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Multisystem inflammatory syndrome in children associated with novel coronavirus SARS-CoV-2: Presentations to a pediatric emergency department in Michigan

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ABSTRACT

The SARS-CoV-2 is a respiratory virus of the coronavirus family responsible for a global pandemic since December 2019. More than 35 million people have been affected with the novel coronavirus disease (COVID-19), with more than one million deaths worldwide. Michigan was one of the top three states in the United States that was severely affected by the SAR-CoV-2 pandemic with more than 7000 deaths in adults and greater than 145,000 confirmed infections. However, compared to adults, the majority of children until recently were either asymptomatic or had a mild illness with SARS-CoV-2. Recently, a rare but potentially serious presentation associated with SARS-CoV-2 called multisystem inflammatory syndrome in children (MIS-C) has been recently reported and the Centers for Disease Control (CDC) released a case definition for the same. We report the clinical and laboratory presentations and outcomes of 34 children with MIS-C who were evaluated within a 12 week period at a pediatric emergency department (PED) of single institution in Michigan. These cases presented approximately three weeks after the peak of adult SAR-CoV-2 related deaths occurred in the state. While many children presented with clinical characteristics similar to incomplete Kawasaki disease (KD), they also exhibited certain unique features which differentiated MIS-C from KD. The information presented below will aid clinicians with early recognition, evaluation and management of MIS-C in the emergency department.

1. Introduction

The coronavirus disease (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has become the most far-reaching health threat of this century, with more than 39 million infected individuals and 1.1 million deaths worldwide [1]. The United States has been one of the most severely affected countries with 2.3 million infected cases and more than 200,000 deaths [2]. Michigan was one of the states in the country that was significantly impacted by the pandemic with more than 7000 deaths and 150,000 confirmed infections. Compared to adults, until recently children were rarely severely affected by this disease with more than 90% being either asymptomatic or with mild disease [3]. However, recent reports from Europe described a pediatric multisystem inflammatory syndrome resembling incomplete Kawasaki Disease (KD) in children [4,5]. The CDC recently named this entity as MIS-C and formulated a case definition [6]. Since then, additional reports of MIS-C from Europe and the US have been published [7-9]. The objective of this report was to describe the initial clinical and laboratory features of MIS-C in a cohort of 34 children at presentation to a pediatric emergency department (PED) of a single institution in Michigan. All of these children met the CDC MIS-C definition and presented to our PED approximately three weeks after the peak of adult COVID-19 cases in our state.

2. Methods

This study was performed at a level one pediatric trauma center with more than 85,000 visits per year. Our hospital is located in Detroit, Michigan which experienced high mortality rates in adults from SARS-CoV-2 infection. We performed a retrospective chart review of thirty four children ≤21 years of age who presented to our PED, met the CDC definition of MIS-C (Supplemental Table 1) and required treatment with intravenous immunoglobulin between April 16, 2020 and July 07, 2020. Data on patient demographics, clinical features, laboratory

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parameters including COVID-19 testing (reverse transcriptase polymerase chain reaction from nasopharyngeal swabs- RT-PCR and/or IgG serology), management and outcomes were abstracted. Descriptive statistics was used to summarize patient and laboratory characteristics. We used percentages, and means with standard deviation to describe normally distributed variables and median and interquartile ranges for those that were not normally distributed. This study was approved by our institutional review board under expedited review with waiver of informed consent.

3. Results

The demographics and clinical features of this cohort of children at presentation to the PED are noted in Table 1. The majority were African American, older than 5 years of age, and many had at least one prior health care visit in the preceding 48 hours. Comorbidities occurred in more than one third of the children with asthma being the most common. Fever ≥2 days, gastrointestinal symptoms (vomiting, abdominal pain or diarrhea) anorexia and rash were the most common symptoms, while respiratory symptoms were rare. While generalized abdominal tenderness was elicited in 44.4% of patients, specific right lower quadrant tenderness was present in two patients that resulted in a work up for appendicitis which was found to be negative. Shock (persistent hypotension requiring >20 mL/kg fluids or need for vasopressors) occurred more than one third of the patients overall, with 10 (29%) requiring vasopressor addition (dopamine or epinephrine) in the PED. Elevated inflammatory markers such as C- reactive protein (CRP), ferritin and D-dimer were noted in the majority of children with MIS-C while elevation of transaminases and hypoalbuminemia were less common at presentation (Table 2). Patients had significant cardiac involvement at presentation with abnormalities noted in 33% of electrocardiograms (EKG) and more than 60% of echocardiograms (Supplemental Table 4). Further, of the patients with elevated troponin who also had an EKG ($n = 18$) or ECHO ($n = 17$) performed, 50% and 88.2% were abnormal respectively.

