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Non-SARS-CoV-2 Infections Among Patients Evaluated for MIS-C Associated With COVID-19

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Abstract

Clinical features of Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 are non-specific. In this retrospective cohort study of 39 patients evaluated for MIS-C, 11 had non-SARS-CoV-2 infections, 3 of whom were also diagnosed with MIS-C. Clinical features were similar in patients with MIS-C and patients with non-SARS-CoV-2 infections. Clinicians should consider non-SARS-CoV-2 infections in patients undergoing MIS-C evaluation.

Keywords

COVID-19; Severe acute respiratory syndrome; coronavirus; Pediatric multisystem inflammatory disease; COVID-19 related Infections; Multisystem inflammatory syndrome in children

Background

Multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 was first described in spring 2020 (1–3). Available MIS-C case definitions note that alternative explanations of symptoms and laboratory findings of multisystem inflammation should be evaluated and excluded before assigning this diagnosis. However, the clinical and laboratory features of MIS-C included in case definitions to date overlap with many infectious and auto-inflammatory diseases. Determining how extensively to search for alternative or concomitant infectious explanations for clinical and laboratory features of MIS-C has significant implications for the use of diagnostic testing and immunomodulatory therapy. Evaluating the overlap between features of MIS-C and non-SARS-CoV-2 infections can highlight the strengths and limitations of existing case definitions, and can identify infectious processes that can mimic or confound the diagnosis of MIS-C. Our objective in this study was to describe and compare clinical characteristics and treatments among patients who were evaluated for MIS-C and who were ultimately diagnosed with MIS-C, with non-SARS-CoV-2 infections, with both, and with neither.

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Methods

We conducted a retrospective cohort study of hospitalized patients evaluated for MIS-C at a single freestanding children's hospital in Massachusetts between May 14 and June 6, 2020. We included all patients ages < 21 years who underwent echocardiogram and rheumatology consultation to assess for MIS-C, per the hospital's MIS-C evaluation protocol. The selected time period corresponds to approximately 1 month after the initial peak of new SARS-CoV-2 infections in Massachusetts.

We queried our hospital's electronic medical records to identify patients meeting inclusion criteria. We reviewed included patients' records to ascertain demographic characteristics, baseline comorbidities, clinical/laboratory/microbiologic features, and treatments. For patients hospitalized before concern for MIS-C arose, we defined time of evaluation as the first time MIS-C appeared in the medical record or evaluation for MIS-C was undertaken.

We used the Massachusetts Department of Public Health (DPH) MIS-C case definition to classify patients with MIS-C (4), since our hospital was required to report suspected MIS-C cases according to this definition. Notably, this case definition excludes patients with "evidence of alternative plausible diagnoses", but does not categorically exclude patients found to have non-SARS-CoV-2 infections (4). We labeled patients with MIS-C as those patients who had been reported to DPH as cases (as adjudicated by a team of cardiologists, rheumatologists, and infectious diseases specialists), even if other infections were present, as permitted by the DPH case definition. We defined non-SARS-CoV-2 infections as detection of pathogen(s) on microbiologic testing in patients with consistent clinical features, or clinical diagnosis based on history, examination, and testing, as documented in the patient's chart by an attending physician.

We specified four groups of subjects prior to data analysis: 1) patients who met the MIS-C case definition without a non-SARS-CoV-2 infection (MIS-C alone); 2) patients who did not meet the MIS-C case definition but were found to have a non-SARS-CoV-2 infection (infection alone); 3) patients who met the MIS-C case definition and had a non-SARS-CoV-2 infection (MIS-C + infection); and 4) patients who did not meet the MIS-C case definition and were not found to have a non-SARS-CoV-2 infection (no MIS-C, no infection).

We used descriptive statistics to characterize patients evaluated for MIS-C with and without non-SARS-CoV-2 infections. We conducted *post hoc* exploratory comparisons of ferritin, C-reactive protein (CRP), and procalcitonin between patients with and without MIS-C using the Wilcoxon rank-sum test. Because ferritin was found to be significantly different between patients with and without MIS-C, we used the STATA "cutpt" function to calculate an adjusted optimal ferritin cut-point to discriminate MIS-C diagnosis. Analysis was conducted using STATA version 16.0 (College Station, Texas). The institutional review board at our hospital reviewed the protocol and determined that it qualified as exempt.

