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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, 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 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, Vasopressin Milrinone                | 9                |
| 12      | 12          | Female | Positive | – | – | 122/69 | 404                      | 3177                | 13               | 61               | 29,171                    | Moderately reduced          | Adrenaline, Vasopressin Milrinone                | 10               |
| 13      | 1.1         | Female | Negative | Positive | 80/50     | 227                      | 788                   | 16               | 7                | 15,901                    | Moderately reduced          | Adrenaline, Vasopressin Noradrenalin Milrinone | 7                |
| 14      | 7           | Male   | Positive | Negative | 107/69    | 450                      | 1806                  | 13               | 113              | 16,882                    | Moderately reduced          | Milrinone                                 | 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 take 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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