Risk factors of cardiac insufficiency in children with multisystem inflammatory syndrome and COVID-19: A prospective cohort study

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INTRODUCTION

SARS-CoV-2 infection was first described in late December 2019 in Wuhan, China [1]. In the beginning, it seemed that children displayed more benign symptoms or were even asymptomatic [2]. Nevertheless, 2–3 months later, an increasing number of pediatric patients with a new inflammatory condition that appeared to be geographically and temporally connected with COVID-19 were being admitted to hospitals at a high rate. The first reports of Multisystem Inflammatory Syndrome in Children (MIS-C) were published in May 2020 by Centers for Disease Control and Prevention [3]. Subsequent reports of cardiac involvement have also been published in other clinical presentations, including myocardial dysfunction, valvar regurgitation, pericarditis, coronary artery abnormalities, and arrhythmias [4]. This study aimed to analyze the clinical course of MIS-C with particular emphasis on the involvement of the circulatory system in a population of Polish children. Thus, we sought to identify risk factors of cardiac insufficiency in patients with MIS-C.

METHODS

Study design

A prospective, single-center study was conducted at the Department of Pediatrics, Jagiellonian University, Kraków, between December 1, 2020 and April 30, 2021. The study protocol was approved by the Jagiellonian University Medical College Ethical Committee (issue no. KBET/1072.6120.360.2020). Written and informed consent was obtained from the parents.

Inclusion criteria

Patients who fulfilled Centers for Disease Control and Prevention criteria for clinical diagnosis of MIS-C at admission were included in the study [5] (Supplementary material, *Table S1*).

Study procedures

On admission, nasopharyngeal swab tests for SARS-CoV-2 infection were performed by a polymerase chain reaction in all children. The levels of IgM and IgG antibodies against the viral spike glycoprotein using an Enzyme-Linked Immunosorbent Assay test were determined on admission. Moreover, serum concentrations of C-reactive protein, procalcitonin, troponin T, ferritin, albumin, fibrinogen, D-dimer and N-terminal pro-brain natriuretic peptide were measured.

Evaluation of the heart

Echocardiography was performed in all children. The following echocardiographic parameters were calculated: (1) left ventricular ejection fraction based on Simpson's method; (2) fractional shortening based on M-Mode measurements. The presence of fluid in the pericardium, the presence of atrioventricular valve insufficiency, and the presence of coronary artery abnormalities were assessed.

Study groups

Based on the results of the cardiovascular evaluation, children were divided into 2 groups:

Table 1. Comparison of the results of cardiological assessment between the studied groups

	Cardiac dysfunction group (n = 20)	Non-cardiac dysfunction group (n = 46)	*P*-value
Systolic blood pressure	14 (2–31)	66 (29–92)	<0.001[a]
Diastolic blood pressure	14 (9–40)	68 (28–92)	0.002[a]
FS	27 (23.6–32.1)	32 (30–34.4)	0.003[a]
EF	52 (48–55)	61 (59–65.2)	<0.001[a]
Abnormal imaging of the coronary arteries	3 (15)	15 (33)	0.18[b]
Aneurysms of coronary arteries	1 (5)	3 (6.5)	0.85[b]
Hyperechogenicity of the coronary arteries	2 (10)	13 (28)	0.12[b]
Pericardial effusion	10 (50)	16 (35)	0.28[b]
Mitral valve regurgitation	10 (50)	20 (43)	0.79[b]
Tricuspid valve regurgitation	14 (70)	26 (57)	0.41[b]
Pericardial effusion 48–72 hours after admission	10 (50)	5 (10.8)	0.001[b]
Mitral valve regurgitation 48–72 hours after admission	8 (40)	6 (13)	0.02[b]
Tricuspid valve regurgitation 48–72 hours after admission	11 (55)	7 (15)	0.002[b]
Abnormal imaging of the coronary arteries on discharge	0	5 (10.8)	0.31[b]

[a]*P*-value for U Mann–Whitney test; [b]*P*-value for Fisher exact test

Data are presented as number (%) of patients or median (interquartile range [IQR]) unless otherwise indicated

Abbreviations: EF, ejection fraction; FS, fractional shortening

- A: MIS-C with significant cardiac dysfunction (CD) and/or shock (CD group);
- B: MIS-C without significant cardiac dysfunction or shock (the Non-CD group).

The following definitions of significant CD and/or shock were used:

- Presence of hypotension as defined by systolic and/or diastolic blood pressure below the 5th percentile for sex, age, and height [6]; or
- Decreased left ventricular ejection fraction below 55%; or
- Decreased fractional shortening below 25%.

Statistical analysis

The continuous variables were presented as median (interquartile range [IQR]) and compared between two groups using the Mann-Whitney U test. Fisher's exact test was used to compare the categorical variables. A *P*-value of 0.05, or less, was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics v. 27 software (Armonk, NY, USA).

