REVIEW

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Severe acute respiratory syndrome coronavirus 2-induced multisystem inflammatory syndrome in children

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ABSTRACT
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced multisystem inflammatory syndrome in children (MIS-C) is a life-threatening illness that has been reported in the United States and Europe. It affects multiple organ systems and often requires patient admission to an intensive care unit. Although some features of MIS-C overlap with Kawasaki disease, MIS-C is more common among older children and adolescents, more often affects cardiovascular and gastrointestinal systems, and more frequently presents with elevated inflammatory markers. Rapid and complete clinical recovery is possible in nearly all patients following immunomodulation therapy. Thus far, MIS-C pathophysiology and long-term prognosis are not sufficiently clear; further studies are needed.

KEYWORDS
Multisystem inflammatory syndrome in children, Kawasaki-like disease, COVID-19, SARS-CoV-2

Introduction

Novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic. Initial studies from China and the United States have indicated that COVID-19 typically manifests as a mild infection in children.[1-3] However, since April 2020, several countries affected by COVID-19 have begun to report cases of severe disease in children; these affected children required hospitalization in intensive care units. In such children, COVID-19 has been associated with multisystem inflammatory syndrome in children (MIS-C), a rare condition with features similar to the Kawasaki disease (KD) and toxic shock.[4-6] According to the World Health Organization and Centers for Disease Control and Prevention, the diagnostic criteria for MIS-C include the following[7-8]: age ≤21 years, subjective or objective fever (>38°C) lasting ≥24 h, clinically severe illness requiring hospitalization because of multiple organ system involvement (i.e., at least two organ systems), laboratory-confirmed SARS-CoV-2 infection or COVID-19 exposure within 4 weeks before the onset of symptoms, laboratory evidence of inflammation, and no alternative plausible diagnoses. In this review, we discuss the demographic characteristics of affected patients, disease pathophysiology, clinical presentation, pathological findings, treatment, and outcomes of MIS-C.

Epidemiology

MIS-C is a rare condition. A Pediatric Surveillance Unit study has been initiated to explore the extent of MIS-C in the United States.[9,10] Two recent studies have described the epidemiology and clinical features of MIS-C in the United States.[9,10] Feldstein et al[9] reported 186 cases identified through targeted surveillance in 26 United

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States (U.S.) states from March 15, 2020 to May 20, 2020. Dufort et al[10] described the results of MIS-C surveillance conducted in 106 hospitals in the state of New York. Of 191 suspected cases reported to the New York State Health Department as of May 10, 2020, 99 met the definition of MIS-C.[10] MIS-C was uncommon among patients in New York cohort, because it was diagnosed in only two per 100 000 persons <21 years of age; in contrast, SARS-CoV-2 infection was laboratory-confirmed in 322 per 100 000 persons <21 years of age.[10] The apparent incidence of MIS-C is lower than that of KD, which affects 264 per 100 000 children ≤4 years of age in Japan and 25 per 100 000 children aged <5 years in North America.[11]

MIS-C has a high occurrence rate in older children and adolescents who were previously healthy. The median age of affected children reportedly varied among case series from different countries, from 7.5 years to 10 years (overall age range, 3 months to 17 years[4-6,9,10,12-15]; no sex differences were observed in those series, except male predominance (2:1) in the case series from 26 U.S. states.[9] In contrast, KD reportedly occurs mainly in children aged <5 years and more frequently affects boys, compared with girls.[16] The epidemiological observations of MIS-C are not consistent with previous reports that severe COVID-19 manifestations develop in infants (<1 year of age) and children with underlying health problems.[1-3]

Black and Hispanic children may be disproportionally affected. In the study from New York, 40% of the affected children were black, while 36% were Hispanic.[9] The case series involving 26 U.S. states reported that 31% of children with MIS-C were Hispanic or Latino, 25% were black non-Hispanic, and 22% were white non-Hispanic.[10] A study in the United Kingdom, however, showed that 31% of patients with MIS-C were Asian.[12] Surprisingly, no studies have described instances of illness similar to MIS-C in Asian countries, although KD has been shown to disproportionately affect Asian children.[11] The reasons for this discrepancy are unclear, but may involve differences in racial and ethnic backgrounds, geographic locations, or viral strains.