Results

We identified 39 patients who underwent screening for MIS-C between May 14 and June 6, 2020 (Table 1). Median age was 5 years (IQR 1.9 – 12.0 years); 24/39 (62%) were female. Nine patients (23%) had history of a complex chronic condition (5), and 1 (3%) was immune compromised due to chronic immunosuppression for inflammatory bowel disease. Nineteen (49%) patients were diagnosed with MIS-C according to the DPH case definition. Eight (21%) patients were found to have a non-SARS-CoV-2 infection without MIS-C (6 bacterial, 2 viral), and 3 patients with MIS-C were found to have non-SARS-CoV-2 infections (2 bacterial, 1 viral) (see Table, Supplemental Digital Content 1).

Clinical features including presenting vital sign abnormalities, days of fever, laboratory abnormalities, illness severity (including initial admission to the floor versus ICU, need for vasopressor or enhanced respiratory support), and non-cardiac outcomes (duration of ICU stay, discharge alive) were similar between patients presenting with MIS-C and patients presenting with non-SARS-CoV-2 infections. Coronary artery dilatation and ventricular dysfunction were observed only in patients diagnosed with MIS-C.

In *post hoc* exploratory analysis, we found significantly higher ferritin levels in patients with MIS-C (whether alone or with concomitant non-SARS-CoV-2 infection) compared to patients without MIS-C (median 538 ng/mL vs 111 ng/mL respectively, $P<0.001$). We identified ferritin of 228 ng/mL as an optimal cut-point to differentiate patients with and without MIS-C. Sensitivity at this cut-point value was 0.83, and specificity was 0.95. There was no significant difference in CRP (median 11.3 mg/dL [IQR 5.5 mg/dL – 21.7 mg/dL] versus 8.5 mg/dL [IQR 4.9 mg/dL – 15.0 mg/dL] for MIS-C versus no MIS-C, respectively, $P=0.293$), or PCT (median 0.40 ng/mL [IQR 0.13 ng/mL – 1.19 ng/mL] vs 1.01 ng/mL [IQR 0.21 ng/mL – 2.89 ng/mL] for MIS-C versus no MIS-C, respectively, $P=0.248$).

Among 19 patients with MIS-C, including the 3 patients with MIS-C plus infection, most received immune-modulatory therapy (4 received anakinra; 15 received IVIG; 14 received methylprednisolone) and antithrombotics (11 received aspirin; 15 received enoxaparin). Among the 8 patients with infection alone, 2 patients with bacterial lymphadenitis were treated with IVIG due to concern for incomplete Kawasaki disease, and 1 patient with staphylococcal toxic shock syndrome received IVIG and methylprednisolone. The majority (69%) of patients with MIS-C but no identified infection received empiric antibiotics. Nine patients (23%) were found to be SARS-CoV-2 PCR positive at time of MIS-C evaluation; all of these patients were diagnosed with MIS-C. Four of these patients received remdesivir, and one received hydroxychloroquine while awaiting remdesivir.

Discussion

In this cohort of patients evaluated for MIS-C, non-SARS-CoV-2 infections were common. We observed similar patterns of symptoms and clinical findings in patients with MIS-C and patients with non-SARS-CoV-2 infections, including in presenting symptoms, laboratory findings, and severity of illness. Our analysis underscores the imperative to avoid premature diagnostic closure in patients presenting with symptoms and findings of MIS-C, since a

substantial proportion of patients may have alternative explanations for their presentations even in the setting of high COVID-19 incidence.