RESULTS AND DISCUSSION

Sixty-six children with MIS-C were included in the study. The clinically significant CD was diagnosed in 20 (30%) children. The most common reason for including the patient to the CD group was a reduced ejection fraction as identified by echocardiography, which was observed in 16 (80%) patients. A reduction in shortening fraction and hypotension were noted in 12 (60%) and 10 (50%) patients from the CD group, respectively. The clinical characteristics and laboratory findings in the studied groups are presented in Supplementary material, *Table S2* and *S3*.

The CD group was characterized by significantly higher inflammatory markers and granulocytosis with concomitant lymphopenia as well as significantly lower serum albumin and sodium concentrations. N-terminal pro-brain natriuretic peptide (NT-proBNP) values were significantly higher in the CD group.

Details of the cardiological assessment are presented in Table 1. Coronary artery abnormalities during hospitalization were observed in 18 (27%) patients. The frequency of atrioventricular valve insufficiency and the presence of pericardial effusions were similar in both groups.

All patients received an intravenous infusion of immunoglobulins (IVIG) at a dose of 2 g/kg body weight. Additionally, 64 children were treated with low to moderate doses of steroids.

In 4 patients who did not respond to IVIG or the low-to-moderate dose of glucocorticoids, IV pulse glucocorticoids (10–30 mg/kg/day) were given (3 CD group patients and 1 non-cardiac group patient). No patient needed to receive other immunomodulating agents.

Systemic hypotension was treated with intravenous fluids as a first step. CD was treated with an intravenous infusion of milrinone. In the cases with no response to treatment, children were transferred to the intensive care unit (n = 11) and treated with cardiac pressors.

All patients received antiplatelet therapy based on low doses of aspirin (3–5 mg/kg), and in cases of severe left ventricular dysfunction or increased D-dimer levels, they were administered an additional anticoagulation treatment (23 patients).

All children were discharged home in good general condition. The hospitalization time was longer in the CD group than in the non-cardiac group (median [IQR]: 14 [13–16] days vs. 10 [9–12] days; *P* <0.001).

Our study described 66 previously healthy children who developed an inflammatory condition related to COVID-19. The median age of our cohort was 6.5 years, whereas in other studies patients were slightly older [7, 8]. All patients presented a wide spectrum of symptoms,

including fever, skin rash, conjunctivitis, vomiting, abdominal pain, diarrhea, and cardiac symptoms. A third of the patients developed heart dysfunction which required inotropic support. Our data contradict the data from the cohort described by Whittaker et al. [9], in which nearly half of the patients required cardiac support, and the data in the study by Ramcharan et al. [7], in which nearly 70% of MIS-C patients required inotropic support or vasopressors.

Davies et al. [10] found that "a third (28 [36%] of 78) of patients were found to have coronary artery abnormalities on echocardiography during Pediatric Intensive Care Unit admission, 18 had evidence of aneurysms and 10 had coronary arteries that were characterized as unusually echogenic". In our study, we observed coronary artery abnormalities during hospitalization in 27% of patients with MIS-C. Additionally, these changes were more frequent in the non-CD group (33% vs. 15%). Although hyperechogenic coronary arteries were common on the 2D echocardiogram, all patients from the cardiac group had coronary artery dilation at the time of discharge from the hospital. However, it is worth noting that even the youngest children with MIS-C may develop extensive aneurysms of the coronary vessels [11].

Furthermore, we found no differences in the demographic data, fever duration, presence of skin rash, or gastrointestinal symptoms between CD and non-CD groups, and these observations were like previous findings [8, 10]. Interestingly, we observed a strong positive correlation between conjunctivitis and the development of cardiac failure — in our cohort, 95% of children with heart insufficiency presented conjunctival hyperemia, whereas in the control group 77% developed such symptoms. These observations are contrary to previously published data, in which only 38% of patients with cardiac involvement suffered from conjunctivitis [9].

CD markers (troponin I, NT-proBNP), as well as D-dimers, were elevated in all patients. The elevation was statistically higher in patients with cardiac insufficiency, however, in our cohort we did not observe values at levels previously reported [7–9]. We noted decreased levels of albumin and sodium, which were statistically lower in the cardiac group and identical to other described cohorts [7–9]. We can presume that patients with serum levels of albumin over 35 g/l and NT-proBNP levels below 1000 pg/ml were at low risk of developing cardiac insufficiency. Based on the laboratory tests, we can exclude severe courses of MIS-C with heart involvement in only 20% of patients. However, if cardiac markers and/or indicators of inflammation are increased, we may not be able to identify children who develop significant heart dysfunction.

Transferring patients with MIS-C and significantly abnormal laboratory values to the hospital with a higher level of care should be considered. All patients with MIS-C should be examined by a pediatric cardiologist upon admission to the hospital. We recommend a close follow-up for all patients diagnosed with MIS-C.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

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