Although the majority of patients with MIS-C are otherwise healthy, obesity might be a risk factor for MIS-C. Specifically, obesity was present in 37% and 29% of patients in the case series involving 26 U.S. states and in the New York cohort study, respectively.[9,10] Furthermore, a study conducted in the United Kingdom showed that two of eight patients with serious MIS-C had obesity (i.e., body mass index >30 kg/m^2).[4] Several studies have demonstrated that obesity is associated with SARS-CoV-2-induced critical illness in adults.[17,18] This may stem from enhanced expression of angiotensin-converting enzyme 2 in individuals with obesity, due to higher adipocyte number. No studies have reported independent risk factors for MIS-C; thus, further research is needed to identify these factors.

Pathophysiology

The pathophysiology of MIS-C is not well understood. Coronaviruses are a group of highly diverse, enveloped, positive-sense, single-stranded RNA viruses. Immune response to SARS-CoV-2 involves both cell-mediated immunity and antibody production.[19] During SARS-CoV-2 infection, cytotoxic T cells (i.e., CD8$^+$ T cells) and interleukin (IL)-6 play a vital role in virus clearance. SARS-CoV-2 has been found to cause milder disease in children, which may be due to a lower level of IL-6 and a significantly higher level of total T cells in pediatric patients, compared with adults.[19]

Notably, an epidemiological study showed that the epidemic curve of MIS-C cases followed the curve of COVID-19 with a lag period of 4–5 weeks[9]; this supported the hypothesis that MIS-C is a manifestation of COVID-19.[20] A median interval of 25 days between the onset of COVID-19 symptoms and hospitalization for MIS-C has been reported.[9] In the majority of patients with MIS-C, nasal SARS-CoV-2 viral load was low or negative, while up to 82% of those patients exhibited anti-SARS-CoV-2 antibodies.[5,6,12-14] Although a direct link between MIS-C and SARS-CoV-2 has not yet been established, the findings in published studies have supported the hypothesis that MIS-C develops because of the immune response to SARS-CoV-2. Compared with children who have KD, children who have MIS-C exhibit elevated levels of pro-inflammatory markers such as C-reactive protein (CRP) and IL-6,[5,12] which implies that a stronger immune response is induced by SARS-CoV-2. In particular, elevated levels of IL-6 were reported to be directly related to risk of death in adult patients with COVID-19.[21] Thus, we speculate that MIS-C with elevated inflammatory markers is a delayed immunological phenomenon associated with inflammation.

A myocarditis-like syndrome termed acute COVID-19 cardiovascular syndrome (ACovCS) has also been recognized in adults.[22] MIS-C and ACovCS have been described as distinct entities, although they have several overlapping manifestations. Similar to MIS-C, ACovCS can occur days to weeks after SARS-CoV-2 infection and can occur with or without pulmonary disease. Inflammatory markers are universally elevated in patients with ACovCS. Because endomyocardial biopsies have not shown evidence of direct cardiomyocyte infection in patients with ACovCS, the striking similarities between MIS-C and the ACovCS myocarditis-like syndrome suggest similar pathogenesis involving a post-infectious inflammatory state.[22,23]

In addition to the abnormal immune response to the virus, extensive vascular endothelial damage caused by viral infection may also contribute to the pathogenesis of