Nineteen children (79%) were admitted to the intensive care unit directly from the PED while 5 patients (15%) were transferred to the intensive care unit a few hours after admission to the general floor due to decompensation in their clinical condition (either hypotension not responding to fluids or cardiac arrhythmias). Of the 24 patients (70.5%) admitted to the pediatric intensive care unit, interventions included vasopressor support in 16 (66.6%) patients (dopamine, epinephrine or milrinone), mechanical ventilation in 8 (33.3%) patients and extra corporeal membrane oxygenation (ECMO) in 2 patients (8.3%). All children were treated with intravenous immunoglobulin and high dose aspirin while twelve received infliximab additionally for persistent inflammation. There were no deaths in our cohort and all patients were discharged home without major sequelae.

Of the 34 patients, only 8 (23.5%) tested positive for COVID-19 RT- PCR. However, of the 25 patients who had IgG serology testing, 18 (72%) were positive, indicating a prior exposure to SARS-CoV-2. Four patients tested positive for both COVID −19 PCR and IgG antibodies. EKG and ECHO abnormalities of these patients are shown in Supplemental Table 5.

Table 1
Demographics, clinical and laboratory features at presentation to the Emergency Department.

Characteristic	Number ($n = 34$ unless stated otherwise)
Demographics	
Age in years (Median ± IQR)	6 (8)
Males (*n*, %)	16 (47)
African American (*n*, %)	23 (68)
Prior visit (*n*, %)	16 (47)
Co morbidities	*n* (%)
Asthma	9(26.4)
Obesity	2 (5.8)
Clinical features	*n* (%)
Fever ≥2 days	30 (88.2)
Anorexia	29 (85.2)
Abdominal pain	20(58.8)
Vomiting	14(41.1)
Diarrhea	13 (52)
Rash	19(55.8)
Conjunctivitis	9(26)
Sore throat	9(26.4)
H/O Covid-19 exposure	6 (17.6%)
Abnormal Vital signs	*n* (%)
Tachycardia for age	33 (97)
Tachypnea for age	9(26.4)
Hypoxia ≤95% on room air	1(3)
Hypotension[a]	6 (17.6)
Shock	13(38.4)
Vital signs	(Mean ± SD)
Temperature^{0}C	38.8 ± 0.8
Heart rate/min	140 ± 17
Respiratory rate/min	32 ± 10
Systolic BP mmHg	98 ± 13
Diastolic BP mmHg	59 ± 11
Laboratory Abnormalities	*n*, %
Absolute lymphopenia (<1.6 K/CUMM)	21 (61.7)
Elevated C Reactive protein >5 mg/L	25 (97)
Elevated LDH > 271Units/L, $n = 31$	24 (77.4)
Sodium <135 mMol/L	25 (73.5)
Acute kidney injury	10(29.4)
Elevated Alanine transferase,>52 units/L, $n = 24$	9(37)
Low albumin <3.0 g/dL	11(32.3)
Elevated Ferritin >306.8 ng/ml	16 (47)
Elevated Fibrinogen >466 mg/dL, $n = 28$	18 (64.2)
Elevated Troponin >17 ng/L	18 (52.9)
Elevated D dimer >0.5 mg/L FEU, $n = 31$	26 (83.8)

[a] Hypotension definition: <70 mmHg in infants (1 month to 12 months), <70 mmHg + (2 × age in years) in children 1 to 10 years and <90 mmHg in children ≥10 years of age. Kleinman ME, Chameides L, Schexnayder SN et al. 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010; 122:S876–S908.

4. Discussion

Our case series of 34 children from a single institution is one of the largest reports in the US of MIS-C temporally associated with SARS-CoV2 that predominantly resulted in myocardial injury. Our report parallels that of those reported from both Europe and other parts of United States [5,7-9]. DeBiasi et al. reported severe illness in 9 critically ill children with a median age of 9.6 years in the metro DC area while Kaushik et al. described 33 children with severe MIS-C with a median age of 10 years who were admitted to the intensive care units of multiple centers in the state of New York [7,8]. Similar to the other reports, MIS-C occurred in our cohort of children when infections in adults in our state

