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Characteristics, Cardiac involvement, and Outcomes of Multisystem Inflammatory Disease of Childhood (MIS-C) Associated with SARS-CoV-2 Infection

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We report on the presentation and course of 33 children with multisystem inflammatory syndrome in children (MIS-C) and confirmed SARS-CoV-2 infection. Hemodynamic instability and cardiac dysfunction were prominent findings, with most patients exhibiting rapid resolution following anti-inflammatory therapy.

Abbreviations:

MIS-C multisystem inflammatory syndrome in children

CDC Centers for Disease Control

WHO World Health Organization

AKI acute kidney injury

RCA right coronary artery

LAD left anterior descending

NAA nucleic acid amplification

LV left ventricular

LVEF left ventricular ejection fraction

Since the first descriptions of COVID-19 due to acute infections from the SARS-CoV-2 virus in November of 2019, reports have identified the relatively low

incidence of acute infections in children, who predominantly manifest mild respiratory symptoms with few requiring hospitalization or intensive care.(1, 2) A report from 46 North American intensive care units identified only 48 children receiving critical care between March14 through April 3, 2020, with 4% of children coming to medical attention with circulatory failure.(2) Multiple reports from Europe alerted the medical community to a new clinical syndrome associated with SARS-CoV-2 infection in children.(3, 4) Patients were primarily presenting with a febrile inflammatory disease with some features of Kawasaki disease and toxic shock syndrome, with profound cardiovascular involvement. Evidence suggests this disease is an immunologically mediated inflammatory syndrome associated with a prior SARS-CoV-2 infection. (3)

The Centers for Disease Control and Prevention (CDC) published a case definition for this syndrome, termed the multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19; the World Health Organization (WHO) issued a different case definition.(5, 6) The objective of this report is to describe a large cohort of this COVID-19-related inflammatory syndrome, focusing on clinical manifestations, disease severity, therapeutic interventions, and early outcomes.

Methods

This case series was approved by the Northwell Health Institutional Review Board. No case included in this report has been published previously in the medical literature, or as

part of a multicenter registry. This is a single-center retrospective study of pediatric patients admitted to Cohen Children's Medical Center, located in New Hyde Park in Queens, NY. New York state has been the epicenter of COVID-19 in the United States and the borough of Queens (Queens County) has had the highest number of cases of COVID-19 of any county in New York state (6a)

All sequentially hospitalized febrile patients from April 17, 2020 through May 13, 2020 with fever and an inflammatory illness that met the CDC case definition for MIS-C were included.(5) Importantly, all cases were required to have a positive test for SARS-CoV-2 by detection of serum antibodies or nucleic acid from a nasopharyngeal specimen. Patients with COVID-like lower respiratory tract involvement were excluded.

Data were collected from the enterprise electronic health record (Sunrise Clinical Manager, Allscripts, Chicago, IL), and all analyses were performed using Excel (Office Professional +13, Microsoft, Seattle, WA). Data included patient demographic information, presenting symptoms, respiratory support requirements, use of vasoactive medications, and initial laboratory and other test results, including markers of inflammation and cardiac function. Acute kidney injury (AKI) was defined by KDIGO criteria(7) and liver dysfunction was defined as an ALT of >80.

Left ventricular (LV) dysfunction was defined as a LV ejection fraction (LVEF) of < 55% based on Boston Z-scores; mild dysfunction was defined as LVEF, 45-54% (Z-score -2.0 to -4.0), moderate, 35-44% (Z-score -4.0 to -6.0), and severe, <35% (Z-score < -6.0). Aneurysm and dilation of a coronary artery (right coronary artery [RCA] and/or left

anterior descending [LAD]) artery were defined by a Z-score ≥ 2.5 and 2.0 to 2.49, respectively.(8)

Continuous variables were summarized using median and interquartile range and categorical variables using frequency.

Results:

We identified 33 patients who met CDC(5) criteria for MIS-C and had laboratory evidence of SARS-CoV-2 infection; all patients also met WHO criteria for multisystem inflammatory syndrome in children and adolescents.(6) The peak of hospitalizations occurred approximately five weeks after the peak of hospitalizations with acute COVID-19 (Figure). Patients were predominantly male (20, 61%), non-Hispanic (24, 73%) with a median age of 8.6 years (IQR 5.5-12.6) (Table). Most patients were previously healthy with the exception of a high proportion of patients who were overweight (2,6%) or obese (12, 39%). This compares to our general in-hospital population (2019 data) of 71% non-Hispanic, and by race, 37% white, non-Hispanic, 21% Black non-Hispanic,15% Asian, and 24% Other. Our region has a childhood obesity rate of 18%. Patients presented with a median of 4 days (4, IQR 3-5) of fever and almost all (32, 97%) had gastrointestinal symptoms as well as involvement of other organ systems. In the total cohort, 21 (64%) had symptoms and signs fulfilling complete criteria for KD. The majority of patients with complete KD criteria had shock (16, 76%).

