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A Review of Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic, with a high morbidity and mortality rate, has affected all age groups. COVID-19 infection in children usually has minimal symptoms, but the number of children with the inflammatory syndrome with clinical features similar to the Kawasaki disease has increased during the COVID-19 pandemic. Information about this emerging COVID-19 manifestation also called the multisystem inflammatory syndrome in children (MIS-C), is still incomplete. Patients typically present with persistent fever, followed by shock or multi-organ involvement. Laboratory findings and clinical presentation of this multi-organ involvement is part of the diagnostic criteria. Early treatment and multidisciplinary referral to pediatric specialists are essential. The prognosis of MIS-C is not yet fully understood. Although most children survive, several deaths have also been reported. Based on relevant evidence, this study aimed to review the pathophysiology, clinical manifestations, laboratory and imaging findings, diagnosis, treatment recommendations, and prognosis of MIS-C associated with COVID-19.

Keywords: COVID-19, Kawasaki Disease, Inflammatory Syndrome, Children

1. Context

On December 31, 2019, a cluster of pneumonia cases of unknown etiology was reported in Wuhan, Hubei Province, China (1). On January 7, 2020, a new type of coronavirus was recognized by the China Center for Disease Control and Prevention (1). The World Health Organization (WHO) temporarily named the virus 2019-nCoV. On February 11, 2020, the International Committee on Taxonomy of Viruses (ICTV) suggested the virus name SARS-CoV-2 because of its resemblance to SARS (2). Accordingly, WHO named the disease caused by SARS-CoV-2 infection COVID-19 (3) and declared it a pandemic on March 11, 2020 (3).

The COVID-19 infection in children is thought to be relatively mild compared with adult patients and often asymptomatic or minimally symptomatic (4-7). However, some children who contracted the COVID-19 infection or have been exposed to the virus present with clinical symptoms similar to the diagnostic criteria of Kawasaki disease (KD), along with shock (8, 9). In late April 2020, the National Health Services (NHS) of the United Kingdom and Pediatric Intensive Care Society (PICS) warned about a new COVID-19 manifestation in children similar to incomplete KD or toxic shock syndrome (10, 11). An association between the COVID-19 infection and late manifestations of vasculitis has been suspected, especially in asymptomatic younger patients, which may be related to post-viral immunological reactions (12, 13).

Kawasaki disease is known as the most common primary vasculitis in children, with impacts predominantly on medium- and small-size arteries (14). Although the cause of KD is still unknown, the role of a viral trigger in genetically predisposed children is considered, as well as several respiratory viral agents associated with the disease (15-17). In some studies, in addition to these respiratory viral agents, seasonal coronavirus has also been mentioned (18, 19). Clinical reports from the United States (20), Italy (21), and other parts of the world (9, 21-24) confirm that this new clinical syndrome associated with COVID-19, which causes significant inflammation and resembles KD, may be seen in children. The syndrome has been termed multisystem inflammatory syndrome in children (MIS-C). As COVID-19 infection is an emerging disease, this clinical manifestation is new and important. The aim of this review was, therefore, to identify the epidemiological features, pathophysiology, clinical findings, laboratory tests, imaging findings, and management recommendations for MIS-C.

2. Epidemiology

On April 7, 2020, a report was published by the American Academy of Pediatrics regarding a case of classic KD in a six-month-old girl who was tested positive for COVID-19 (9, 25). Then, on April 25 in the UK, a cluster of children of various ages presenting with MIS-C was reported, where the patients were admitted to the intensive care unit with manifestations of toxic shock syndrome and atypical Kawasaki disease; then, a test was taken that confirmed severe COVID-19 (8, 26). Since then, there have been reports of children with MIS-C in other parts of the world, too, including Europe, Canada, and the United States (9, 23, 27-30). Comparing the epidemiological manifestations of MIS-C and Kawasaki disease, most cases of MIS-C occur in older children and adolescents (21, 22, 28-30). In contrast, KD typically affects infants and young children (31). On the other hand, the epidemiology of MIS-C is different from that of acute COVID-19 infection in children where the most severe cases occur in infants under one year and children with certain serious underlying conditions (5).

