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Correspondence

Emergency department levels of NT-proBNP and inotropic/vasoactive support in multi-inflammatory syndrome in children (MIS-C)


Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe hyperinflammatory condition in children and adolescents. The presentation can be varied, and occurs 2–6 weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. MIS-C can affect multiple organ systems, including cardiac, gastrointestinal, hematological, dermatological, neurological, respiratory, and renal systems [1]. In this syndrome, patients frequently have preserved cardiac function throughout the illness and, on Emergency Department (ED) presentation, patients are usually non-toxic, have no signs of acute distress, and lack the clinical signs of shock or decreased cardiac function [2,3]. However, some MIS-C patients develop cardiac decompensation that requires inotropic/vasoactive support [4]. Identifying ED patients who have cardiac dysfunction and may require treatment with inotropic/vasoactive medications is important.

In MIS-C, increased concentrations of peak laboratory values of cardiac N-terminal pro-brain natriuretic peptide (NT-proBNP) have been shown to be associated with Intensive Care Unit (ICU) admission and decreased left ventricular (LV) function [1]. Level of NT-proBNP drawn at the time of ED presentation of MIS-C patients has not yet been described. In the pediatric ED of Rambam Health Care Center, Haifa, Israel, any patient clinically suspected of having MIS-C must meet the United States (US) Centers for Disease Control and Prevention (CDC) case definition to be diagnosed [5], and is also tested for the level of NT-proBNP. All patients undergo echocardiography on day two of hospital admission and pre-discharge. This is routine for any patient with MIS-C in Rambam Health Care Center.

In this context, we retrospectively reviewed all cases of MIS-C admitted to the Pediatric ED between March 1, 2020 and May 31, 2021. The following variables were abstracted from the medical records: Patient demographics, ED vital signs, echocardiography results, ICU and hospital length of stay, inotropic/vasoactive treatment in ICU, nasal SARS-CoV-2 polymerase chain reaction (PCR) and serology results, and levels of D-dimers, C-reactive protein, fibrinogen, troponin, and NT-proBNP. Descriptive statistics were used to analyze the data. The study was approved by the hospital ethics committee.

Fourteen patients with a median (interquartile range) age of 8.5 (4–12) years and a male/female ratio of 8/6 were diagnosed with MIS-C (Table 1). Hospital median length-of-stay was nine (6–11) days. Thirteen patients were treated with intravenous immunoglobulin and methylprednisolone. One patient was treated with intravenous immunoglobulin only. Six patients had normal echocardiography and an uneventful clinical course, and did not require inotropic/vasoactive support (Patients 1 to 6, Table 1); four patients had normal ED levels of NT-proBNP, and two patients had levels of 3331 and 3689 pg/ml

(Table 1). Eight patients required inotropic/vasoactive support (Patients 7 to 14, Table 1). Four patients were treated with an inotropic medication only (Patients 7 to 10, Table 1); these patients had NT-proBNP levels of 7309 pg/ml or lower, normal LV function or mild LV dysfunction on echocardiography, and ICU length of stay of 3–6 days. Four patients were treated with inotropic and vasoactive medications (Patients 11 to 14, Table 1); these patients had NT-proBNP levels of 15,901 pg/ml or higher, mild or moderate LV dysfunction on echocardiography, and ICU length of stay of 7–10 days. No patient required extracorporeal membrane oxygenation (ECMO) support. Pre-discharge echocardiography revealed normal cardiac function for all patients.

In this case-series report, we described the course of 14 children with MIS-C, eight of whom required inotropic/vasoactive support. The main finding is that 8/10 patients who had elevated ED levels of NT-proBNP required inotropic/vasoactive support. Patients who had NT-proBNP levels at the range of tens of thousands had moderately decreased LV function, required vasopressor treatment, and had longer ICU stays. Their troponin levels were normal or mildly elevated. The high NT-proBNP levels in patients who required vasopressor support, along with mild troponin elevation and rapid resolution of LV dysfunction, are corroborated by previous reports [1,4].