Results of tests of inflammation were markedly elevated (Table). All patients had evidence of SARS-Co-2 infection including a positive serology in 30 patients; the remaining 3 came to attention prior to availability of serology testing, but had detection

of viral nucleic acid. Blood cultures were negative in all patients; multiplex nucleic acid amplification test for multiple respiratory pathogens was negative in all patients with the exception of 1 patient who had influenza virus detected. During hospitalization, 26 (79%) patients required intensive level of care and 6 (18%) required mechanical ventilation. Hemodynamic dysfunction was common with 58% having myocardial dysfunction and 76% requiring vasoactive medications. Coronary artery aneurysm and dilation were detected in 5 (15%) and 3 (9%) patients, respectively. All patients received IVIG, 88% received aspirin, and 70% received a corticosteroid. After incomplete response to these initial therapies, 24% received therapy with a biologic modifying medication. Most patients exhibited rapid clinical improvement. There were no deaths and median length of hospital stay was 4 days (IQR 4, 8). At the time of hospital discharge, mild cardiac dysfunction was still present in 9 of 19 patients who had impaired function during hospitalization.

Discussion:

In this report we describe 33 cases of a newly recognized inflammatory syndrome in a single U.S. children's medical center that exhibit some clinical and laboratory features of KD and appear to be related to antecedent COVID-19.(9) The association with COVID-19 is supported by two lines of evidence) -all cases had COVID-19 as evidenced by the detection of SARS-CoV-2 serum antibodies or SARS-CoV-2 nasal RNA, and the onset and peak occurrence of cases followed the peak in the number of children with COVID-19 admitted to the same hospital by approximately 3 and 5.5 weeks, respectively (Figure). The latent period between the peak of pediatric cases of

COVID-19 and MIS-C suggests that MIS-C has a post-infectious, possibly immunologically mediated pathogenesis.(9, 10)

Our case series shares many similarities with the smaller international case series reported as Kawasaki-like disease from Italy (3) and the hyperinflammatory shock syndrome reported from the United Kingdom.(4) Similar features include a patient population composed of previously healthy children of similar median ages, manifesting fever and gastrointestinal symptoms, and development of shock with cardiac dysfunction in most patients and detection of coronary abnormalities in some patients. Additionally, many patients in our cohort were overweight or obese, similar to a smaller previous case series.(4) Similar to the report of Verdoni et al, we found a spectrum of severity with 21% of our patients not requiring ICU care.(3) Across studies, most patients had antibodies against SARS-COV2 virus, suggestive of a post-infectious, immunologically mediated pathophysiology.

As our patients with MIS-C demonstrated some clinical and laboratory similarities with KD, we applied the principles of therapy for KD to our patients. The regimen included initial treatment with IVIG and aspirin, with the addition of corticosteroid therapy for those with shock or at higher risk of coronary artery aneurysm.(11) Biologic modifying medication was given in addition to those who were unresponsive to IVIG and corticosteroid.(12) This treatment protocol was associated with rapid clinical improvement and reduction in inflammatory markers in most patients and no mortalities. Considering the severity of cardiocirculatory manifestations, median

length of hospitalization of only 4 days is remarkable and probably is unique to MIS-C associated with SARS-CoV-2. Although almost all had organ dysfunction, most had resolved by hospital discharge. However, a subset of patients had coronary abnormalities and decreased cardiac function at hospital discharge. The incidence of coronary artery aneurysms and cardiac function in convalescence will be informed by follow-up evaluations.

Although the clinical presentation had features in common with KD, notable differences include the predominance of gastrointestinal symptoms and older age range with a median age of 8.6 years in the MIS-C patients compared with a median age of 2.5 years for patients with KD previously admitted to our hospital.(13) The most significant clinical differences are the markedly elevated measurements of inflammation and higher proportion of patients with shock and/or impaired cardiac function (76%) in our patients with MIS-C compared with the less than 3% of reported complication rate of shock in KD.(13)(14). Thus, as discussed by Shulman, MIS-C may be a syndrome distinct from KD. (14a)

None of the patients in our cohort developed a recognized thrombotic event such as a pulmonary embolus or stroke. Hypercoagulability has been widely reported in adults with COVID-19(15) and patients with Kawasaki disease are at risk for coronary artery thrombosis. Our patients were treated with aspirin as is routine for children with Kawasaki disease; additionally, enoxaparin was administered to patients with

significantly elevated d-dimer and fibrinogen, if they had left ventricular dysfunction, coronary artery involvement, or electrocardiographic changes.

