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Review Article

Multisystem Inflammatory Syndrome in Children Associated with Covid-19- A Comprehensive Literature Review

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Abstract

During the Covid 19 pandemic, a cluster of cases was reported in April 2020. United Kingdom and subsequently in New York City with high fever, shock, and hyperinflammation. RCPCH, CDC and ACR addressed this as Pediatric Multisystem Inflammatory syndrome. Many of these cases had toxic shock-like syndrome or Kawasaki-like syndrome associated with a positive diagnostic test for covid-19. The goal of this review is to fill the knowledge gap for this novel syndrome and send a message to all pediatric healthcare providers to be alerted for multisystem inflammatory syndrome in children (MSIS-C), as it does not present with typical mucocutaneous symptoms and can mimic a routine diagnosis. Early diagnosis and appropriate treatment are critical for better outcomes.

Keywords: *Multisystem Inflammatory Syndrome in Children Associated with Covid-19; MIS-C; Kawasaki Disease; Macrophage Activation Syndrome; Toxic Shock Syndrome*

Abbreviations

RCPCH: Royal College of Pediatrics and Child Health; ECDC: European Centre for Disease Prevention and Control; NHS: National Health Service, UK; RT-PCR: Reverse Transcription Polymerase Chain Reaction; IVIG: Intravenous Immunoglobulin; ARDS: Acute Respiratory Distress Syndrome; NETs: Neutrophil Extracellular Traps; WHO: World Health Organization; IVIG: Intravenous Immunoglobulin; TSS: Toxic Shock Syndrome; KD: Kawasaki Disease

Introduction

Although Covid-19 in children, did not report initially severe morbidities, and mortalities, only 2 - 6% of children required intensive care treatment. However, since mid-April 2020, a cluster of cases similar to Kawasaki disease have been reported linked with covid-19 infection in previously healthy children with unremitting fever, multisystem inflammation, shock, and pan carditis. This syndrome termed Multisystem inflammatory Syndrome in children [1,2] the Centers for Disease Control and Prevention (CDC) and the WHO. It was reported in children with persistent fever (100%), conjunctivitis (68%), skin rash (75%), raised inflammatory markers (100%), coagulopathy (100%), gastrointestinal manifestation (85%), and cardiac involvement (75%). The overlap between MIS-C, Kawasaki disease (KD), and macrophage activation syndrome suggests that MIS-C represents a spectrum of diseases [3]. Positive PCR or serology for Covid-19 and close contact with a covid19 positive case, helps to differentiate MIS-C from other illnesses [3]. However, a growing number of similar case

series have been reported from the United Kingdom, Italy, the United States and many other countries [4]. A case series included twenty children admitted to four academic tertiary care ICUs with shock, fever, and acute myocarditis with suspected SARS-CoV-2 infection between April 15th and April 27th, 2020 [5]. While reviewing the literature so far at least sixteen cases of MSIS-C have been reported from Saudi Arabia, the majority from the Eastern Province with one mortality [6,7]. The primary purpose of this case reporting is to enable the physicians to diagnose and make informed clinical decisions when caring for patients with MIS-C, in addition, this comprehensive review will reduce the knowledge gaps for this novel syndrome.

