RESEARCH LETTER

Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City

Severe coronavirus disease 2019 (COVID-19) has been reported rarely in children.[1,2] International data suggest the development of a proinflammatory syndrome with features of Kawasaki disease (KD) or toxic shock syndrome (TSS) in children, possibly related to COVID-19.[3]

Methods | Patients were included if they (1) were 21 years or younger; (2) were hospitalized at Columbia University Irving Medical Center/NewYork-Presbyterian Morgan Stanley Children's Hospital in New York City between April 18 and May 5, 2020; (3) presented with a clinical syndrome characterized by prolonged fever, systemic inflammation, shock, end-organ dysfunction, or symptoms reminiscent of KD or TSS; and (4) had evidence of recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. SARS-CoV-2 infection was determined by reverse transcriptase–polymerase chain reaction (RT-PCR) of nasopharyngeal swabs or positive serology. Serology testing was done using a New York State Department of Health–approved combined assay for IgM and IgG antibodies against SARS-CoV-2 spike trimer or nucleocapsid protein (96% specificity, 93% sensitivity). Admission testing included hematologic parameters, chemistries, co-infections, and inflammatory markers along with assessments of cardiac function (electrocardiograms, transthoracic echocardiograms). The Columbia University ethics committee approved the study with a waiver of informed consent.

Editorial

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Results | Among 17 patients (8 male; median age, 8 years [range, 1.8-16 years]) (**Table 1**), most were white (n = 12) and previously healthy (mild asthma in 3). All patients had fever (median duration, 5 days). Fourteen had gastrointestinal symptoms, with 1 showing acute ileocolitis on imaging. Mucocutaneous findings were common (rash [n = 12], conjunctivitis [n = 11], and lip redness/swelling [n = 9]). Three patients were hypoxic at presentation, and 13 had shock. Fourteen had abnormal chest radiograph findings, most commonly bilateral, interstitial opacities. Eight met criteria for KD and 5 for incomplete KD.[4]

Eight patients tested positive for SARS-CoV-2 by RT-PCR and the other 9 by serology. Levels of inflammatory markers were elevated in all patients, and most had lymphopenia (n = 12), bandemia (n = 11), elevated troponin T level (n = 14), and elevated NT-proBNP level (n = 15). Studies suggesting co-infections were infrequent (n = 3) (**Table 2**). Serum IL-6 level was elevated in 16. Cytokine profiling in 8 patients showed

Table 1. Demographics, Clinical Characteristics, Treatment, and Outcomes of Patients With COVID-19–Related Multisystem Inflammatory Syndrome in Children (N = 17)

	No. (%)[a]
Age, median (range), y	8 (1.8-16)
Male	8 (47)
Race/ethnicity/ancestry[b]	
Ashkenazi Jewish	6 (35)
White	
Non-Hispanic	2 (12)
Hispanic	4 (24)
Black	4 (24)
Asian	1 (6)
Presenting symptoms	
Median days of fever (range)	5 (1-12)
Gastrointestinal (abdominal pain, vomiting, and/or diarrhea)	15 (88)
Shock at presentation	13 (76)
Rash	12 (71)
Conjunctivitis	11 (65)
Lip redness/swelling	9 (53)
Neurologic (headache, stiff neck, vision change)	8 (47)
Respiratory (cough, dyspnea)	7 (41)
Myalgia	6 (35)
Cervical lymphadenopathy	6 (35)
Skin desquamation	3 (18)
Hypoxia at presentation	3 (18)
History of COVID-19 sick contact	11 (65)
Admission to ICU	15 (88)
Treatment of shock in ICU	10 (59)
Hypoxia in ICU	9 (53)
Mechanical ventilation	0
Treatment[c]	
Methylprednisolone	12 (71)
Hydrocortisone	3 (21)
Intravenous immunoglobulin	13 (76)
Anticoagulation	
Enoxaparin	
Prophylaxis	10 (59)
Treatment	1 (6)
Aspirin	4 (24)
Disposition	
Length of stay, mean (range), d	
ICU	6.4 (3-12)
Hospital	7.1 (3-18)

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.

[a] Unless otherwise indicated.

[b] Race/ethnicity was classified by parent or self-reporting as documented in the electronic health record. Race/ethnicity was assessed to evaluate population at risk for disease and to contextualize to other similar diseases with known race/ethnic predilections.

[c] Patients may have received more than 1 of the treatments.