MIS-C. Gupta et al[24] demonstrated COVID-19-induced endothelial dysfunction and hypercoagulation, which led to systemic microvascular disease. The condition was aggravated when SARS-CoV-2 accessed host cells via angiotensin-converting enzyme 2 receptors that are highly expressed in the endothelial cells of the lung, kidney, heart, intestines, brain, and other organs.[25] The pathogenesis of MIS-C involves multiple organ systems, including the cardiovascular system.[9,10] In the New York cohort study, however, 47% of patients with MIS-C had negative SARS-CoV-2 real-time polymerase chain reaction test results,[9] whereas eight of 10 children in an Italian cohort had negative SARS-CoV-2 real-time polymerase chain reaction test results.[6] These findings suggested that many patients with MIS-C do not have an active viral infection. Further studies are warranted to determine whether the multiple organ damage observed in patients with MIS-C is caused directly by the virus, an abnormal immune response, or both.

Clinical manifestations

Patients with MIS-C present with manifestations associated with multiple organ systems, including the cardiovascular, respiratory, urinary, gastrointestinal, and nervous systems. Table 1 shows common clinical findings in patients with MIS-C, based on a series of published reports.[4-6,9,10,12-15] Although MIS-C is generally more likely to occur in older children, its symptoms and manifestations differ according to age. MIS-C with characteristics typical of KD most often occurs in children <5 years of age, whereas the prevalence of myocarditis is highest among adolescents.[10]

TABLE 1 Comparison of clinical manifestations between patients with multisystem inflammatory syndrome in children and patients with Kawasaki disease (percentages of patients affected).[5,6,9-10,12-16,26,27]

Clinical findings	MIS-C (%)	KD (%)
Gastrointestinal symptoms	50–90	20–30
Shock	50–81	2–7
Cardiac dysfunction on echocardiography with an elevated troponin/brain natriuretic peptide (BNP)/pro-BNP	53–80	10
Respiratory symptoms	21–70	uncommon
Meeting the diagnostic criteria for complete KD	22–64	80–95
Acute kidney damage	22–52	13
Liver function damage	62–76	63
Serositis (small pleural, peritoneal, and pericardial effusions)	57	uncommon
Neurological symptoms or signs	12–57	uncommon

MIS-C, multisystem inflammatory syndrome in children; KD, Kawasaki disease.

In previous studies, 22%–64% of patients with MIS-C met the diagnostic criteria for KD.[5,6,9,10,12-14] Although classical signs of partial or complete KD are reportedly present in patients with MIS-C, clear differences from typical KD can be identified. For example, gastrointestinal symptoms are the most common symptoms of MIS-C.[4-6,9,10,12-15] All age groups of patients with MIS-C have shown gastrointestinal symptoms. The New York cohort and the case series from 26 U.S. states reported that 80% and 92% of children exhibited gastrointestinal symptoms (including abdominal pain and/or diarrhea, and vomiting), respectively,[9,10] which was considerably greater than the 30% proportion among patients with KD.[26,27] Likewise, a cohort study in France found gastrointestinal symptoms (predominantly acute abdominal symptoms) in all enrolled children (n = 21) during the early course of MIS-C.[5] A few patients presented with an acute (surgical) abdomen, but aseptic peritonitis was confirmed during abdominal surgical exploration. The New York cohort study revealed inflammation or enlargement of the appendix or gall bladder in 17 patients who underwent abdominal imaging.[9]

Although MIS-C and KD can both involve the cardiovascular system, there are clear differences in prevalence and severity.[9,10] Patients who have MIS-C exhibit greater prevalence of myocarditis and hemodynamic instability shock, compared with patients who have KD. Shock is often refractory to volume resuscitation and requires the use of vasopressors; in rare instances, it requires extracorporeal membrane oxygenation support. Patients with severe KD might develop hemodynamic instability, a condition also known as KD shock syndrome.[28] This syndrome may be related to myocardial dysfunction, as well as enhanced vascular permeability and vascular leakage, caused by the release of cellular inflammatory factors in the acute phase of disease. In the case series involving 26 U.S. states, the cardiovascular system was involved in 80% of affected patients (n = 149), while 48% of the patients (n = 90) received vasoactive support[9]; approximately 5% of U.S. children with KD presented with cardiovascular shock requiring vasopressor or inotropic support.[28] In the New York cohort, one-third of the patients presented with hypotension and one-half presented with myocarditis; the condition rapidly deteriorated in both groups.[10] Approximately 80% of patients were transferred to an intensive care unit within 1 day of admission and 62% of patients received vasopressor therapy.[10] In addition, all eight patients in the study from the United Kingdom progressed to warm vasoplegic shock; volume recovery was ineffective and the patients eventually required noradrenaline and milrinone.[4]