Discussion

Only, USA, covid-19 cases reported 'tragic' 1 million, constitutes about 11.5% of the total cases, 1.6% hospitalization, 0.01% death among children [8]. Although the hospitalization rate ranged from 2.5 to 4.1 percent from 14 states of the USA by late July 2020, surprisingly thirty-three percent required critical care and 6 percent required ventilatory support [8]. The initial presentation of Covid-19 in children was noted to be milder, difficult to diagnose unless screening is done. A systemic review of 7480 confirmed pediatric patients age < 18 years noted 15 percent cases were asymptomatic, 42 percent mild, 39% moderate without oxygen requirement, 2 percent severe with hypoxia needed positive pressure ventilation and 0.7 percent were critical, shocked, ARDS, besides, mortality was 0.06% [8]. Notably, children with a pre-existing disorder like cystic fibrosis, chronic asthma, congenital heart diseases, malnutrition, and obesity appeared associated with poor outcomes [9,10]. During the covid-19 pandemic, in April 2020 [11] a cluster of cases 1st reported in the UK, with high-grade fever, shock and hyperinflammation. RCPCH, UK addressed this as Pediatric Multisystem Inflammatory Syndrome temporarily associated with COVID-19, whereas CDC and the American College of Rheumatology (ACR), named it Multisystem Inflammatory Syndrome in Children Associated with COVID-19 (MIS-C), on the other hand, European CDC (ECDC) assigned it as Pediatric Inflammatory Multisystem Syndrome temporally associated with SARS-CoV-2 (PIMS-TS) [12]. But in our discussion, we will refer to it as MIS-C. The multisystem inflammatory syndrome in children should have six principal elements: persistence fever, pediatric age group, high laboratory marker of inflammation, signs or symptoms of organ disorder, absence of an alternative diagnosis, and associated with laboratory confirmation of covid-19 infection or exposure [13]. NHS of the United Kingdom in April 2020 raised the alarm of children with serious multisystem hyperinflammatory syndrome associated with the confirmed covid-19 test. Subsequently, a similar case was reported in many countries such as France, the USA, Italy, Spain, and India [14]. The Centers for Disease Control and Prevention (CDC) issued a national health advisory on May 14, 2020, with a case definition for multisystem inflammatory syndrome in children (MIS-C) [14,15]. Table 1 additional case definitions were made by RCPCH and WHO [16,17]. Eventually, the epidemiology and clinical course of the multisystem inflammatory syndrome in children (MIS-C) and its temporal association with Covid-19 had been published in the New England Journal of Medicine, included 186 patients in 26 states in the USA. All patients fulfilled the diagnostic criteria for MIS-C, median age 8.3 years, 62% male, about 70% positive for SARS-CoV-2 by RT-PCR or antibodies. Organ involvement, GI 92%, cardiovascular 80%, hematological 76%, mucocutaneous 74%, Respiratory 70%, ICU care 80%, and received ventilatory support 20%. Mortality observed 2%, Coronary-artery aneurysms reported 8%. Kawasaki's disease-like features were documented at 40%. Most of the patients elevated at least four inflammatory biomarkers [18]. Dated on 6th January 2021, so far, a total of 1288 cases of MIS-C were diagnosed, and 23 died in 44 states of the USA [19]. 1st May to 24th June 2020, three children's hospitals from Santiago, Chile, reported a case series (n = 27) child with MIS-C with demographic, epidemiological, clinical as well as laboratory tests, in addition to cardiac findings, and clinical outcomes [20].

An individual aged < 21 years presenting with fever*, laboratory evidence of inflammation**, 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 exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms. *Fever > 38.0°C for ≥ 24 hours, or fever lasting ≥ 24 hours **Elevated one or more of the following: CRP or ESR or fibrinogen, procalcitonin, d -dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin. Additional comments: • Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C. • Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

Table 1: *The case definition for MIS-C (CDC).*

12th May 2020, France and Italy observed an unusually higher incidence of TSS with some feature of KD in Pediatric ICU some of them positive for SARS-COV-2 either PCR or serology [21]. Early Warning and Response system declared by EU's, Austria, Germany and Portugal [22]. Prospective Multicenter cohort study conducted, in 17 pediatric intensive care unit from March to July 2020 in Brazil, fifty-six patients were included who met the MIS-C diagnostic criteria. This study well described the clinical, laboratory, and radiological characteristics, in addition to the outcomes of MIS-C [23]. Few additional MIS-C cases have been reported from Canada (n = 12) and Switzerland (n = 3) [22]. Surprisingly, from May 15, 2020, to July 30, 2020, Dr. Tahera Nasrin, a pediatric cardiologist from Bangladesh published an article, described 15 children with echocardiographic features of multisystem inflammatory syndrome. 75% of the case presented more than one week, had a poor outcome [24]. Department of Infectious Diseases, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran, published an exclusive article on Multisystem inflammatory syndrome associated with SARS-CoV-2 infection a case series 45 children involved, 21st August 2020. They reported markedly elevated ESR (97%), Abnormal ferritin (73%, > 500 ng/ml), high median fibrinogen, d-dimer, cardiac Involvement 56%, in addition to renal failure 29% cases [25].

An observational study conducted in Mumbai, India from 1st May to 15th July 2020, recruited 23 patients with median age 7.2 (0.8 - 14) years, 39.1% covid-19 positive, either RT-PCR or antibodies, 34% patients had positive contact history, 65% children presented shock, evidence of myocarditis, left ventricular dysfunction, and coronary artery dilatation (26%) with a satisfactory outcome. Steroid (96%) and IVIG (65%) received, with one child died [26]. Current situation of Saudi Arabia at the time of scripting this review, 362979 people had been infected with Covid-1, 6239 died, critical care admission rate 0.1%, mortality rate 1.7%, recovery 97.6% [27] and children affected 3% with age less than fourteen years. Highest cases in Makkah and Eastern Province. It is listed in the 15th position among the countries affected by the covid-19 pandemic [28]. In Eastern province, Al-Ahsa, Saudi Arabia reported multicenter case series of MIS-C included 10 patients, 90% were positive for Covid-19, all the patients had GI manifestation, required vasopressor or vasoactive support and presented with Kawasaki-like features as well as a shock. Two patients had co-morbidities, type-1 diabetes and G6PD deficiency [6]. The girl with G6PD deficiency died [7]. In July 2020, Suliman Habib Hospital reported a case with clinical-laboratory characteristics of a 2.5-year-old boy who tested positive for SARS-CoV2 and exhibited a picture of MIS-C [29].