In a UK case series (n = 37), 46% of patients were black, 19% white, 11% Asian, and 5% biracial (28), and in the New York case series (n = 33), 24% were black, 27% Hispanic, 9% white, and 9% Asian (28). In another case series of 21 children and adolescents in France, 57% had at least one parent of African ancestry, and 14% had at least one parent of Asian ancestry (32). As a result, black and Hispanic children account for a large number of cases, and Asian children constitute only a small fraction of cases. Furthermore, 95% of children in the UK series, 89% in the France series, and 79% in the New York series were previously healthy, and the most common comorbidities were obesity and asthma (28, 32). However, based on available data about the underlying conditions of 345 children with COVID-19 infection studied in the United States, 23% had an underlying disease, and the most commonly reported problems were cardiovascular disease, chronic pulmonary disease (including moderate to severe asthma), and immunosuppression (4, 5). In the UK, the peak of COVID-19 cases occurred in the first two weeks of April, while the peak of MIS-C cases occurred in the first two weeks of May; therefore, there seems to be a gap between the peak of COVID-19 and the peak of MIS-C (28, 33). This gap may indicate that MIS-C represents a post-infectious complication rather than an acute infection.

3. Pathophysiology

The pathogenesis of the condition is unknown (9, 28). It has been suggested that, like Kawasaki disease, a possible antibody-dependent enhancement is involved in facilitating the entry of the virus into host cells by developing antibodies (9). It has also been suggested that MIS-C is caused by COVID-19 cytokine storms (34). On the other hand, a hypothesis for the pathogenesis of Kawasaki disease includes a hyperinflammatory response to viral infection in some genetically predisposed children (35). SARS-CoV-2 is now on the list of viral triggers (36). The association between KD and COVID-19 suggests that SARS-CoV-2 can cause systemic vasculitis by targeting endothelial tissue through the angiotensin-converting enzyme 2 (ACE2), a protein that the virus uses to enter the cell (37). In the early case series of children undergoing both polymerase chain reaction (PCR) test and serology, 68% had positive serology with negative PCR, 26% were positive on both tests, and 6% were negative on both tests (21, 22, 28). As a result, many infected children have a negative PCR test for SARS-CoV-2 but have positive serology, a finding that supports the hypothesis that MIS-C is associated with an immune system disorder that develops after the acute infection has passed.

4. Clinical Presentations

As stated, MIS-C is a systemic inflammation with clinical features such as significant inflammation, persistent fever, and organ dysfunction, temporally associated with exposure to COVID-19 (28, 38). The symptoms may correspond to some or all of the diagnostic criteria for KD (38). Besides, MIS-C may have clinical features of further pediatric inflammatory diseases, such as toxic shock syndrome and septic shock (29). Children may develop symptoms that are not usually associated with KD (36), such as acute gastrointestinal symptoms, including abdominal pain, diarrhea, or vomiting (27). In the available case reports, clinical presentations were similar: Persistent fever was observed in all children, and other symptoms included gastrointestinal symptoms (abdominal pain, vomiting, and diarrhea), rashes, neurocognitive symptoms (headache, lethargy, and confusion), cough, and respiratory symptoms, conjunctivitis, mucous membrane changes, swollen hands/feet, and sore throat (9, 10, 21, 28). Respiratory symptoms may occasionally be seen, and difficulty breathing is usually associated with shock (9). The clinical features of pericarditis, valvulitis, or myocarditis may also be reported in the cardiological findings. Beside, abnormalities of the coronary artery such as dilatation (9, 27, 38) have also been seen, and some patients have coronary artery aneurysms (8, 9). The clinical features and their prevalence in several case series are summarized in Table 1 (22, 39-42).

