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COMPARISON OF FIRST AND SECOND WAVE COHORTS OF MULTISYSTEM INFLAMMATORY DISEASE SYNDROME IN CHILDREN

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Abstract: Comparing first and second wave MIS-C cohorts at our quaternary pediatric institution, second wave were older, presented more frequently with shortness of breath, higher maximum troponin and N-terminal BNP, and more frequently required advanced respiratory and inotropic support. Despite increased severity in the second cohort, both cohorts had similar rates of coronary artery abnormalities, systolic dysfunction, and length of stay.

Key Words: pediatric multisystem inflammatory syndrome, PMIS, multisystem inflammatory syndrome in children, MIS-C, 2019 coronavirus disease, immunomodulation, myocarditis, critical care

Multisystem inflammatory syndrome in children (MIS-C) is a newly described severe hyperinflammatory multisystem illness specific to the pediatric population, which is thought to be an immune-mediated complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1,2] Our center managed 2 distinct cohorts of MIS-C patients, each following periods of maximal virus circulation and surge (waves) in our community by 4–6 weeks. Multiple centers (including ours) and consortia, as well as the CDC, have published key demographic and clinical features of MIS-C following the first wave of patients with this rare presentation. These reports have included patients with varying degrees of severity, cardiac dysfunction, requirement for critical care, respiratory, inotropic, and immunomodulatory support.[3,4] The second wave of MIS-C patients at our institution was larger than the first wave, following the largest surge in SARS-CoV-2 circulation in the United States and our community. Herein, we provide the first comparison of clinical features and outcomes for MIS-C patient cohorts treated at our facility during the first and second large waves of presentation, under a standard institutional evaluation and treatment protocol that prioritizes prompt immunomodulatory therapy.

MATERIALS AND METHODS

This was a prospective cohort study of 106 patients sequentially diagnosed and treated for MIS-C according to the Centers for Disease Control and Prevention MIS-C case definition and admitted to our quaternary pediatric center in Washington, DC.[5] Patients' demographic, clinical, laboratory, radiographic, including echocardiography, therapies, and outcomes were extracted from electronic medical records. Wave 1 MIS-C Cohort patients (N = 43) were hospitalized between March and October 2020; Wave 2 MIS-Cohort patients (N = 63) were hospitalized between November 2020 and April 2021.

All patients were managed under the same standardized institutional protocol that utilizes intravenous immunoglobulin (IVIG) and aspirin with or without Anakinra as initial therapy, as well as escalation to additional corticosteroid immunomodulation depending on defined clinical parameters. The institutional algorithm was developed by a multidisciplinary committee (Children's National Hospital MIS-C Task force).[3,6] Cardiac complications were defined as abnormal coronary artery (Z score ≥ 2) or decreased systolic function (ejection fraction < 55% or shortening fraction < 28%).[7,8]

Statistical Analysis

The analysis compared the 2 MIS-C cohorts with respect to demographics, clinical features, diagnostic biomarkers, radiographic procedures including echocardiogram, immunomodulatory and vasopressor support, and clinical outcomes. All data were summarized using descriptive statistics of the median and interquartile (IQR) range and frequency. Continuous variables were analyzed using the nonparametric Wilcoxon rank sum test as normality was

not assumed. Categorical variables were analyzed using the χ^2 and Fisher's exact test. A $P \leq 0.05$ was considered statistically significant and $P > 0.05$ but <0.1 was considered a trend. All analyses were performed using STATA version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.).

Children's National Hospital Institutional Review Board approved this study with a waiver of consent granted. Authors A.S.H., M.P.S., J.E.B., and R.L.D. had full access to all the data in the study and take responsibility for its integrity and the data analysis.

RESULTS

The median patient age was 8.4 years (4.7–13.4), 49 (46%) were female, 56 (54%) were Black, and 41 (39%) were Hispanic. No underlying medical conditions were noted in 80 (75%) patients. Thirty-four (32%) met diagnostic criteria for Kawasaki disease (Table 1). No mortality occurred and all patients were discharged home at a median (IQR) of 11 (7–14) days.