Among the published studies, 14%–38% of patients were diagnosed with coronary artery abnormalities.[4,9,10,12-15] Toubiana et al[5] found that coronary artery abnormalities were present after 5–11 days of fever. In the U.S. case series, 8%–9% of patients with MIS-C had coronary aneurysms (Z-score ≥2.5) diagnosed using echocardiography.[9,10] However, no significant differences were observed in the incidence of coronary aneurysms between patients with MIS-C and patients with KD

(4%–13%).[29] Notably, that study was limited by the short follow-up duration regarding patients with MIS-C. In addition, 30%–66% of affected patients showed varying degrees of reduction in left ventricular ejection fraction.[4,9,10,12-15]

In China, children with SARS-CoV-2 infection were either asymptomatic or had respiratory symptoms.[1,2] In the U.S. study, 70% of patients with MIS-C (n = 186) had respiratory symptoms, but pulmonary imaging findings of the patients were not described.[9] In a study from the United Kingdom, 50% of the children required positive pressure ventilation; however, dyspnea was most commonly observed because of shock or myocarditis.[12] Furthermore, because only 12% of the patients had respiratory symptoms, respiratory involvement was not a prominent feature.[12] Although angiotensin-converting enzyme 2 receptors are highly expressed in lung tissues, children with MIS-C are critically ill without apparent lung manifestations; this observation suggests that MIS-C is not a consequence of direct virus-induced damage.

Laboratory findings

The majority of patients with MIS-C have high levels of inflammatory markers. The U.S. study showed that 92% of patients had elevated levels of at least four of the following inflammatory markers[9]: leukocytes, CRP, erythrocyte sedimentation rate, ferritin, procalcitonin, and IL-6. In addition to inflammation markers, patients with MIS-C may have thrombocytopenia, lymphopenia, anemia, mildly elevated transaminases, elevated D-dimer and fibrinogen, hypertriglyceridemia, reduced natural killer cell count, enhanced cardiac troponin I, and enhanced brain natriuretic peptide. In the New York cohort study, two-thirds of the patients had lymphopenia, while approximately one-tenth of the patients had low platelets ($< 80\times10^9$/L).[10]

Biochemical features differ between patients with MIS-C and patients with KD. For example, the study from the United Kingdom compared laboratory findings between 58 children with MIS-C and 1132 children with KD.[12] White blood cell count was higher in patients with MIS-C (median, 17×10^9/L) than in patients with KD (median, 13.4×10^9/L). Similarly, neutrophil count was higher in patients with MIS-C (median, 13×10^9/L) than in patients with KD (median, 7.2×10^9/L). CRP levels (median, 229 mg/L) and troponin levels (median, 45 mg/L) in patients with MIS-C were also threefold and fourfold higher than the corresponding levels in patients with KD (CRP, 67 mg/L; troponin, 10 mg/L). Additionally, patients with MIS-C had substantial lymphocytopenia [$(0.5–1.5)\times10^9$/L)], in contrast to mildly reduced or normal lymphocyte counts [$(1.5–4.4)\times10^9$/L] in patients with KD. Moreover, platelet counts in patients with MIS-C were either reduced (median, 151×10^9/L) or within the normal range, whereas the patients with KD had elevated platelet counts. In that study, the MIS-C subgroup that met the KD diagnostic criteria was then compared with the typical KD group. The MIS-C subgroup who met the diagnostic criteria for KD had higher neutrophil count and higher levels of CRP, ferritin, fibrinogen, and troponin, as well as lower lymphocyte counts (Table 2). Importantly, that study had several limitations including small sample size, many comparison items, and lack of statistical analysis. Another study involving 21 patients who had MIS-C[5] also found relatively high procalcitonin levels (median, 22.5 ng/mL) and IL-6 levels (median, 170 pg/mL), compared with patients who had KD (procalcitonin, 0.56 ng/mL; IL-6, 54 pg/mL) and those who had KD shock syndrome (procalcitonin, 2.33 ng/mL).[30]