We identified a subset of patients who presented with apparent MIS-C and were ultimately given this diagnosis despite identification of non-SARS-CoV-2 infections. These patients improved on combinations of infection-directed and MIS-C-directed therapies. Published case definitions differ as to whether identification of non-SARS-CoV-2 infection excludes the diagnosis of MIS-C (2–4), and prior case series have included patients with non-SARS-CoV-2 infection (1, 6, 7). Others recommend extensive testing for pathogens in patients presenting with moderate or severe MIS-C features, including diagnostics for bacteria in blood, urine, throat, and stool, viral nucleic acid from blood and stool, and consideration of other epidemiologically likely pathogens (8). Yet it remains unclear how to categorize and treat patients who are found to have non-SARS-CoV-2 infection who otherwise meet criteria for MIS-C. The decision of whether to use immunomodulatory agents for these patients highlights the perils posed by the lack of clarity in existing case definitions. Our data also illustrate the indistinct boundary between COVID-19 and MIS-C. It is unclear whether SARS-CoV-2 RNA detected in patients diagnosed with MIS-C in our cohort reflected prolonged viral shedding versus ongoing active disease. Resolving this indistinct boundary will be useful for determining which therapies are most likely to benefit children who are PCR positive but have signs and symptoms of MIS-C.

Patients with MIS-C in our cohort generally had less severe clinical and laboratory findings than patients in other published case series and cohorts, including lower rates of shock, elevated cardiac biomarkers and ICU admission (7, 9). This may reflect the relative permissiveness of the Massachusetts DPH case definition of MIS-C compared to other organizations' definitions (2, 3) (e.g. it only requires self-reported fever, and dysfunction of one organ system). More severe MIS-C phenotypes may have more features to distinguish them from active infectious processes, such as higher rates of echocardiographic abnormalities.

Although we did not initially aim to identify predictors of MIS-C, in preliminary data review we noted that patients with MIS-C had higher median serum ferritin levels compared to those with non-SARS-CoV-2 infections. Ferritin has previously been used to distinguish infectious from non-infectious causes of fever of unknown origin (10). Our analysis suggests that ferritin warrants further investigation in larger studies as a potential biomarker to distinguish MIS-C from mimicking syndromes.

Our study has several limitations, including small sample size, heterogeneous diagnoses among patients presenting with non-SARS-CoV-2 infections, and reliance upon hospital clinical teams to request evaluation for MIS-C and determine extent of microbiologic testing.

In conclusion, non-SARS-CoV-2 infections were identified in over a quarter of patients in our cohort evaluated for MIS-C, including in 3/19 patients diagnosed with MIS-C, highlighting the need to consider other infections in the differential diagnosis when suspicion for MIS-C is present. Additional research aimed at identifying the potential role of

biomarkers in this diagnosis, and further refinement of the case definition, will likely assist clinicians when evaluating patients for MIS-C.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Clinical characteristics of patients evaluated for MIS-C.