Table 2
Laboratory values at presentation to the Emergency Department

Laboratory parameter	Mean ± SD (unless stated otherwise)
WBC count K/CUMM	11.6 ± 1.9
Hemoglobin gms/dL	11.3 ± 1.9
Absolute Lymphocyte count K/CUMM	1.7 ± 1.3
Platelets K/CUMM	219 ± 116.8
C Reactive protein mg/L, Median (IQR)	143 (161.5)
Serum sodium mMol/L	132 ± 5.1
Albumin gms/dL	3.7 ± 0.7
Ferritin ng/ml, Median (IQR)	331 (342)
D dimer mg/L FEU, Median (IQR)	2.3 (2.3)
Troponin ng/L (Median, IQR)	18.5(104.5)

due to SARS-COV-2 were on the decline. The peak of MIS-C cases trailed the peak of COVID-19 infections in our community by approximately 3 weeks. Following exposure to the virus, the children were initially either asymptomatic or only mildly symptomatic until the development of MIS-C a couple of weeks later, thus suggesting that MIS-C is the result of an immune response to the viral infection. However, while Kaushik et al. reported predominance of MIS-C in Hispanic/Latino populations, children in our cohort were largely African Americans [8]. This could be reflective of the population race and ethnicity distribution in our PED which is predominantly non Hispanic, African American. Further, compared to other reports, children in our series were slightly younger the reasons for which are unclear. In contrast to adults, the clinical features of COVID-19 in children had previously been mild with most presenting with fever and respiratory symptoms. Critical illness was rare and usually secondary to respiratory illness without cardiac involvement [3]. In contrast, most of the children in our cohort with MIS-C required admission to the intensive care unit for circulatory and hemodynamic support given their significant myocardial injury involvement.

Some children with MIS-C presented with similar clinical and laboratory features as incomplete KD [10]. However, notable differences that distinguished MIS-C from incomplete KD included older age, predominantly gastrointestinal symptoms and more shock and myocardial injury at presentation [8,9,11,12].

The most striking occurrence in our cohort was the myocardial injury associated with MIS-C. While reports of troponin elevation in KD have conflicted, more than half of our patients with MIS-C had an elevated troponin associated with myocardial injury at presentation [13,14]. Many children in our cohort had myocardial dysfunction with predominantly LV dysfunction and 3 children had coronary dilation at presentation, suggesting a rapid and severe inflammation with a predilection for the heart. Further, the majority of those who did not have myocardial dysfunction in the PED developed worsening myocardial function later in their course. In fact, the myocardial involvement in our children bears similarity to that seen in adult acute COVID-19 cardiovascular syndrome which presents with reduced left ventricular ejection fraction in the absence of obstructive coronary artery disease [15]. Although the exact reason for this myocardial involvement is unclear in children, in adults it has been hypothesized to be secondary to acute coronary syndrome, microvascular ischemic injury, myocarditis or cytokine dysregulation.

A striking feature was that most children with MIS-C had lymphopenia which has been reported commonly in adults with severe COVID-19 [16]. Postulated reasons for this lymphopenia in COVID-19 include direct cell lysis due to interaction with the expressed ACE 2 receptor on cell surface and apoptosis caused by circulating cytokines [17]. The hyponatremia observed in a large proportion of MIS-C at presentation was likely secondary to dehydration, renal or cardiac failure. While hyponatremia has been described as a predictor of poor outcome in both COVID-19 and KD, its role as a prognosticator in MIS-C is unclear [18,19]. Further, while elevated D dimer levels have been associated with treatment resistant KD, its significance in cardiac involvement in MIS-C is unclear [20]. Lastly, a recent report describes a MIS-A (multisystem inflammatory syndrome in adults) which clinical features very similar to the MIS-C in children thus suggesting a possible common pathophysiology that warrants further investigation [21].

Certainly, as the pandemic continues, it is critical for emergency department providers to recognize the various clinical presentations of MIS-C and its serious cardiovascular complications. A more comprehensive evaluation may be warranted in any child presenting with a fever in combination with a rash, conjunctivitis or gastrointestinal symptoms regardless of COVID-19 exposure. Laboratory investigation should include an evaluation of markers for inflammation and myocardial injury including a troponin level, an EKG and an echocardiogram. Clinicians should also anticipate sudden clinical deterioration in these children and consider early critical care unit admission.

5. Conclusion

Clinicians need to be on high alert for MIS-C in previously healthy children. Since many of these children present with myocardial injury and recover completely with timely treatment, institution of a standardized screening protocol in the emergency department may facilitate the early identification and evaluation of these children. Evidence of increased inflammation and myocardial injury should prompt immediate admission to the pediatric critical care unit to optimize management and prevent morbidity and mortality.

Meetings

The preliminary findings of these MIS-C patients were presented by Dr. Usha Sethuraman at a pediatric emergency medicine webinar on 05/20/20.

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Credit author statement

US, NK and CS conceived the design and write up of the case series. US undertook data collection, any statistical calculations and write up of the manuscript. AS, RH and JPM drafted the tables, researched the references and revised manuscript. JA contributed to design and write up of manuscript and revisions. All authors contributed substantially to its revision. US takes responsibility for the paper as a whole.

Declaration of Competing Interest

Usha Sethuraman – No conflicts of interest.
Nirupama Kannikeswaran- No conflict of interest.
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Rita Haddad- No conflict of interest.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2020.10.035.

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