TABLE 2 Comparison of laboratory findings between patients with MIS-C and patients with Kawasaki disease or Kawasaki disease shock syndrome.[5,12,13,17]

Variables	MIS-C	KD	KDSS
Neutrophilia	+	+	+
Lymphopenia	++	±	±
PLT	↓ or normal	↑	↓, normal, or ↑
CRP	↑↑	↑	↑
PCT	↑↑	normal or ↑	↑
IL-6	↑↑	normal or ↑	↑↑
FER	↑	normal or ↑	normal or ↑
Troponin	↑↑	normal or ↑	normal or ↑
Pro-BNP	↑↑	normal or ↑	↑

++, almost always present; +, generally present; ±, may be present or absent; ↑↑, highly increased; ↑, increased; ↓, decreased. MIS-C, multisystem inflammatory syndrome in children; KD, Kawasaki disease; KDSS, Kawasaki disease shock syndrome; PLT, platelets; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin 6; FER, ferritin; Pro-BNP, pro-brain natriuretic peptide.

Treatment and prognosis

Although 80% of affected patients in the U.S. case series received intensive care support, most recovered after treatment with immunomodulatory agents, including intravenous immunoglobulins, glucocorticoids, anti-tumor necrosis factor, and IL-1 or IL-6 inhibitors.[9] The average hospital stay was 7 days (range, 4–10 days). Nearly all patients quickly recovered in both the U.S. case series and New York cohort study.[9,10] The MIS-C subgroup that met the criteria for the diagnosis of KD had a higher resistance rate to the first intravenous immunoglobulin treatment, compared with the typical KD group (10/16 vs. 45/220); thus, the MIS-C subgroup often needed corticosteroid therapy.[13]

The prognosis of MIS-C remains unclear and the broader understanding of the disease continues to evolve. Two individuals in the United Kingdom and one in France died, according to data from mid-May 2020.[31] As of late May 2020, the two publications from the U.S. had reported a

total of 285 affected patients, including six deaths (2% mortality rate).[9,10] The case series involving patients from 26 U.S. states reported four deaths in patients between 10 and 16 years of age, as well as an average hospital stay of 2–5 days; two of the patients who died also had an underlying disease.[9]

Future directions

Because it constitutes a new clinical disease syndrome or a component of the COVID-19 spectrum, MIS-C does not yet have unified diagnostic standards. The current standards are based on data from patients with severe disease and findings in nonrespiratory samples, including feces. Patients with mild disease can be overlooked or diagnosed late in the course of disease. Furthermore, the disease definition may need refinement to capture the wider spectrum of illness. There is a need to further investigate its clinical characteristics, long-term prognosis, and the potential mechanistic link with SARS-CoV-2; this information will aid in treatment decisions with respect to multiple organ dysfunction and coronary aneurysms, which occur during the course of disease. Although most children with SARS-CoV-2 infection exhibit mild or asymptomatic disease, they may subsequently develop MIS-C. Early blood pressure monitoring, electrocardiography and echocardiography assessments, and post-infection follow-up are important strategies for the early identification of MIS-C in children with SARS-CoV-2 infection.

CONFLICT OF INTEREST

None.

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