	Cohort (N = 39)	MIS-C alone (n = 16)	Infection alone (n = 8)	MIS-C + Infection (n = 3)	No MIS-C, No Infection (n = 12)
Age (median, IQR)	5 (1.9 – 12.0)	10.9 (7.2 – 16.5)	2.9 (0.9 – 8.4)	7.3 (1.8 – 10.3)	2.3 (1.6 – 3.6)
Female (n, %)	24 (62)	8 (50)	5 (63)	2 (67)	9 (75)
Immunocompromised (n, %)	1 (3)	1 (6)	0 (0)	0 (0)	0 (0)
History of complex chronic condition	9 (23)	3 (19)	1 (13)	1 (33)	4 (33)
Clinical features					
Days of fever preceding presentation (median, IQR)	4 (4–7)	4 (4 – 7)	7 (3 – 9)	5 (4 – 7)	5 (4 – 7)
Febrile in 24 hours following presentation (%)	27 (69)	11 (69)	7 (88)	2 (67)	7 (58)
Tachycardic in 24 hours following presentation (n, %)	35 (90)	15 (94)	8 (100)	3 (100)	9 (75)
Tachypneic in 24 hours following presentation (n, %) (missing = 1)	23 (60)	13 (81)	2 (25)	1 (50)	7 (58)
Hypotensive in 24 hours following presentation (%)	26 (66)	13 (81)	4 (50)	3 (100)	6 (50)
Symptoms at or following presentation (n, %)					
Fatigue/malaise	10 (26)	6 (38)	1 (13)	1 (33)	2 (17)
Sore throat	7 (18)	3 (19)	1 (13)	1 (33)	2 (17)
Cough	4 (10)	4 (25)	0 (0)	0 (0)	0 (0)
Dyspnea	5 (13)	5 (31)	0 (0)	0 (0)	0 (0)
Diarrhea	11 (28)	6 (38)	2 (25)	0 (0)	3 (25)
Vomiting	9 (23)	5 (31)	2 (25)	1 (33)	1 (8)
Abdominal pain	13 (33)	9 (56)	2 (25)	0 (0)	2 (17)
Headache	7 (18)	3 (19)	2 (25)	0 (0)	2 (17)
Other neurological symptoms	2 (5)	0 (0)	1 (13)	0 (0)	1 (8)
Kawasaki Disease clinical criteria					
Rash	18 (46)	7 (44)	3 (38)	1 (33)	7 (58)
Extremity changes	5 (13)	4 (25)	0 (0)	0 (0)	1 (8)
Mucous membrane changes	4 (10)	3 (19)	0 (0)	1 (33)	0 (0)
Lymphadenopathy > 1.5cm	2 (5)	0 (0)	2 (25)	0 (0)	0 (0)
Conjunctivitis	9 (23)	6 (38)	1 (13)	1 (33)	1 (8)

	Cohort (N = 39)	MIS-C alone (n = 16)	Infection alone (n = 8)	MIS-C + Infection (n = 3)	No MIS-C, No Infection (n = 12)
Other*	24 (62)	11 (69)	5 (63)	3 (100)	5 (42)
SARS-CoV-2 Diagnostics					
PCR-positive prior to MIS-C evaluation (n, %)	4 (10)	3 (19)	0 (0)	1 (33)	0 (0)
PCR-positive at time of MIS-C evaluation (n, %)	9 (23)	6 (38)	0 (0)	3 (100)	0 (0)
SARS-CoV-2 serology positive (n, %) (missing/not performed = 5)	15/34 (44)	12/13 (92)	0/8 (0)	1/2 (50)	2/11 (18)
Laboratory features					
Blood cell counts					
WBC (K cells/μL) (median, IQR)	11.5 (7.4 – 15.4)	7.5 (4.9 – 11.9)	15.1 (13.8 – 18.8)	6.4 (4.3 – 8.6)	12.4 (11.0 – 15.3)
ANC (cells/μL) (median, IQR)	8025 (2100 – 14780)	6540 (3385 – 8960)	10625 (9130 – 13945)	4465 (2480 – 6450)	8025 (4170 – 9335)
ALC (cells/μL) (median, IQR)	1725 (960 – 3330)	1130 (745 – 1970)	3870 (1880 – 6155)	1230 (1030 – 1430)	2795 (1510 – 3705)
Platelet count (K cells/μL) (median, IQR)	223 (157 – 324)	155 (125 – 235)	311 (251 – 625)	128 (32 – 223)	276 (205 – 368)
CRP (mg/dL) (median, IQR) (missing = 1)	9.27 (5.5 – 17.6)	11.2 (4.9 – 20.4)	8.5 (6.0 – 15.0)	15.6 (9.6 – 21.7)	7.7 (4.8 – 14.5)
ESR (mm/hr) (median, IQR) (missing = 6) †	51 (34 – 60)	55 (22 – 58)	51 (43 – 61)	40 (NA)	45 (30 – 62)
Ferritin (ng/mL) (median, IQR) (missing = 1)	185.7 (102.5 – 536.8)	538.4 (253.0 – 1293.5)	146.7 (104.5 – 185.5)	537.8 (176.5 – 899.0)	96.3 (61.5 – 138.5)
Procalcitonin (ng/mL) (median, IQR) (missing = 5)	0.54 (0.17 – 1.74)	1.02 (0.17 – 2.93)	0.59 (0.13 – 2.81)	0.77 (0.28 – 2.89)	0.4 (0.09 – 1.19)
Elevated AST, (n, %) (missing = 2)	14/37 (38)	9/15 (60)	2/8 (25)	1/2 (50)	2/12 (17)
Elevated ALT (n, %) (missing = 2)	11/37 (30)	9/15 (60)	1/8 (13)	1/2 (50)	0/12 (0)
Hypoalbuminemia (n, %) (missing = 3)	4/36 (11)	2/15 (13)	0/7 (0)	1/2 (50)	1/12 (8)
Elevated BNP (n, %) (missing = 3)	9/36 (25)	6/16 (38)	0/7 (0)	0/2 (0)	3/11 (27)
Elevated troponin (n, %) (missing = 4)	2/35 (6)	2/16 (13)	0/6 (0)	0/2 (0)	0/11 (0)
Elevated D-Dimer (n, %)	31 (79)	12 (75)	8 (100)	3 (100)	8 (67)
Echocardiographic abnormalities					
Ventricular dysfunction (n, %)	8 (21)	7 (44)	0 (0)	1 (33)	0 (0)
Coronary artery dilatation (n, %)	6 (15)	4 (25)	0 (0)	2 (67)	0 (0)
Severity					
Initially admitted to the general pediatrics floor (versus ICU) (n, %)	28 (72)	8 (50)	6 (75)	2 (67)	12 (100)
Required >40 mL/kg fluid resuscitation in 24 hours following presentation (n, %) (missing = 1)	8 (21)	3 (19)	2 (25)	1 (50)	2 (17)

