

Letters

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.

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 <i>Streptococcus</i>	1 (5.8)
Laboratory studies on admission, mean (range)	
White blood cell count, $\times 10^3/\mu\text{L}$	14.0 (4-35.9)
Neutrophils, %	76.2 (65-95)
Lymphocytes, %	9.6 (1-31)
Bands, %	6.8 (0-24)
Absolute lymphocyte count, $/\mu\text{L}$ (reference, $<1500/\mu\text{L}$)	1212.1 (115.5-6444.9)
Hemoglobin, g/dL	11.2 (7.9-12.9)
Hematocrit, %	32.7 (23.2-36.9)
Platelets, $\times 10^3/\mu\text{L}$	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 $\mu\text{g/mL}$)	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 $\mu\text{mol/L}$, multiply by 88.4; D-dimer values to nmol/L , multiply by 5.476; aspartate and alanine aminotransferase values to $\mu\text{kat/L}$, multiply by 0.0167; lactate dehydrogenase values to $\mu\text{kat/L}$, 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, $540/\mu\text{L}$); elevated levels of pro-BNP (44 677 pg/mL), ferritin (1195.0 ng/mL), and D-dimer (1.39 $\mu\text{g/mL}$ [7.61 nmol/L]); normal troponin T level (19 ng/L); and thrombocytopenia ($105 \times 10^3/\mu\text{L}$). 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 KD⁵ 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.

Eva W. Cheung, MD
Philip Zachariah, MD, MS
Mark Gorelik, MD
Alexis Boneparth, MD
Steven G. Kernie, MD
Jordan S. Orange, MD, PhD
Joshua D. Milner, MD

Author Affiliations: Department of Pediatrics, Columbia University Irving Medical Center, New York, New York.

Corresponding Author: Eva W. Cheung, MD, Divisions of Cardiology and Critical Care, Department of Pediatrics, Columbia University Irving Medical Center, 3959 Broadway, CHN 2 North, New York, NY 10032 (ec2335@cumc.columbia.edu).

Accepted for Publication: May 27, 2020.

Published Online: June 8, 2020. doi:10.1001/jama.2020.10374

Author Contributions: Drs Cheung and Zachariah had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Cheung and Zachariah contributed equally to the authorship of this article.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: Cheung, Zachariah, Gorelik, Boneparth, Orange, Milner.

Drafting of the manuscript: Cheung, Zachariah, Gorelik, Boneparth, Milner.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Cheung, Zachariah.

Administrative, technical, or material support: Zachariah, Gorelik, Orange.

Supervision: Kernie, Orange, Milner.

Conflict of Interest Disclosures: Dr Orange reported receiving personal fees from ADMA Biologics, CSL Bhering, Gigagen, Grifols, and Takeda. No other disclosures were reported.

Additional Contributions: Candace Johnson, MD, Kara Gross-Margolis, MD, Irene Lytrivi, MD, Angela Chan, MD, and Brian Jonat, MD MPH (Department of Pediatrics, Columbia University Irving Medical Center), contributed to data collection and analysis and editing assistance for this letter. Eldad A. Hod, MD (Department of Pathology and Cell Biology, Columbia University Irving Medical

Center), contributed to data collection and writing of the manuscript. None of these individuals were compensated for their contributions.

1. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr*. Published online April 22, 2020. doi:10.1001/jamapediatrics.2020.1467

2. Tagarro A, Epalza C, Santos M, et al. Screening and severity of coronavirus disease 2019 (COVID-19) in children in Madrid, Spain. *JAMA Pediatr*. Published online April 8, 2020. doi:10.1001/jamapediatrics.2020.1346

3. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020; 395(10237):1607-1608. doi:10.1016/S0140-6736(20)31094-1

4. McCrindle BW, Rowley AH, Newburger JW, et al; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation*. 2017;135(17):e927-e999. doi:10.1161/CIR.0000000000000484

5. Li Y, Zheng Q, Zou L, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN- γ as biomarkers for early recognition. *Pediatr Rheumatol Online J*. 2019;17(1):1. doi:10.1186/s12969-018-0303-4

6. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130(5):2620-2629. doi:10.1172/JCI137244