Short Communication

Myocardial damage in multisystem inflammatory syndrome associated with COVID-19 in children and adolescents

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Background: In multisystem inflammatory syndrome in children (MIS-C) temporarily associated with coronavirus disease-19 (COVID-19), myocardial damage has been reported. **Materials and Methods:** A retrospective observational cohort study included children under 18 who had a myocardial injury related to COVID-19 treated in mother and child health institute from April 2020 to August 2020. Myocardial injury related to COVID-19 was manifested by elevated serum cardiac troponin and NT-proBNP with LV dysfunction, arrhythmias, and coronary arteries (CAs) dilatation or aneurysms. During the short-term follow-up, cardiac testing (electrocardiography, laboratory analysis, echocardiography, 24-h Holter monitoring, exercise stress test, and cardiac magnetic resonance) was performed. **Results:** Six male adolescents (14.7 ± 2.4 years) were included in the analysis (2/6 had MIS-C shock syndrome). All patients had elevated acute-phase reactants and NT-proBNP, whereas troponins were elevated in 5/6 patients. Echocardiography revealed left ventricular (LV) systolic dysfunction (EF 45.2 ± 6.9%); 2/6 had dilated CAs. IVIG was prescribed to all patients with MIS-C. Four patients required inotropic drug support. During hospitalization, a significant reduction of CRP, LDH, NT-proBNP, and D-dimer ($P < 0.05$) was registered. LV systolic function recovery was registered 3 days after applied therapy ($P < 0.001$). None of the patients developed dilated cardiomyopathy or CA aneurysms. **Conclusions:** With early recognition and adequate MIS-C therapy, children recovered entirely, maintained in the short-term follow-up period.

Key words: Adolescents, multisystem inflammatory syndrome in children, myocarditis, SARS-CoV-2

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INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) temporarily associated with the coronavirus disease-19 (COVID-19) is sporadically presented after an infection caused by a novel coronavirus (SARS-CoV-2).[1-6] These pediatric cases' clinical features are similar to the previously described inflammatory syndromes such as viral myocarditis, Kawasaki disease (KD), KD shock syndrome, and toxic shock syndrome.[2] MIS-C was defined as acute febrile state lasing at the least 24 hours with elevated inflammatory markers, and the existence of the following criteria: (1) clinically severe illness requiring hospitalization and two or more organ involvement and (2) positive serology, reverse transcription-polymerase chain reaction (RT-PCR), or antigen test; or COVID-19 exposure within the past 4 weeks before symptom onset.[7] Many children with MIS-C had positive antibodies to SARS-CoV-2, but negative RT-PCR test because MIS-C typically manifests 3–6 weeks after SARS-CoV-2 infection.[1,5,8] The delay in presentation proposes that this inflammatory syndrome is postponed immune responses on SARS-CoV-2.[2]

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Our work analysed cardiovascular findings in MIS-C concerning premorbidity status, incubation period, laboratory characteristics, diagnostics methods, treatment and outcome of diseases.

MATERIALS AND METHODS

A retrospective observational cohort study included children under 18 years who had a myocardial injury related to COVID-19 treated in Mother and child health Institute of Serbia from April 2020 to August 2020. Myocardial injury related to COVID-19 was manifested by elevated serum cardiac troponin (cTn) and NT-proBNP with left ventricle (LV) dysfunction, arrhythmias, and coronary arteries (CAs) dilatation or aneurysms.[2] In all patients, PCR to detect cardiotropic viral nucleic acid in the blood was performed. In all patients, serological examination for SARS-CoV-2 was done. Laboratory analyses, electrocardiography (ECG), X-ray, and echocardiographic examination were performed at the admission, the 3rd, the 7th day of in-hospital stay, and the discharge. Patients with MIS-C were treated according to the standard protocols.[2,8]

During the short-term follow-up, cardiac testing (ECG, laboratory analysis, echocardiography, 24-h Holter monitoring, exercise stress test, and cardiac magnetic resonance) was performed. If cardiac testing has normalized, we advised to athletes gradually increase physical activity.

The study was approved by the institutional ethical committee (reference number 2099/1).

RESULTS

Our study included six male adolescents; the average years of age were 14.7 ± 2.4. They had a history of fever (6/6), fatigue (3/6), headache (3/6), gastrointestinal manifestations (abdominal pain, vomiting, and diarrhea (4/6), and thoracic pain (1/6). The fever with gastrointestinal manifestations lasted 5 days,[3-7] averagely, before the myocardial injury was established. Polymorph cutaneous rash, bilateral (nonexudative) conjunctivitis, and conjunctival suffusion had 5/6 patients. Systemic hypotension and oliguria were registered in two patients. Two patients had SARS-CoV-2 exposure 4 weeks before symptom onset. Diagnosis of MIS-C was made in 6 adolescents, whereas MIS-C shock syndrome had 2/6.