Comparing MIS-C patient from the wave 1 and wave 2 cohorts, patients in Wave 2 included a higher proportion of children 15 years of age or older [13/63 (21%) vs. 2/43 (5%); $P = 0.024$]. Wave 2 cohort patients were less likely to fulfill diagnostic criteria for Kawasaki disease [13/63 (21%) vs. 21/43 (49%), $P = 0.003$] and more likely to present with shortness of breath [11/63 (18%) vs. 1/43 (3%); $P = 0.025$]. Wave 2 Cohort patients were less likely to be polymerase chain reaction-positive for SARS-CoV-2 [10/63 (16%) vs. 21/43 (49%); $P < 0.001$], had higher maximum median Troponin I (ng/mL) values [0.43 (IQR 0.14–1.665) vs. 0.145 (IQR 0.08–0.66); $P = 0.022$], and higher maximum N-terminal B-type natriuretic peptide (pg/mL) values [17,825.5 (IQR 7827–29,569) vs. 9780 (2426–17,886); $P = 0.005$]. Wave 2 cohort patients were more likely to require additional immunomodulation with methylprednisolone [18/63 (29%) vs. 3/43 (7%), $P = 0.006$] and a trend toward more frequent requirement for ICU level of care [51/63 (81%) vs. 28/43 (65%), $P = 0.074$]. Wave 2 cohort patients were more likely to require vasopressors [46/63 (73%) vs. 22/43 (51%), $P = 0.025$], had higher maximum vasoactive index score [median 10 (IQR 0–20) vs. 3 (0–15), $P = 0.042$], had increased utilization of bi-level positive airway pressure (BiPAP) [25/63 (40%) vs. 8/43 (19%); $P = 0.032$], and were thus less likely to utilize only high flow nasal cannula [6/63 (10%) vs. 11/43 (26%); $P = 0.033$] (Table 1). Despite the increased degree of clinical severity and laboratory abnormalities in the wave 2 cohort, no significant differences were noted comparing wave 2 and wave 1 cohorts with respect to rate of coronary artery abnormalities [3/56 (5%) vs. 6/41 (15%); $P = 0.16$], systolic dysfunction [17/58 (29%) vs. 12/37 (32%); $P = 0.821$] or length of stay [10 days (IQR 8–14) vs. 12 days (IQR 7–14); $P = 0.437$] (Table 1).

DISCUSSION

Our center managed a large number of MIS-C patients under a standardized MIS-C evaluation and treatment algorithm throughout the first year of SARS-CoV-2 circulation in the United States, with 2 distinct cohorts of MIS-C patients presenting 4–6 weeks following 2 distinct large waves of viral circulation and primary COVID infection and admissions in our region. In the second (later) wave following the largest surge of virus in the United States, MIS-C patients presented with more severe respiratory and cardiovascular symptoms, had more abnormal BNP and Troponin levels, had a tendency for more frequently requiring ICU level of support, more frequently required inotropic and advanced respiratory support. Although a larger proportion of patients in the Wave 2 Cohort met criteria for escalation of immunomodulation to include adjunctive corticosteroid therapy (in addition to first line IVIG and aspirin with or without anakinra), the majority of wave 1 and wave 2 patients did not require escalation to methylprednisolone (93% wave 1 cohort; 71% wave 2 cohort). Despite the overall increased severity of disease observed in the wave 2 cohort, the incidence of coronary artery abnormalities and ventricular systolic dysfunction were not different between the 2 cohorts.

The reasons for the observed increased clinical severity at presentation in the wave 2 cohort are not entirely clear, but were not due to differences in underlying sex, race, or ethnicity (overwhelmingly Black or Hispanic), or presence of underlying medical condition which were similar in both cohorts. The exact immunologic mechanisms by which MIS-C is triggered and the specific factors accounting for its rare occurrence are still not fully understood. However, in comparison to the wave 1 cohort, children in the wave 2 MIS-C cohort had potentially experienced additional intermittent or multiple repeated exposure(s) to circulating SARS-CoV-2 virus in their communities, which may have served as repeated immune triggers to augment or accelerate the dysregulated hyperimmune response that is unique to MIS-C. Differences in the proportion of circulating variants within the time periods defining each cohort could also have contributed to differences in degree of immune dysregulation; it should be noted that there was minimal circulation of the delta variant in the United States or our community during either period. The timing and characterization of a potential third delta variant-associated MIS-C surge remains to be seen, but has not yet materialized at our institution, despite 7 weeks since inception of our current SARS-CoV-2 surge.