Our study results suggest that, when a child presents to the ED with MIS-C, the NT-proBNP levels can be used to suspect the presence of LV dysfunction and the need to vasopressor support. The findings raise the possibility that, if a high NT-proBNP level is detected, a more severe disease course is expected and early administration of inotropic/vasoactive medications may be required. This is particularly important when a cardiology consult is not readily available and referral to an institution with an increased level of care may be warranted.

The normal to mildly elevated troponin levels in the patients who were treated with inotropic/vasoactive medications support the hypothesis that the mechanism of LV dysfunction in MIS-C is not the result of myocardial damage associated with acute infection with SARS-CoV-2 but, more likely, resulted from myocardial edema [4].

In conclusion, our findings suggest that high ED levels of NT-proBNP can serve as early warning indicators for the requirement of inotropic/vasoactive support in MIS-C. Further larger investigations are warranted to confirm this conclusion. Until more information is available about the pathophysiology of MIS-C, it seems reasonable to suggest that these patients should be tested for NT-proBNP as early as possible. The main limitations of this report are the small sample size and its retrospective nature.

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Contributors' statement page

Dr. Rami Tibi conceived the idea for the study, collected and analyzed the data, and critically revised the manuscript, and approved the final manuscript as submitted.

Table 1
Demographic characteristics, laboratory data at Emergency Department presentation, and outcomes.

Patient	Age (years)	Sex	COVID-19 PCR	COVID-19 Serology	BP (mmHg)	Fibrinogen (180–450 mg/dl)	D-dimer (0–500 µg/ml)	CRP (0–0.5 mg/dl)	Troponin (0–34 ng/l)	NT-proBNP (0–391 pg/ml)	LV function in echo-cardiography	Treatment with inotropic or vasoactive drug at ICU	Length of ICU stay (days)
1	17	Female	–	Positive	112/53	370	2330	17	5	216	Normal	–	–
2	9	Female	Negative	Negative	118/74	520	2224	30	5	271	Normal	–	–
3	8	Male	Positive	Negative	103/74	415	>5000	10	5	3689	Normal	–	–
4	4	Female	Negative	Positive	96/56	427	1136	11	5	3331	Normal	–	–
5	3	Male	Negative	Negative	101/56	724	>5000	28	5	391	Normal	–	–
6	11	Male	Positive	–	111/42	419	1954	10	5	226	Normal	–	–
7	15	Male	Negative	–	113/58	533	875	23	5	1878	Mildly reduced	Milrinone	6
8	8	Male	Negative	Positive	102/60	561	1121	28	38	7309	Normal	Milrinone	3
9	0.2	Male	Positive	Negative	116/66	560	2232	26	10	2234	Moderately reduced	Milrinone	5
10	11	Female	–	Positive	107/70	473	1524	27	381	3972	Mildly reduced	Milrinone	6
11	16	Male	Negative	Positive	120/65	469	1977	24	922	35,000	Moderately reduced	Adrenaline	9
12	12	Female	Positive	Negative	122/69	404	3177	13	61	29,171	Moderately reduced	Vasopressin Milrinone	10
13	1.1	Female	Negative	Positive	80/50	227	788	16	7	15,901	Moderately reduced	Adrenaline Vasopressin Milrinone	7
14	7	Male	Positive	Negative	107/69	450	1806	13	113	16,882	Moderately reduced	Noradrenaline Milrinone Adrenaline	7

Notes: BP=Blood Pressure, COVID-19 = Coronavirus Disease 2019, PCR = Polymerase Chain Reaction, CRP = C-Reactive Protein, N-terminal pro-brain natriuretic peptide = NT-proBNP, ICU=Intensive Care Unit, LV = Left Ventricular.

Dr. Amir Hadash assisted in data extraction, carried out the initial analyses, critically reviewed the manuscript, and approved the final manuscript as submitted.

Dr. Asaad Khoury critically reviewed the manuscript, and approved the final manuscript as submitted.

Dr. Yonatan Butbul-Aviel critically reviewed the manuscript, and approved the final manuscript as submitted.

Dr. Josef Ben-Ari critically reviewed the manuscript, and approved the final manuscript as submitted.

Dr. Itai Shavit reviewed the literature, designed the study, coordinated and supervised data collection, analyzed the data, and drafted the manuscript.

Drs. Rami Tibi and Itai Shavit have full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

None declared for all 6 authors.

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