syndrome, multisystem inflammatory syndrome (MIS), hemophagocytic lymphohistiocytosis (HLH), staphylococcal toxic shock, and severe cases of COVID-19.

Therefore, inflammatory conditions such as macrophage activation syndrome, Kawasaki disease, secondary HLH, and sepsis share a lot of common features with MIS-C [8].

Clinical presentation

Although there is little knowledge about the SARS-CoV-2 infection in children, most of the symptoms are related to upper respiratory tract infection and pneumonia with some cases of gastrointestinal symptoms. [9] According to some studies, children and adolescents have shown rapid and severe clinical picture with progression to cardiogenic shock and may require hospitalization (Table 1) [14].

Author	No. of patients	Age	Symptoms	SARS-CoV-2 detection	Laboratory tests	Imaging findings
Riphagen S., *et al.* United Kingdom [10]	8	4-14 years	Unrelenting fever, rash, conjunctivitis, peripheral edema, gastrointestinal symptoms, extremity pain, pleural and pericardial effusion. No significant respiratory involvement	RT-PCR not detected, serology not specified	↑ CRP ↑ PCT ↑ ferritin ↑ triglycerides ↑ D-dimer Negative blood cultures One positive RT-PCR enterovirus/adenovirus	X-Ray/CT: pleural effusion, ascites, lung consolidations, ileitis. ECHO and EKG: myocardial dysfunction, ventricular dilatation, arrythmias, non-specific EKG, echobright coronary vessels giant coronary aneurysm
Whittaker E., *et al.* United Kingdom and USA [11]	58	5-14 years	Fever, headache, vomiting, abdominal pain, diarrhoea, rash, sore throat, conjunctival infection, lymphadenopathy, cracked lips, swollen hands and feets, acute kidney injury and shock	RT-PCR detected (26%) Serology IgG detected (87%)	↑ CRP and neutrophil counts ↓ albumin and lymphocyte counts ↑ troponin and BNP concentrations	ECHO and EKG: non-specific EKG myocardial dysfunction, arrhythmia, coronary abnormalities such as aneurysms and giant aneurysms

Toubiana J., *et al.* France (Paris) [12]	21	3-16 years	Headache, cough, fever, anosmia, coryza, polymorphous skin rash, changes in the lips/ oral cavity, conjunctival infection, gastrointestinal symptoms, peritoneal effusion, confusion. Myocarditis, hypotensive shock.	RT-PCR detected (38%) Serology IgG detected (90%)	↓ albumin ↓ lymphocytes and platelets ; ↑ CRP, PCT, lipase, D-dimer, neutrophil count ↑, ↑ alanine transaminases, ↑ IL-6, ↓Na, Acute kidney injury, Anaemia, No other pathogen identified except one serology suggestive of recent Epstein-Barr virus infection	X Ray/CT: Ground glass opacities, local patchy shadowing, interstitial abnormalities ECHO and EKG: Increased QT interval, arrhythmias, signs of ischemia, pericardial effusions, myocardial dysfunction. Coronary artery abnormalities.
Belhadjer., *et al.* France and Switzerland [13]	35	2-16 years	Fever, asthenia (100%), abdominal pain, vomiting, diarrhea (80%), respiratory distress (65%), skin rash, cheilitis, cervical adenopathy, meningism, chest pain, heart failure, cardiogenic shock.	RT-PCR detected Serology IgG detected (86%)	↑ leukocytes and neutrophils ↑ IL-6 ↑ CRP, PCT, D-dimer, troponin, and BNP	ECHO and EKG: Unspecific EKG, signs of ischemia ↓ LV ejection fraction, pericardial effusion, coronary arteries dilatation. No coronary aneurysm

Table 1: *Imaging and laboratory findings of children and adolescents presenting with SARS-CoV-2-related symptoms and signs of MIS-C, according to the authors [14].*

Comparison between MIS-C and other known syndromes

Comparison between patients with MIS-C and other well-defined syndromes helps in studying the pathogenesis of the disease and in treatment planning [15].