Table 1. Clinical Features Extracted From Waltuch et al. (39), Whittaker et al. (40), Cheung et al. (41), Chiotos et al. (42), Belhadjer et al. (22)

	Waltuch et al. (N = 4)	Whittaker et al. (N = 58)	Cheung et al. (N = 17)	Chiotos et al. (N = 6)	Belhadjer et al. (N = 35)	Prevalence, % (N total = 120)
Fever	4	58	17	6	35	100
Respiratory symptoms	2	12	7	4	23	40
Gastrointestinal symptoms	4	31	15	5	29	70
Skin Rash	2	30	12	2	20	55
Lymphadenopathy	1	9	6	0	21	31
Conjunctivitis	3	26	11	2	31	61
Strawberry tongue/fissured lips	1	17	9	3	19	41
Chest pain	0	0	0	0	6	5
Shock	4	27	13	6	28	65
Decreased ventricular function	1	18	11	3	35	57

5. Laboratory Findings

Based on the available case series, the laboratory abnormalities are listed in Table 2 (43).

6. Imaging Findings

Most of the patients had normal chest radiographs, but abnormal findings included small pleural effusions, patchy consolidations, focal consolidation, and atelectasis. Chest computed tomography (CT) had similar findings to chest radiography, and few patients had nodular ground-glass opacities (43). The findings on abdominal ultrasound or CT included free fluid, ascites, terminal ileitis, mesenteric adenopathy, and pericholecystic edema (44). In a study by Belhadjer et al. (22) on 35 children, echocardiography revealed a depressed Left Ventricular (LV) systolic function with an ejection fraction below 30% in 10 out of 35 patients, and between 30% and 50% in 25 patients. Besides, LV hypokinesis was global in 31 out of 35 patients, and three patients manifested segmental wall hypokinesis. Pericardial effusion was present in three cases, and dilatation of coronary arteries was found in six patients (22).

Table 2. The Laboratory Abnormalities Reported in Different Case Series

Laboratory Findings	Category	Frequency, %
Abnormal blood cell counts	Lymphocytopenia	80 - 95
	Neutrophilia	80 - 90
	Mild anemia	70
	Thrombocytopenia	30 - 80
Elevated inflammatory markers	C-reactive protein	90 - 95
	Erythrocyte sedimentation rate	80
	D-dimer	80 - 95
	Fibrinogen	90 - 100
	Ferritin	55 - 75
	Procalcitonin	80 - 95
	Interleukin-6	80 - 100
Elevated cardiac markers	Troponin	60 - 95
	BNP or NT-pro-BNP	80 - 100
Others	Hypoalbuminemia	73 - 95
	Mildly elevated liver enzymes	62 - 70
	Elevated lactate dehydrogenase	50 - 60
	Hypertriglyceridemia	70

7. Diagnosis

The Centers for Disease Control and Prevention (CDC) (23), the World Health Organization (WHO) (27), and the Royal College of Paediatrics and Child Health (RCPCH) have published a case definition (38). Table 3 outlines the CDC's and WHO's case definitions of MIS-C. Patients who meet these criteria and also fulfill full or partial criteria for KD should be considered an MIS-C case.

The RCPCH case definition (38) states that the child's test may be positive or negative for COVID-19, but further microbial roots should be ruled out. The criteria described in the RCPHC case definition are persistent fever, inflammation, and evidence of single- or multi-organ dysfunction, along with other clinical and laboratory findings, and ECG and imaging results. ECG and echocardiography may detect coronary artery abnormalities such as dilatation. The biomarkers such as high troponin, low albumin, high ferritin, abnormal fibrinogen levels, and high D-dimers should be considered in the diagnosis (9, 38).