RT-PCR for SARS-CoV-2 was positive in one patient; the other had positive SARS-CoV-2-specific neutralizing antibody. In two patients, cytomegalovirus (CMV) and Epstein–Barr virus (EBV) were isolated from blood samples. Laboratory analysis at the admission is shown in Table 1.

The X-ray showed an enlarged heart shadow in 3/6. A prolonged QTc interval was observed in all patients with MIS-C in the recovery period. All echocardiography parameters are presented in Table 2. Two patients with MIS-C had mildly dilated CAs.

The patients were treated with IVIG (5/6), corticosteroids (3/6), and vasoactive and inotropic drugs (6/6).

Laboratory analysis and the difference between their average values measured in the 3rd and the 7th day of in-hospital stay and at discharge are presented in Table 1. By comparing the difference between laboratory parameters at the admission and discharge, a significant reduction of LDH, D-dimers, and NT-proBNP was observed [Figure 1].

Table 1: Laboratory parameters of our patients

	Admission		3rd day		7th day		Discharge		*P*
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
CRP (mg/l)	136	95.6-210.7	121.2	77.9-186.2	48.7	23.8-77.5	2.45	1.3-5.5	<0.05†,‡
WBC (10^9)	11.25	6.7-14.6	9.8	7.8-15.3	9.5	7.8–15.1	6.76	5.44-13.7	>0.05
Hemoglobin (g/l)	125.5	118.2-142.5	123.5	106.7-127.5	128	111.5-135.5	136	121.5-144.5	>0.05
Platelets (10^9)	121	96.7-166.5	156	95.2-214.5	334	149-484	422.5	282.2-505.2	<0.05*,†,‡
Albumin (g/l)	37.5	30.7-41	29.5	27.5-37.2	27	26.5-35	38.5	37.7-41.5	0.02*
Na (mmol/l)	133	132.5-137	135	131.2-138.2	136	134-139.5	136	132.5-139.2	>0.05
Cr (μmol/L)	81	62-117.5	68.5	54-88.5	61	52-78.5	55.5	51-63.25	0.04†,‡
ALT (IJ/L)	43.5	18-82.7	27	13-27	54	32.5-103.5	38.5	22.5-88.7	>0.05
LDH (IJ/L)	462	355.5-617.7	338.5	303-504.5	394	295.7-504.2	317.5	293.7-364.7	0.02‡
D-dimer (ng/ml)	906	510-2052	607	264-1447	327.5	107-327.5	176	104.5-283.5	0.04‡
cTnI (ng/ml)	1.5	0.05-3.9	0.37	0.05-2.5	0.05	0.05-1.92	0.05	0.05-0.05	0.05‡
NT-proBNP (pg/ml)	4368	1446.5-5000	2987	507.5-5000	1414.5	399.5-4154	41.5	30-212.2	0.02‡
Feritin (ug/l)	1288	300-1288	559.2	184.8-559.2	537	182-537	266.5	161.5-451.7	<0.001‡
Procalcitonin (ng/ml)	4.04	0.67-4.04	0.73	0.07-0.73	-	-	0.08	0.02-0.08	<0.001‡

‡Difference between values at the admission and the 3rd day; †Admission to 7th day; ‡Admission to discharge. CRP=C-reactive protein; WBC=White blood cell; Hgb=Hemoglobin; Na=Sodium; Cr=Creatinine; ALT=Alanine transaminase; LDH=Lactate dehydrogenase; cTnI=Cardiac troponin I; NT-proBNP=N-terminal pro hormone B-type natriuretic peptide; IQR=Interquartile range

Table 2: Echocardiography parameters of our patients

	Admission		Third day		Discharge		*P*
	Mean±SD (minimum-maximum)	Z-score	Mean±SD (minimum-maximum)	Z-score	Mean±SD (minimum-maximum)	Z-score	
LV EDD (mm)	52.8±3.41 (48-57)	0.5±0.9	53.7±3.98 (49-61)	0.7±1.1	47.6±4.8 (39-52)	−0.5±0.9	0.02‡ (z - score)
LV ESD (mm)	39.0±3.65 (35-43)	2.27±1.19	36.0±2.65 (32-39)	0.99±1.2	31.1±2.9 (27-35)	−0.2±0.7	0.04‡ (z - score)
IVSd (mm)	10.4±0.9 (9-11)	1.21±0.5	10.6±1.2 (9-12)	1.14±0.5	10.6±0.7 (9.5-11)	1.35±0.5	>0.05 (z - score)
PWd (mm)	9.6±0.9 (8-10)	1.29±0.76	10.2±0.8 (9-11)	1.44±0.71	10±0.6 (9-11)	1.5±0.7	>0.05 (z - score)
LCA (mm)	4.25±0.9 (3-5)	0.96±1.66	3.5±0.7 (3-4)	0.4±0.11	2.83±0.7 (2-3.5)	−0.7±1.66	>0.05 (z - score)
RCA (mm)	3.5±0.9 (3-4.5)	0.90±1.21	3 (3-3)	−0.3±0.14	2.4±0.5 (2-3)	−1.7±1.22	>0.05 (z - score)
LV EF (%)	45.2±6.9 (37-55)	-	60.8±6.5 (50-68)	-	67.2±4.9 (60-74)	-	<0.001†,‡
LV FS (%)	21.25±2.5 (18-24)	-	32.8±5.5 (25-39)	-	36.38±3.12 (34-40)	-	<0.05†,‡