Kawasaki disease (KD)

KD usually causes vasculitis of the medium vessels and is mostly seen in coronary arteries becoming the most common cause of acquired heart disease. Young children in developed countries are most commonly affected [15].

The clinical features are typically seen in KD are cervical lymph node enlargement, rash, ocular and oral mucosal changes, along with the involvement of lungs, liver, gastrointestinal tract, central nervous system, and joints. CRP, which is an inflammatory marker, is increased in KD. Patients with MIS-C show a greater tendency for cardiac dysfunction and hypotension as compared to KD patients who show coronary artery abnormalities [15].

Although the etiology of KD remains unclear, there is proof showing the role of the virus in stimulating an inflammatory response in genetically predisposed children. The treatment of KD in children involves the use of intravenous immune globulin (IVIG), aspirin and other immunomodulators [15].

Toxic shock syndrome (TSS)

TSS occurs due to the activation of the immune system by "superantigens". There is a massive cytokine release that occurs due to the stimulation of T-cells by the superantigens. Bacterias like *Staphylococcus aureus* and *Streptococcus pyogenes* secrete exotoxins that act as superantigens. Studies have shown that even viruses can also act as superantigens [16].

The clinical features seen in toxic shock syndrome include diffuse erythrodermic rash, hypotension, mucous membrane involvement. There are also multiple organs involved, such as hematologic, renal, muscular, hepatic, respiratory, and neurologic) [16].

The management of TSS consists of volume resuscitation, anti-microbials against the causative agent, and sometimes IVIG for managing refractory hypotension. The mechanism of action by which IVIG is supposed to act is by the neutralization of bacterial superantigens and downregulating the overactive immune response [16].

Secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome (SHLH/MAS)

Hemophagocytic lymphohistiocytosis (HLH) consists of a strong immune response that is constant and ceaseless. Any anomaly in the genes regulating the degranulation of natural killer cells and cytotoxic CD8+ lymphocytes results in primary HLH. As a result, the antigenic stimuli that resulted in cellular activation could not be eliminated, causing a "cytokine storm." With an increase in pro-inflammatory cytokines, like interferon (IFN)-gamma, IL-18, and IL-1, there is an activation of cells like macrophages, resulting in the destruction of the organ and the characteristic hemophagocytosis [17].

However, when HLH is initiated by an autoimmune or autoinflammatory condition (MAS), medications, malignancy, or infections, it is known as secondary HLH. Viral infections are considered a well-known trigger factor for SHLH. The typical presentation in patients with SHLH is systemic inflammation with an increase in triglycerides, CRP, and D-dimer. There is also the presence of organ dysfunction, such as liver failure, coagulopathy, CNS, and cardiac dysfunction. Remarkably, there is a fall in the peripheral white blood cell count, platelet count, and ESR in SHLH. The mortality is high in untreated SHLH cases [18].

Management of patients with MIS-C

The primary goal of the treatment for MIS-C patients is to reduce systemic inflammation and reestablish organ function. Supportive treatment such as oxygen supplementation, ventilatory, cardiovascular, and renal support, and pharmacotherapy should be given importance. There is very little evidence regarding the indication and correct time of possible treatments, and a lot of centers advocate the use of intravenous immunoglobulin (IVIG), corticosteroids, immunomodulators, anticoagulants, and antiplatelet agents [8,19].

Along with IVIG, other capable treatment options have been recommended for treating cytokine storms. The presence of hyper inflammation emphasizes the therapeutic possibility of using immunomodulatory agents in COVID-19. In such cases, the inflammation

and mortality can be reduced with the help of IVIG, corticosteroids, selective cytokine blockers (anakinra, tocilizumab), anticoagulants, remdesivir, and convalescent plasma [8,19].