Table 2. Laboratory, Echocardiogram, and Imaging Characteristics of COVID-19–Related Multisystem Inflammatory Syndrome in Children (N = 17)

Characteristic	Value
Echocardiogram findings, No. (%)	
Left ventricular function by echocardiogram at admission, No. (%)	
Normal	6 (35)
Mildly decreased	5 (29)
Mild-moderately decreased	4 (24)
Moderate-severely decreased	2 (12)
Pericardial effusion on admission echocardiogram[a]	8 (47)
Positive microbiologic testing, No. (%)	
EBV IgG/IgM	2 (11.7)
Parvovirus PCR	1 (5.8)
Throat culture for group A *Streptococcus*	1 (5.8)
Laboratory studies on admission, mean (range)	
White blood cell count, $\times 10^3$/μL	14.0 (4-35.9)
Neutrophils, %	76.2 (65-95)
Lymphocytes, %	9.6 (1-31)
Bands, %	6.8 (0-24)
Absolute lymphocyte count, /μL (reference, <1500/uL)	1212.1 (115.5-6444.9)
Hemoglobin, g/dL	11.2 (7.9-12.9)
Hematocrit, %	32.7 (23.2-36.9)
Platelets, $\times 10^3$/μL	237 (69-892)
Serum sodium, mEq/L (reference, 137-145 mEq/L)	133.1 (125-141)
Serum bicarbonate, mEq/L (reference, 19-27 mEq/L)	18.9 (13-25)
Serum creatinine, mg/dL (reference, 0.6-1.0 mg/dL)	0.7 (0.2-3.6)
Aminotransferases, U/L	
Aspartate (reference, 10-37 U/L)	51.5 (18-151)
Alanine (reference, 9-50 U/L)	49.6 (11-167)
Prothrombin time, s (reference, <12.5 s)	16.3 (13.8-19.6)
Activated partial thromboplastin time, s (reference, <36.6 s)	37.9 (27.5-85)
Lactate dehydrogenase, U/L (reference, 120-260 U/L)	362.8 (195-851)
hs-CRP, mg/L (reference, <10)	200 (17-300)
Procalcitonin, ng/mL (reference, ≤0.08 ng/mL)	21.7 (0.8-127)
Ferritin, ng/mL (reference, ≤150 ng/mL)	647.9 (83-1828)
D-dimer, mg/mL (reference, ≤0.5 μg/mL)	4 (0.9-11)
Interleukin 6, pg/mL (reference, ≤5 pg/mL)	226.3 (3.1-315)
Troponin T, high sensitivity, ng/L (reference, <22 ng/L)	56.8 (6-278)
NT-proBNP, pg/mL (reference, <207 pg/mL)	15 833 (631-59 291)

Abbreviations: COVID-19, coronavirus disease 2019; EBV, Epstein-Barr virus; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal-pro-BNP; PCR, polymerase chain reaction.

SI conversion factors: To convert creatinine values to μmol/L, multiply by 88.4; D-dimer values to nmol/L, multiply by 5.476; aspartate and alanine aminotransferase values to μkat/L, multiply by 0.0167; lactate dehydrogenase values to μkat/L, multiply by 0.0167.

[a] All pericardial effusions were trivial to small in size. None required intervention.

elevated IL-2R, IL-18, and CXCL 9 levels in all and mildly increased IFN-γ (n = 3) and IL-8 (n = 2) levels in some. TNF-α, IL-1b, Il-2, IL-4, IL-5, and IL-13 levels were normal. Fifteen patients required pediatric intensive care unit admission; vasoactive support was required in 10. Of 9 patients with hypoxia, none required mechanical ventilation.

Fourteen patients received steroid treatment, either with methylprednisone (dose range, 2-30 mg/kg per day) or hydrocortisone (dose, 2 mg/kg per day); 1 received prednisone. Thirteen patients received intravenous immunoglobulins (dose range, 2-4 g/kg), including 3 patients who did not receive steroids and 8 who met criteria for KD. One patient received tocilizumab.

Electrocardiograms of 16 patients showed nonspecific ST/T-wave abnormalities in 10 and attenuated QRS voltage in 1. Dysrhythmias were noted in 3 (premature ventricular contractions, nonsustained ventricular tachycardia, and sinus bradycardia). Admission echocardiograms showed normal to mildly decreased left ventricular function (n = 11) or moderate or more ventricular dysfunction (n = 6). All patients had normal coronary arteries by measurement, though coronary arteries were described as prominent or echogenic in 7. Most patients had improved function on follow-up echocardiogram (range, 2-18 days from admission)—12 with normal and 1 with mildly decreased function. One patient (aged 4 years) had a medium-sized aneurysm (*z* score, 5.2) of the left anterior descending coronary artery. This patient presented with fever, diarrhea, and shock, with no additional features of KD. Admission testing revealed lymphopenia (absolute lymphocyte count, 540/μL); elevated levels of pro-BNP (44 677 pg/mL), ferritin (1195.0 ng/mL), and D-dimer (1.39 μg/mL [7.61 nmol/L]); normal troponin T level (19 ng/L); and thrombocytopenia (105×10^3/μL). Thirteen days later, thrombocytosis developed (maximum, 671).

By May 20, after a mean total length of hospital stay of 7.1 (range, 3-18) days, all patients had been discharged home with no fatalities.

Discussion | This study describes 17 previously healthy children and adolescents who developed an inflammatory phenotype related to COVID-19. Features overlapped with, but were distinct from, those of KD and TSS. The observed pattern of cytokine expression suggests an interferon signaling component, along with IL-6 and IL-10 production, seen in KD[5] and acute pulmonary COVID-19 infection. The lack of elevated TNF-α or IL-13 levels may differ from acute pulmonary COVID infections.[6] The occurrence of abnormal cardiac findings suggests the need for long-term surveillance. Limitations include the small number of patients, short follow-up period, and the inability to establish causality.

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