Possible pathogenesis of multisystem inflammatory syndrome in children well illustrated by Mangla Sood [30]. The period from infection to the clinical presentation of MIS-C is unclear, whether MIS-C manifested as a result of acute infection or postinfectious process [11]. It could develop between 1st and 2nd weeks of illness or up to six weeks of exposure without any laboratory positive test for Covid-19 [31]. Pathophysiology of MIS-C proposed a delayed immunological phenomenon associated with Stage-3 hyper-inflammatory phase following either symptomatic or asymptomatic COVID-19 infection in children [32]. A recent study by Carter., *et al*. reported immunophenotypic of patients with MIS-C from the UK, concluded similar immunopathogenic disorder, but distinct from KD [33]. The literature reported that MIS-C classically manifested 3-4 weeks after SARS-CoV-2 infection, the majority of cases associated with positive antibodies to SARS-CoV-2, but negative RT-PCR test at the time of MIS-C diagnosis [34]. Antibody detection [35] was higher than that of RT-PCR detection (81% vs 37%), Virus-antibody interaction with Fc receptors, additional complement activation led to overproduction of these inflammatory mediators, cytokine storm causing vascular hyper-permeability, high fever, shock, and even evolve severe multi organ dysfunction [31,36]. Neutrophil extracellular traps (NETs) induced by the virus can trigger uncontrolled inflammatory and immunological responses, resulting in an exaggerated systemic inflammatory response, similar to hyperinflammation in MIS-C. For this reason, NETs have been shown to be elevated in the plasma of patients infected with SARS-CoV-1 [37]. Thus, MIS-C appears to be a clinical syndrome that shares aspects with other clinical conditions in which a massive amount of cytokines damage the various organs, such as Kawasaki disease, sepsis, macrophage activation syndrome, and secondary Hematophagocytic lymphohistiocytosis [31]. Clinical manifestation of MIS-C (Table 2 and figure 1) and summary of clinical and laboratory findings (Table 3 and 4).

• Persistent fevers (median duration four to six days) - 100 percent.
• Gastrointestinal symptoms (abdominal pain, vomiting, diarrhea) - 60 to 100 percent.
• Rash - 45 to 76 percent.
• Conjunctivitis - 30 to 81 percent.
• Mucous membrane involvement - 27 to 76 percent.
• Neurocognitive symptoms (headache, lethargy, confusion) - 29 to 58 percent.
• Respiratory symptoms - 21 to 65 percent.
• Sore throat - 10 to 16 percent.
• Myalgia - 8 to 17 percent.
• Swollen hands/feet - 9 to 16 percent.
• Lymphadenopathy - 6 to 16 percent.

Table 2: *Clinical manifestation of MIS-C from available case series.*

1.	Shock - 32-76 percent.
2.	Criteria met for (KD) 22 to 64 percent.
3.	Myocardial dysfunction: 51 to 90 percent.
4.	Arrhythmia - 12 percent.
5.	Acute respiratory failure requiring noninvasive or invasive ventilation - 28 to 52 percent.
6.	Acute kidney injury (most cases were mild) - 8 to 52 percent.
7.	Serositis (small pleural, pericardial, and ascitic effusions) - 24 to 57 percent.
8.	Hepatitis or hepatomegaly - 5 to 21 percent.
9.	Encephalopathy, seizures, coma, or meningoencephalitis - 6 to 7 percent.

Table 3: *Clinical finding of MIS-C from available case series.*

- **Abnormal blood cell counts, including:**
    - Lymphocytopenia - 80 to 95 percent.
    - Neutrophilia - 68 to 90 percent.
    - Mild anemia - 70 percent.
    - Thrombocytopenia - 31 to 80 percent.
- **Elevated inflammatory markers, including:**
    - C-reactive protein (CRP) - 90 to 100 percent.
    - Erythrocyte sedimentation rate - 75 to 80 percent.
    - D-dimer - 67 to 100 percent.
    - Fibrinogen - 80 to 100 percent.
    - Ferritin - 55 to 76 percent.
    - Procalcitonin - 80 to 95 percent.
    - Interleukin-6 (IL-6) - 80 to 100 percent.
- **Elevated cardiac markers:**
    - Troponin - 50 to 90 percent.
    - BNP or N-terminal pro-BNP (NT-pro-BNP) - 73 to 90 percent.
- **Abnormal Liver functions:**
    - Hypoalbuminemia - 48 to 95 percent.
    - Mildly elevated liver enzymes - 62 to 70 percent.
    - Elevated lactate dehydrogenase - 10 to 60 percent.
    - Hypertriglyceridemia - 70 percent.