A potential limitation of this study is that some patients included in this case series may in fact have had acute COVID-19 with “cytokine storm” rather than MIS-C because of the difficulty in differentiating these clinical entities. However, we attempted to avoid inclusion of patients with acute COVID-19 by limiting included cases to a time period after the peak of acute COVID-19 at our center and excluding patients with lower respiratory tract involvement, a hallmark of acute COVID-19.(16) It is also possible that some pediatric patients diagnosed with acute COVID-19 and cytokine storm may in fact have had MIS-C. Additionally, for clarity in reporting, only cases with confirmed CoV infection were included; 3 additional patients who were hospitalized during the study period and met criteria for MIS-C but did not have a positive SARS-CoV-2 test were not included.

It is likely this newly described inflammatory syndrome is related to recent COVID-19 infection. A large proportion of patients developed shock requiring vasoactive medications, but with supportive intensive care and anti-inflammatory therapy most patients demonstrated a rapid clinical improvement. Further study to elucidate the pathophysiologic basis of MIS-C, to optimize treatment regimens, and to determine sequelae of this syndrome are of paramount importance.

References

(1) Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics 2020. doi.org/10.1542/peds.2020-0702

(2) Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr 2020. doi:10.1001/jamapediatrics.2020.1948.

(3) Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395:1771-1778.

(4) Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607-1608.

(5) Center for Disease Control and Prevention. Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19). 2020; Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed May 18, 2020.

(6) World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. Available at: https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Accessed May 18, 2020.

(7) New York State Department of Health. NYSDOH COVID-19 Tracker. Available at: covid19tracker.health.ny.gov/views/NYS-COVID19-Tracker/NYSDOHCOVID-19Tracker-Map?%3Aembed=yes&%3Atoolbar=no&%3Atabs=n#/views/NYS%2dCOVID19%2dTracker/NYSDOHCOVID%2d19Tracker%2dMap. Accessed June 8, 2020.

(8) Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1-138.

(9) McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 2017;135:e927-e999.

(10) Rowley AH, Shulman ST. The epidemiology and pathogenesis of Kawasaki disease. Front Pediatr 2018;6:374.

(11) Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis 2005;191:499-502.

(12) Dionne A, Burns JC, Dahdah N, Tremoulet AH, Gauvreau K, de Ferranti SD, et al. Treatment Intensification in Patients With Kawasaki Disease and Coronary Aneurysm at Diagnosis. Pediatrics 2019;143:e20183341.

(13) Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, et al. Recognition of a Kawasaki disease shock syndrome. Pediatrics 2009;123:e783-9.

(14) Baer AZ, Rubin LG, Shapiro CA, Sood SK, Rajan S, Shapir Y, et al. Prevalence of coronary artery lesions on the initial echocardiogram in Kawasaki syndrome. Arch Pediatr Adolesc Med 2006;160:686-690.

(15) Schuster JE, Palac HL, Innocentini N, Rowley AH, Young LT, Shulman ST. Hyponatremia is a feature of Kawasaki disease shock syndrome: a case-control study. J Pediat Inf Disc Soc 2017;6:386-388.

(16) Shulman ST. Pediatric COVID-associated Multi-system Inflammatory Syndrome (PMIS) [Editorial]. J Pediat Inf Disc Soc 2020. doi.org/10.1093/jpids/piaa062

(17) Zhang T, Sun LX, Feng RE. Comparison of clinical and pathological features between severe acute respiratory syndrome and coronavirus disease 2019. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:E040.

(18) Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323:2052-2059.

Figure Title: Weekly COVID-19 and MIS-C Admissions

Figure Legend: Hospital admissions of patients diagnosed with Acute COVID-19 and MIS-C by week