Strengths of this study include the ability to compare well characterized cohorts accurately, since a single, standardized evaluation, and treatment approach was used at a single site across the entire period for the study, encompassing both waves of MIS-C presentation. Protocolization and standardization of care has been shown to improve patient care.[9] Despite more severe clinical presentation and a higher degree of laboratory abnormalities, children in the second wave MIS-C cohort had a similar, not increased, incidence of cardiac abnormalities, length of stay, and outcome with no mortality in either cohort. Belay et al reported an increased need for immunotherapy in MIS-C patients presenting later in the pandemic, that was also associated with a lower incidence of cardiac dysfunction.[10] The standardized approach implemented at our center was associated with stable rates of cardiac complications despite more severe clinical presentation in the more recent MIS-C cohort (wave 2). Limitations of our study include the fact that we limited cardiac complications for comparison to coronary artery abnormalities or decreased systolic function, and did not include valvular regurgitation or pericardial effusion, although in our overall institutional cohort, these findings have been observed to be the most transient and likely to resolve during short-term follow-up.[3]

CONCLUSIONS

MIS-C remains a diagnostic and therapeutic challenge for pediatricians and subspecialists. Although a spectrum of clinical severity has been observed across centers, this report highlights that severity of disease may also evolve over different time points of the pandemic. Despite increased severity, mortality was prevented, and morbidity was mitigated with rapid implementation of a standardized, protocolized, and coordinated immunomodulatory approach.

ACKNOWLEDGMENTS

TABLE 1. Demographics, Patient Characteristics, Laboratory findings, Diagnostics, Treatments, Clinical Outcomes and Echocardiographic Findings Among MIS-C Patients Stratified by Wave Cohort

Variable of Interest	All Cases (N = 106) n (%)	Wave 1 Cohort (N = 43) n (%)	Wave 2 Cohort (N = 63) n (%)	*P* value Wave 1 vs. Wave 2 Cohort
Demographics				
Age in months (median and IQR)	101 (56–161)	95 (44–151)	109 (61–171)	0.126
Specific age bands all patients				0.173
<1	2 (2%)	1 (2%)	1 (2%)	
1–<5	27 (25%)	13 (30%)	14 (22%)	
5–<10	35 (33%)	15 (35%)	20 (32%)	
10–<15	27 (25%)	12 (28%)	15 (24%)	
15+	15 (14%)	2 (5%)	13 (21%)	
Specific age bands all patients				**0.024**
<15	91 (86%)	41 (95%)	50 (79%)	
≥15	15 (14%)	2 (5%)	13 (21%)	
Sex (% Female)	49 (46%)	19 (44%)	30 (48%)	0.843
Race				0.249
Black	56 (54%)	21 (50%)	35 (56%)	
Caucasian	6 (6%)	1 (2%)	5 (8%)	
Asian	2 (2%)	0 (0%)	2 (3%)	
Other	40 (38%)	20 (48%)	20 (32%)	
Ethnicity				0.417
Hispanic	41 (39%)	19 (44%)	22 (35%)	
Non-Hispanic	65 (61%)	24 (56%)	41 (65%)	
Patient characteristics				
Presence of any underlying condition	26 (25%)	13 (30%)	13 (21%)	0.358
Known sick contact	33 (34%) N = 98	15 (39%) N = 39	18 (31%) N = 59	0.513
Presence of Kawasaki disease Criteria	34 (32%)	21 (49%)	13 (21%)	**0.003**
Specific Symptoms				
Mucous membrane changes	62 (58%)	29 (67%)	33 (52%)	0.160
Peripheral extremity changes	14 (13%)	7 (17%)	7 (11%)	0.559
Conjunctival injection	56 (53%)	26 (60%)	30 (48%)	0.236
Rash	49 (46%)	19 (44%)	30 (48%)	0.843
Fever	104 (98%)	42 (98)	62 (98%)	0.999
Cough	18 (17%) N = 104	9 (21%) N = 42	9 (14%) N = 62	0.432
Shortness of breath	12 (12%) N = 99	1 (3%) N = 39	11 (18%) N = 60	**0.025**
Abdominal pain	79 (75%)	35 (81%)	44 (70%)	0.256
Vomiting	63 (61%) N = 103	25 (59%) N = 42	38 (62%) N = 61	0.838
Diarrhea	50 (49%) N = 102	19 (46%) N = 41	31 (51%) N = 61	0.690
Chest pain	12 (14%) N = 85	2 (7%) N = 28	10 (17%) N = 57	0.321
Myalgias	24 (23%)	9 (30%)	15 (26%)	0.801
Laboratory findings				
SARS-CoV-2 PCR positive	31 (29%) N = 106	21 (49%) N = 43	10 (16%) N = 63	**<0.001**
SARS-CoV-2 PCR cycle time (median and IQR)	32.0 (28.95–33.1) N = 28	31.3 (28–32.65) N = 19	32.6 (32.2–33.7) N = 9	0.069
SARS-CoV-2 Antibody positive	100 (96%)	40 (97%)	60 (95%)	0.999
Troponin I–maximum (ng/mL) (Normal <0.04) (median and IQR)	0.35 (0.09–1.04) N = 98	0.145 (0.08–0.66) N = 38	0.43 (0.14–1.665) N = 60	**0.022**
N-terminal B-type natriuretic peptide–maximum (pg/mL) (Normal <1100) (median and IQR)	12,991 (4617.5-23,478.5) N = 104	9780 (2426-17,886) N = 42	17,825.5 (7827-29,569) N = 62	**0.005**
Diagnostics				
Chest radiograph abnormal	60 (61%)	27 (64%)	33 (59%)	0.677