Intravenous human immunoglobulin

Whenever Kawasaki disease is considered as a part of the differential diagnosis, IVIG is the first line of treatment for MIS-C at multiple centers [20]. Most of the suspected cases of MIS-C with a differential diagnosis of atypical Kawasaki or Kawasaki-like disease were given IVIG (2 g/kg). These patients required recurrent admission to the ICU, and there was progression into shock and myocardial dysfunction, which required vasoactive support. IVIG therapy was advised for previously reported cases of COVID-19 and Kawasaki-like disease [12].

Belhadjer., *et al*. reported a case series of 35 children diagnosed with MIS-C who were admitted to the ICU. All the patients suffered from myocardial dysfunction, and 80% of them were given inotropic drugs for hemodynamic support. Out of the 35 patients, 25 patients were given IVIG resulting in recovery from myocardial function, therefore proving that IVIG has a good prognosis [13].

Corticosteroids

The general use of corticosteroids in the management of severe COVID-19 has not been recommended as per the current WHO guidelines unless there was a clinical condition in where the corticosteroids had a verified beneficial effect [21].

A meta-analysis consisting of 2,746 patients who were suffering from Kawasaki disease showed that the risk of the coronary aneurysm was less when both corticosteroids and immunoglobulins were given as opposed to just IVIG therapy. As per the case series published in pediatrics, corticosteroids such as methylprednisolone and hydrocortisone are the most commonly administered drugs in MIS-C. In the majority of the studies, 2 mg/kg of methylprednisolone was given, and the treatment duration was not specified [12-19].

IL-6 inhibitors

Tocilizumab is a recombinant monoclonal antibody that acts by binding to the IL-6 receptor directly. It not only crosses the blood-brain barrier and releases prostaglandin E2 but also causes a rise in temperature [22]. If the IL-6 receptors are inhibited, they cause a fall in cytokine production, thereby suggesting a possible treatment option for hyper inflammation, although there are no studies done in the pediatric population yet. Adults and children with autoimmune diseases can be given otocilizumab, which is approved by the US Food and Drug Administration (FDA) whenever there is cytokine release syndrome. As the cytokine storm in COVID-19 and the cytokine release syndrome are very similar, there are many studies being undertaken to assess the safety and efficacy of this therapeutic modality [22].

Antiviral drugs

Remdesivir has shown *in vitro* and *in vivo* effectiveness against SARS-CoV-2 and other beta-coronaviruses [23]. A multicenter, randomized, placebo-controlled study showed that remdesivir reduced the duration of hospitalization for adult patients with COVID-19 [24].

Anticoagulation

Cytokine storm results in activation of the coagulation cascade, thereby causing thrombosis [8]. In addition, critical COVID-19 patients also suffer from vascular injury, which could be very severe. Pulmonary microthrombi were seen in great numbers along with other organs during autopsy due to hypercoagulability and extensive endothelial injury. A retrospective study showed that adults who had high levels of D dimer and were on enoxaparin had a low mortality rate as compared to those who were not. Such observations have resulted in the use of anticoagulant therapy in adults. However, in the reported case series of MIS-C, the use of anticoagulants was not constant and fluctuated from 12.5% to 90.1% [25].

Conclusion

In a very short duration of time, we have learned a lot about MIS-C and its temporal association with COVID-19; nevertheless, there are still many uncertainties. It is an uncommon disease with varying symptoms and severity. It may have an unstable course leading to multiple organ failure and the need for critical care.

Patients with critical conditions should be admitted to intensive care, but if that is not available, supportive therapy including immunomodulation, and anticoagulation, should be started in the critical care unit.

There are a lot of hurdles that should be crossed to understand this disease. It is absolutely necessary to clarify whether MIS-C is a new condition or shares a common mechanism with other pathologies. Evidence indicates that it is an immune-mediated disease, and SARS-CoV-2 acts like a spark that initiates it. Although an association does exist between SARS-CoV-2 and COVID-19, more serological tests and viral research need to be conducted to establish definitive evidence of COVID-19 being caused by SARS-CoV-2.

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