Table 4: *Lab finding for MIS-C available case series.*

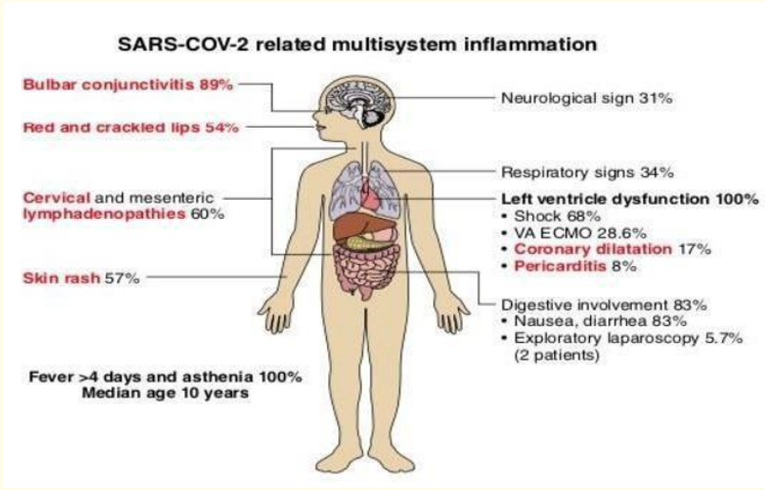

Figure 1: *Multiorgan involvement in children with MIS-C. Reprinted [Adopted] from" Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic" by Zahra Belhadjer. Journal Circulation originally published 17 May 2020.*

After reviewing 570 cases of MIS-C, the researchers concluded that there are three subtypes [38] of the syndrome. First group: MIS-C without overlap with acute COVID-19 or Kawasaki disease (KD) [16]. This group includes 35%. All patients were found to have GI, CSV involvement, and fifty percent had equal or more than four additional organ involvement, notable shock, cardiac dysfunction, elevated CRP, ferritin, and all patients had positive COVID-19 serology with or without positive PCR [39]. Secondly, MIS-C overlaps with severe acute COVID-19, this cohort was associated with a classic ARDS-like picture with high mortality, account 30%, and PCR positive with negative seropositivity. Finally, MIS-C overlaps with KD, 35% in this cohort, clinically noted rash, mucocutaneous involvement, less frequent stock or cardiovascular dysfunction, and younger age group. The majority of these patients had positive serology without positive PCR for Covid-19. MIS-C typically affects older children and adolescents, whereas classic KD affects the younger age group [39]. Toxic shock syndrome, macrophage activation syndromes [38], vasculitis, scarlet fever [40] and other viral infections should be considered as differential diagnoses of MIS-C [12,41,42].

Specialized Pediatric Center with multidisciplinary teams, such as critical care, infectious disease, immunology, cardiology and rheumatology, should be included for optimal MIS-C management [43]. Matthew D. Elias and other colleagues reviewed, the International Kawasaki Disease Registry across 38 institutions and eleven countries for the management of MIS-C. All cases received IVIG, steroid was used in severe cases or in the absence of response to IVIG. Aspirin 91% and a significant number of patients received prophylactic anticoagulation, especially patients at higher risk for venous thromboembolism. Echocardiographic evidence of giant coronary artery aneurysms treated with therapeutic anticoagulation [44]. American College of Rheumatology and COVID-19- Related Hyperinflammation Task Force [30] published guidelines for immunomodulatory, antiplatelet, and anticoagulant therapy in addition to cardiac management for MIS-C [16,30,45].

Conclusion

Carefully designed research is imperative to understand the pathophysiology and long-term outcome of MIS-C. As the differential diagnosis of MIS-C is broad, and pediatricians should involve a multidisciplinary treatment team for early diagnosis and optimal management of multisystem inflammatory syndrome in children.

Conflict of Interest Disclosures and Financial Disclosures

Author do not have any conflict of interest to disclose.

Author Contributions

Mohammed Shahab Uddin- Manuscript preparation. Submission Mohammed Al Qahtani- Review the final Manuscript Saleh Al fulayyih- Literature collection.

Sarah Al Baridi- Fund collection and selection of journal for manuscript submission.

All the authors approved the final manuscript prior to submit.

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