For any child suspected of having MIS-C, other differential diagnoses, including non-infectious and infectious inflammatory conditions, should be excluded (45). Differential diagnosis in children with MIS-C-consistent symptoms includes bacterial infections/sepsis, KD, toxic shock syndrome, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), myocarditis, and other viral infections (43). In children with persistent fever and elevated inflammatory markers, one of the important differential diagnoses is bacterial infections/sepsis that should be evaluated for focal sources such as soft tissue, meningitis, or pneumonia, as well as bacterial culture to differentiate it with MIS-C (46). Differential diagnosis of MIS-C and KD is challenging due to the lack of diagnostic tests for both diseases (47). However, some features are more common in MIS-C, including gastrointestinal symptoms, myocardial dysfunction, and older children (48). On the other hand, rapid diagnosis and timely treatment of KD is very important to prevent its complications. It is recommended that all children with prolonged fever, especially children under one year of age, have a high clinical suspicion of KD (49). Microbiologic tests such as bacterial cultures can be used to differentiate staphylococcal and streptococcal shock syndromes from MIS-C. HLH/MAS is an excessive immune activation syndrome, which is differentiated from MIS-C by specialized immunologic testing (43). MIS-C may overlap with other viral infections, including adenovirus, enteroviruses, Epstein-Barr virus, and human herpesvirus 6, which can be differentiated by serology or RT-PCR (43).

8. Treatment

The level of care is determined by the severity of the disease. Children with moderate to severe symptoms should be hospitalized, and children with hemodynamic instability, significant respiratory compromise, or other life-threatening complications should be admitted to the Pediatric Intensive Care Unit (PICU). Little information is available about the effectiveness of different therapies (27, 28). Anti-inflammatory treatments such as intravenous immunoglobulin therapy and corticosteroids have been used (22, 27). The RCPHC proposes that MIS-C cases must be considered as possible COVID-19 cases and treated (38). For non-severe cases, only supportive care is recommended, and in the case of clinical deterioration or severe disease, transfer to PICU should be considered (38). RCPHC recommends that if the patient fulfills the KD criteria, you should consider intravenous immunoglobulin (IVIG) and aspirin, and if fulfills the criteria for toxic shock syndrome, consider IVIG (38). The RCPHC also recommends that candidate antiviral therapies should only be given in the context of a clinical trial if available (38). For immunomodulatory, the therapy should be discussed with clinicians with appropriate experience (e.g., rheumatology, immunology, and hematology) on a case by case basis and should be used in the context of a trial if eligible and available (38).

The treatments that the CDC recommends include supportive care and directed care to target the underlying inflammations (50). Supportive care includes respiratory support, inotropic support, and fluid resuscitation. Extracorporeal membranous oxygenation (ECMO) may be considered in rare cases (50). The CDC also recommends that anti-inflammatory therapies should include the repeated use of IVIG and steroids and that aspirin should commonly be used because of the concerns about coronary artery involvement (50). Waiting for the bacterial culture results, antibiotics are commonly prescribed to treat potential sepsis (50).

Another guideline recommends that broad-spectrum antibiotics should be prescribed in hospitalized patients because of the overlap of MIS-C symptoms with severe bacterial infections (51). Ceftriaxone should be prescribed in patients with milder illness, and metronidazole should be added in patients with predominant GI symptoms. In cases of severe illness or shock, vancomycin, clindamycin, and cefepime or vancomycin, meropenem, and gentamicin are recommended (51). In children who are PCR-positive and/or have typical COVID-19 manifestations, remdesivir at a dose of 5 mg/kg IV once on day 1 with a maximum dose of 200 mg, followed by 2.5 mg/kg (maximum dose 100 mg) IV daily for nine days, is recommended (51). In MIS-C, pa-