	Cohort (N = 39)	MIS-C alone (n = 16)	Infection alone (n = 8)	MIS-C + Infection (n = 3)	No MIS-C, No Infection (n = 12)
Required vasopressors at or following presentation (n, %)	6 (15)	3 (19)	1 (13)	2 (66)	0 (0)
Required inotropes at or following presentation (n, %)	1 (3)	1 (6)	0 (0)	0 (0)	0 (0)
Required respiratory support above baseline (n, %)	9 (23)	7 (44)	1 (13)	1 (33)	0 (0)
Nasal cannula O2	5 (13)	4 (25)	1 (13)	0 (0)	0 (0)
CPAP/BiPAP	3 (8)	3 (19)	0 (0)	0 (0)	0 (0)
Mechanical ventilation	1 (3)	0 (0)	0 (0)	1 (33)	0 (0)
Outcomes					
Hospital days (median, IQR)	6 (2 – 11)	9 (6 – 12)	6 (3 – 9)	14 (5 – 57)	2 (1 – 3)
ICU days (median, IQR)	5 (3 – 8)	5 (5 – 7)	5 (2 – 8)	16 (3 – 29)	NA
Discharged alive (n, %)	39 (100)	16 (100)	8 (100)	3 (100)	12 (100)

*Other symptoms: Decreased oral intake (6), irritability (3), conjunctivitis prior to presentation (2), myalgias (2), nausea (2), neck pain (2), sore on tongue (2), abdominal pain prior to presentation (1), abnormal eye and tongue movements (1), arthralgias (1), chest pain (1), chills (1), decreased urine output (1), dizziness (1), dysuria (1), fussiness (1), generalized body pain (1), hematochezia (1), hypoglycemia (1), hypoxia (1), increased respiratory secretions (1), insomnia (1), labial abscess (1), limb pain (1), neck stiffness (1), oral vesicles (1), periorbital swelling (1), syncopal episode (1), testicular pain (1), unilateral neck swelling (1)

†ESR normal range at our hospital: 0–30 mm/hr

Abbreviations: MIS-C: Multisystem Inflammatory Syndrome in Children (MIS-C) associated with SARS-CoV-2; PCR: Polymerase Chain Reaction; WBC: White Blood Cell count; ANC: Absolute Neutrophil Count; ALC: Absolute Lymphocyte Count; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; BNP: Brain Natriuretic Peptide; ICU: Intensive Care Unit; CPAP: Continuous Positive Airway Pressure; BiPAP: Bilevel Positive Airway Pressure