(Continued)

TABLE 1. (*Continued*)

Variable of Interest	All Cases (N = 106) n (%)	Wave 1 Cohort (N = 43) n (%)	Wave 2 Cohort (N = 63) n (%)	P value Wave 1 vs. Wave 2 Cohort
Treatments				
Immune therapy				
Intravenous immunoglobulin (IVIG)	105 (99%)	42 (98%)	63 (100%)	0.406
Anakinra	78 (74%)	31 (72%)	47 (75%)	0.824
Steroids	37 (37%)	10 (24%)	27 (44%)	0.090
Hydrocortisone	22 (21%)	7 (16%)	15 (24%)	0.466
Dexamethasone	3 (3%)	2 (5%)	1 (2%)	0.565
Methylprednisolone	21 (20%)	3(7%)	18(29%)	**0.006**
Tocilizumab	3 (3%)	0 (0%)	3 (5%)	0.261
Remdesivir	1 (1%)	0 (0%)	1 (2%)	0.999
Aspirin	102 (96%)	41 (95%)	61 (97%)	0.999
ICU admission	79 (75%)	28 (65%)	51 (81%)	0.074
Vasopressors	68 (64%)	22 (51%)	46 (73%)	**0.025**
Vasoactive Index (VIS) Score (Maximum) (median and IQR)	5 (0–17) N = 105	3 (0-15) N = 43	10 (0-20) N = 62	**0.042**
Oxygen therapy of any kind	61 (58%)	24 (56%)	37 (59%)	0.842
Nasal cannula	49 (46%)	16 (37%)	33 (52%)	0.165
Facemask	3 (3%)	1 (2%)	2 (3%)	0.999
High-flow nasal cannula	17 (16%)	11 (26%)	6 (10%)	**0.033**
BiPAP	33 (31%)	8 (19%)	25 (40%)	**0.032**
Mechanical ventilation	15 (14%)	6 (14%)	9 (14%)	0.999
Clinical outcomes				
Hospital LOS (median and IQR)	11 (7–14)	12 (7-14)	10 (8-14)	0.437
ECMO	0 (0%)	0 (0%)	0 (0%)	N/A
Mortality	0 (0%)	0 (0%)	0 (0%)	N/A
Echocardiogram				
Coronary artery abnormalities	N = 97	N = 41	N = 56	0.161
No (Z score < 2)	88 (91%)	35 (85%)	53 (95%)	
Yes (Z score ≥ 2)	9 (9%)	6 (15%)	3 (5%)	
Coronary Artery classifications	N = 97	N = 41	N = 56	0.174
Normal (Z score < 2)	88 (91%)	35 (85%)	53 (95%)	
Dilation (Z score 2 to < 2.5)	7 (7%)	4 (10%)	3 (5%)	
Small aneurysm (Z score 2.5 to <5),	2 (2%)	2 (5%)	0 (0%)	
Moderate aneurysm (Z score 5 to <10),	0 (0%)	0 (0%)	0 (0%)	
Giant aneurysm (8 mm or Z score ≥ 10)	0 (0%)	0 (0%)	0 (0%)	
Ejection fraction (EF) continuous variable (%) (median and IQR)	60 (53.2–63.6) N = 95	60 (51–62) N = 37	60 (53.3–63.8) N = 58	0.625
Systolic function (2 categories)				0.821
Abnormal (EF < 55%)	29 (31%)	12 (32%)	17 (29%)	
Normal (EF ≥ 55%)	66 (69%)	25 (68%)	41 (71%)	
Systolic function discrete variables (4 categories)				0.868
Normal systolic function (EF ≥ 55%)	66 (69%)	25 (68%)	41 (71%)	
Mild systolic dysfunction (EF 41 to <55%)	27 (28%)	12 (32%)	15 (26%)	
Moderate systolic dysfunction (EF 30 to <41%)	1 (1%)	0 (0%)	1 (2%)	
Severe systolic dysfunction (EF <30%)	1(1%)	0 (0%)	1 (2%)	