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Table 1: Demographics, Clinical Characteristics and Hospital Course	Value	%	IQR
Demographic Characteristics			
Patients, n	33		
Age in years, median, IQR	8.6		5.5, 12.6
Age in years, range	2.2-17.0		
Female sex, n, %	13	39%	
Race			
White, n, %	3	9%	
Black, n, %	8	24%	
Asian, n, %	3	9%	
Other/Multiracial, n, %	15	45%	
Unknown/Declined, n, %	4	12%	
Ethnicity			
Hispanic, n, %	9	27%	
Non-Hispanic, n, %	24	73%	
Clinical Characteristics			
No underlying medical conditions (excluding obesity), n, %	26	79%	
Asthma or reactive airway disease, n, %	5	15%	
Other (a), n, %	2	6%	
Weight status categories			
Underweight (<5th %ile), n, %	3	9%	
Normal weight (5th-<85th %ile), n, %	15	45%	
Overweight (85th-<95th %ile), n, %	2	6%	
Obese (>=95th %ile), n, %	13	39%	
Presenting signs/symptoms			
Fever duration prior to presentation, in days, median, IQR	4		3, 5
Neurocognitive symptoms (headache, irritability, lethargy), n, %	19	58%	
Gastrointestinal symptoms (vomiting, diarrhea, abdominal pain), n, %	32	97%	
Respiratory symptoms (cough, congestion, dyspnea, sore throat), n, %	17	52%	
Shock (requiring vasoactive), n, %	25	76%	
Complete Kawasaki disease, n, %	21	64%	
with shock, n, % (of category)	16/21	76%	
Hospitalization			
PICU admission, (n, %)	26	79%	
Length of stay, in days, median, IQR	4		4, 8
Initial Laboratory Results			
White blood cell count, K/uL, median, IQR	9.14		7.19, 12.33
Absolute lymphocyte count, K/uL, median, IQR	0.80		0.49, 1.42

Lymphopenia, n, %	27	82%	
Hemoglobin, g/dL, median, IQR	11.2		10.5, 12.0
Platelet count, K/uL, median, IQR	154		104, 205
C-reactive protein (ref: < 5), mg/L, median, IQR	206		122, 291
D-dimer (ref: < 230), ng/mL, median, IQR	1700		958, 2410
Fibrinogen, mg/dL, median, IQR	736		619, 870
Ferritin (ref: 15-150), ng/mL, median, IQR	640		313, 1192
Lactate dehydrogenase (ref: 135-225), U/L, median, IQR	320		263, 419
INR, median, IQR	1.31		1.20, 1.51
Pro-BNP (ref: < 300), pg/mL, median, IQR	3325		640, 6776
Troponin T (ref: < 14), ng/L, median, IQR	31		6, 78
Procalcitionin (ref: < 0.10), ng/mL, median, IQR	12.05		2.87, 24.96
Sodium, mmol/L, median, IQR	133		131, 135
ALT, U/L, median, IQR	38		30, 64
AST, U/L, median, IQR	54		36, 76
Total Bilirubin, mg/dL, median, IQR	0.5		0.4, 0.6
Albumin, g/dL, median, IQR	3.4		3.0, 3.7
SARS-CoV-2 Testing			
IgG positive and NAA (b) positive, n, %	6	18%	
IgG positive and NAA negative, n, %	24	73%	
NAA positive, serology test unavailable, n, %	3	9%	
Organ Dysfunction			
Acute liver injury (ALT > 80 U/L), n, %	7	21%	
Acute kidney injury (KDIGO - (c)), n, %	23	70%	
Required oxygen or positive pressure, n, %	17	52%	
Mechanical ventilation, n, %	6	18%	
Intubation days, median, IQR	3		2, 4
Maximal Vasoactive Infusion Score (d), median, IQR	10		5, 20
Echocardiogram Findings			
Any coronary abnormality (n, %)	16	48%	
Left Anterior Descending/Right Coronary Artery findings			
Z-score >= 2.5, n, %	5	15%	
Z-score 2-2.49, n, %	3	9%	
Lack of tapering (Z score <2), n, %	8	24%	
Any dysfunction, n, %	19	58%	
Mild (LVEF 45-54%), n, %	11	33%	
Moderate (LVEF 35-44%), n, %	8	24%	

Severe (LVEF < 35%), n, %	0	0%	
Medications for MIS-C			
IVIG, n, %	33	100%	
2nd dose IVIG, n, %	11	33%	
Methylprednisolone, n, %	23	70%	
Aspirin, n, %	29	88%	
Anakinra, n, %	4	12%	
Tocilizumab, n, %	3	9%	
Infliximab, n, %	1	3%	
Enoxaparin, n, %	14	42%	
Disposition			
Cardiac Function at Discharge			
Always normal, n, %	14	42%	
Depressed then normalized, n, %	10	30%	
Mildly depressed, n, %	9	27%	
Status			
Discharged alive, n, %	33	100%	

(a) Patients with other diagnoses included 1 patient with hemodynamically insignificant VSD and 1 patient with renal tubular acidosis

(b) NAA = Nucleic acid amplification

(c) Creatinine > 50% increased from baseline or absolute increase of 0.3 mg/dL [7]

(d) Vasoactive infusion Score = dopamine (mcg/kg/min) + dobutamine (mcg/kg/min) + 100*epinephrine (mcg/kg/min) + 100*norepinephrine (mcg/kg/min) + 10*milrinone (mcg/kg/min) + 10,000*vasopressin (U/kg/min)