Table 3. The Criteria and Case Definition of MIS-C by CDC and WHO

	Case Definition		
CDC (all 4 criteria must be met)	1) Age	< 21 years	
	2) Clinical presentation	A) Fever	Documented fever > 38.0°C for ≥ 24 hours, or subjective fever lasting ≥ 24 hours
		B) Laboratory evidence of inflammation	Elevated CRP
			Elevated ESR
			Elevated fibrinogen
			Elevated procalcitonin
			Elevated D-dimer
			Elevated ferritin
			Elevated LDH
			Elevated IL-6 level
			Neutrophilia
			Lymphocytopenia
			Hypoalbuminemia
		C) Multisystem organ involvement (≥ 2)	Cardiovascular
			Renal
			Respiratory
			Hematologic
			Gastrointestinal
			Dermatologic
			Neurologic
		D) Evidence of clinically severe illness requiring hospitalization	
	3) Recent or current COVID-19 infection (by serology, antigen test, or RT-PCR) or exposure (within four weeks before the onset of symptoms)		
	4) No alternative plausible diagnoses		
WHO (all 5 criteria must be met)	1) Age 0 to 19 years with fever for ≥ 3 days		
	2) Clinical presentation (at least 2 of them)	Mucocutaneous inflammation signs or bilateral non-purulent conjunctivitis or rash	
		Hypotension or shock	
		Features of pericarditis, valvulitis, coronary abnormalities, or myocardial dysfunction	
		Coagulopathy	
		Acute gastrointestinal problems (abdominal pain, diarrhea, or vomiting)	
	3) Elevated inflammatory markers		
	4) No other microbial cause of inflammation, such as bacterial sepsis, streptococcal, or staphylococcal shock syndromes		
	5) COVID-19 infection (antigen test, serology, or RT-PCR), or the possibility of contact with COVID-19 patients		

tients who have an excessive inflammatory response or cardiac involvement, IVIG, and aspirin at doses of 2 g/kg and 80 - 100 mg/kg/day, respectively, are recommended (51). Anakinra and corticosteroids are also recommended in patients with severe inflammation with or without KD features compatible with cytokine storm syndrome (51).

A comparison of the MIS-C treatment guidelines shows that all the mentioned guidelines recommend supportive care for non-severe cases. Regarding immune-modifying treatments, IVIG is recommended for all patients who meet the KD criteria or have cardiac involvement. Because of concerns about coronary artery disease in MIS-C patients, all guidelines recommend aspirin. Except for the RCPHC guideline, other guidelines recommend the administration of steroids, especially in severe inflammation. Although the CDC does not mention antiviral therapy, the

other two guidelines recommend antiviral therapy, such as remdesivir in children who are PCR-positive or have typical COVID-19 symptoms. In terms of antibiotic therapy, although metronidazole is recommended in the guideline for the treatment of patients with GI symptoms, the CDC recommends empiric antibiotics until cultures are negative. The multiple case series from the US, France, Italy, and the UK showed that 75% of children received IVIG treatment, 59% steroids, 57% vasoactive support, 6% anakinra, 6% infliximab, and 3% tocilizumab (52).

The Minnesota Clinical Guidelines for Patient follow-up recommend that the first visit of patients should be within 48 to 72 hours after discharge by the primary care physician, who should examine the child for vital signs, especially blood pressure, and repeat laboratory tests (CBC with differential, CRP, basic metabolic panel (BMP)). Laboratory tests should be repeated 1 - 2 times a week until normalized. Cardiology follow-up should be 1 - 2 weeks after discharge with ECG and echocardiography. Also, one should consider follow-ups with echocardiography 4 - 6 weeks later, and cardiac MRI 1 - 3 months later (53).

9. Prognosis

The prognosis of MIS-C is unclear, given that it is a new clinical manifestation, and our understanding of the disease is still very low. The course of the disease in MIS-C can be more severe, and many children may require intensive care units; even though most of them survive, several deaths have also been reported (9, 10, 23). There were at least five deaths among 230 suspected cases of MIS-C temporally associated with COVID-19 infection in EU/EEA and the UK in 2020 (9).

10. Conclusions

In conclusion, it should be noted that pediatricians should be aware of MIS-C, which is likely to be related to the SARS-CoV-2 infection. It has similarities with Kawasaki disease but has specificities in its presentation. The limited available reports state that in children with COVID-19-associated MIS-C, the health condition can quickly deteriorate, and early diagnosis, management, and early referral to tertiary care should, therefore, be undertaken. Numerous questions have been raised by the recognition of the MIS-C, such as the role of genetics, susceptibility, diagnosis, therapy, and sequelae. Therefore, further studies are needed to investigate latent causality.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

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