BiPAP, bi-level positive airway pressure; ECMO, extracorporeal membrane oxygenation; EF, ejection fraction; ICU, intensive care unit; IQR, interquartile range; N/A, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

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APPENDIX

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POPULATION-BASED INCIDENCE OF MYOPERICARDITIS AFTER COVID-19 VACCINATION IN DANISH ADOLESCENTS

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Abstract: In this prospective nationwide multicenter study from Denmark, myopericarditis after Pfizer-BioNTech mRNA COVID-19 vaccination was identified in 13 males and 2 females between May 15 and September 15, 2021, among 133,477 vaccinated males and 127,857 vaccinated females 12–17 years of age, equaling 97 males and 16 females per million. In conclusion, the incidence of myopericarditis after COVID-19 vaccination among males appears higher than reports from the United States.

Key Words: mRNA COVID-19 vaccine, myopericarditis, adolescents

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Myopericarditis is a complication to mRNA COVID-19 vaccines, especially in male adolescents and young adults.[1] According to the US Vaccine Adverse Event Reporting System (VAERS), the rate of myopericarditis has been reported to be 56–69 per million vaccinated males 12–17 years of age and 8–10 per million vaccinated females 12–17 years of age.[1] However, as underreporting is a limitation of VAERS, the estimates are encumbered with uncertainty.[1,2]

In Denmark, the Pfizer-BioNTech mRNA COVID-19 vaccination was recommended from May 15, 2021, in individuals 16–17 years of age and from July 15, 2021, in individuals 12–15 years of age. We aimed to estimate the incidence of myopericarditis in adolescents after mRNA COVID-19 vaccination among vaccinated individuals based on a nationwide prospective population-based cohort study with detailed clinical phenotyping.

MATERIALS AND METHODS

The study was a prospective population-based cohort study of all individuals 12–17 years of age hospitalized due to myocarditis and pericarditis after COVID-19 mRNA vaccination in the period May 15 to September 15, 2021. The setting was a multicenter study including all 18 Danish Pediatric Departments, providing 24 hours emergency service, and in- and out-patient treatment for all Danish inhabitants ≤ 17 years of age. As part of a pediatric nationwide COVID-19 research set-up, all 18 departments had a principal investigator responsible for prospective real-time data collection of vaccine-associated disease from May 15, 2021. Cases of myopericarditis were cross checked with the Danish VAERS to minimize the risk of missing cases. Due to unusual severity, case 12 has been reported previously.[3]

To calculate the incidence of myopericarditis associated with mRNA COVID-19 vaccination among Danish adolescents, the number of individuals 12–17 years of age who had received 1 dose of mRNA COVID-19 vaccine from May 15 to August 15, 2021, was attained from the National COVID-19-vaccine Database at the Statens Serum Institut.

The incidence of cardiac involvement due to SARS-CoV-2 infection in Danish adolescents 12–17 years of age was calculated