†Difference between values at the admission to 3rd day; ‡Admission to discharge. LV=Left ventricle; EDD=End-diastolic diameter; ESD=End-systolic diameter; IVSd=Interventricular septum diastolic diameter; PWd=Posterior wall diastolic diameter; LCA=Left coronary artery; RCA=Right coronary artery; EF=Ejection fraction; FS=Fractional shortening; SD=Standard deviation

All echocardiographic parameters are presented in Table 2. A significant improvement of LV systolic function was observed on day 3 [Figure 1]. Echocardiography examination after discharge was normal in all patients.

In the short-term (4.2 ± 2.0 months) follow-up period, all patients had normal laboratory parameters, LV systolic, and diastolic function with appropriate CA diameter; none developed dilated cardiomyopathy. On the ECG, 24-h Holter monitor, rhythm, and conduction disturbances were not observed in all patients. The fatal outcome did not observe.

DISCUSSION

A limited number of predisposing children could develop MIS-C temporally associated with SARS-CoV-2 infection. Unsteady clinical presentations in children open the question is it entirely different etiology, or in epigenetically responsive individuals, the virus can initiate some pathophysiological pathways with the consequent clinical presentation of MIS-C.[3,9] In two patients, EBV and CMV were detected in the blood samples, but those patients also had antibodies against SARS-CoV-2. KD-like clinical presentation, gastrointestinal symptoms, laboratory analyses, and echocardiography finding in these patients refer more to MIS-C than acute infection caused by these two viruses. However, both viruses could be associated with KD in children under the age of 5, because most adolescents and adults have developed protective immunity on EBV and CMV.[10-12] In addition, HIV is the most frequently reported infectious disease associated with KD in adults' rare cases.[12] Although MIS-C has overlapping features with KD, our patients with MIS-C were adolescents with frequent gastrointestinal and cardiovascular symptoms.

The predominance of cardiac damage in MIS-C (over 80% of patients) was striking.[2,9,13,14] Cardiomyocyte necrosis in children with COVID-19 might be caused by direct viral acting on ACE-2 receptors or indirect injury due to cytokine releasing or ischemia.[3,9] All patients had a myocardial injury, but two patients had MIS-C shock syndrome with sustained hypotension and clinical signs of low cardiac output with the need for inotropic drug support. In 60.2%–82% of children, MIS-C shock syndrome was observed.[1] Our patients with MIS-C had prolonged QTc, and it might be a result of inflammation and change ion channels activity (especially K + and Ca^{2+} channels-inflammatory cardiac channelopathies).[15]

The most current cardiac abnormality on the echocardiogram was a depressed EF, FS, pericardial effusion, and mitral regurgitation.[1,5] Echocardiography showed LV systolic impairment at the admission, but significant improvement was observed on the 3rd hospital day. Those findings combined with a significant reduction of cardiomyocytolysis markers and NT-proBNP on the 3rd hospital day refers to possible indirect myocardial injury. Ectasias of CAs had 2/6 cases, but diameters were appropriate at the discharge. In <20% of the patients, the CA's mild dilatation without segmental aneurysms was described.[9,14]

The resemblance between KD and MIS-C suggests that they may share similar pathophysiology, with the possibility to response on similar drugs.[1] One of the patients with MIS-C shock syndrome did not respond to IVIG-treatment, so he was treated according to the refractory KD protocol. Children with KD-like during the SARS-CoV-2 pandemic were more common unresponsive to IVIG-treatment than children with classic KD.[15]

In patients with MIC-S, the mortality rate was 1.7%.[1] We did not observe the fatal outcome and fulminant myocarditis. None of the patients during the short-term follow-up developed dilated cardiomyopathy and CAs aneurysms.

CONCLUSION

MIS-C is a life-threatening state distinguished by excessive inflammation, consequent fever, abdominal symptoms, conjunctivitis, rash, and myocardial injury. Children

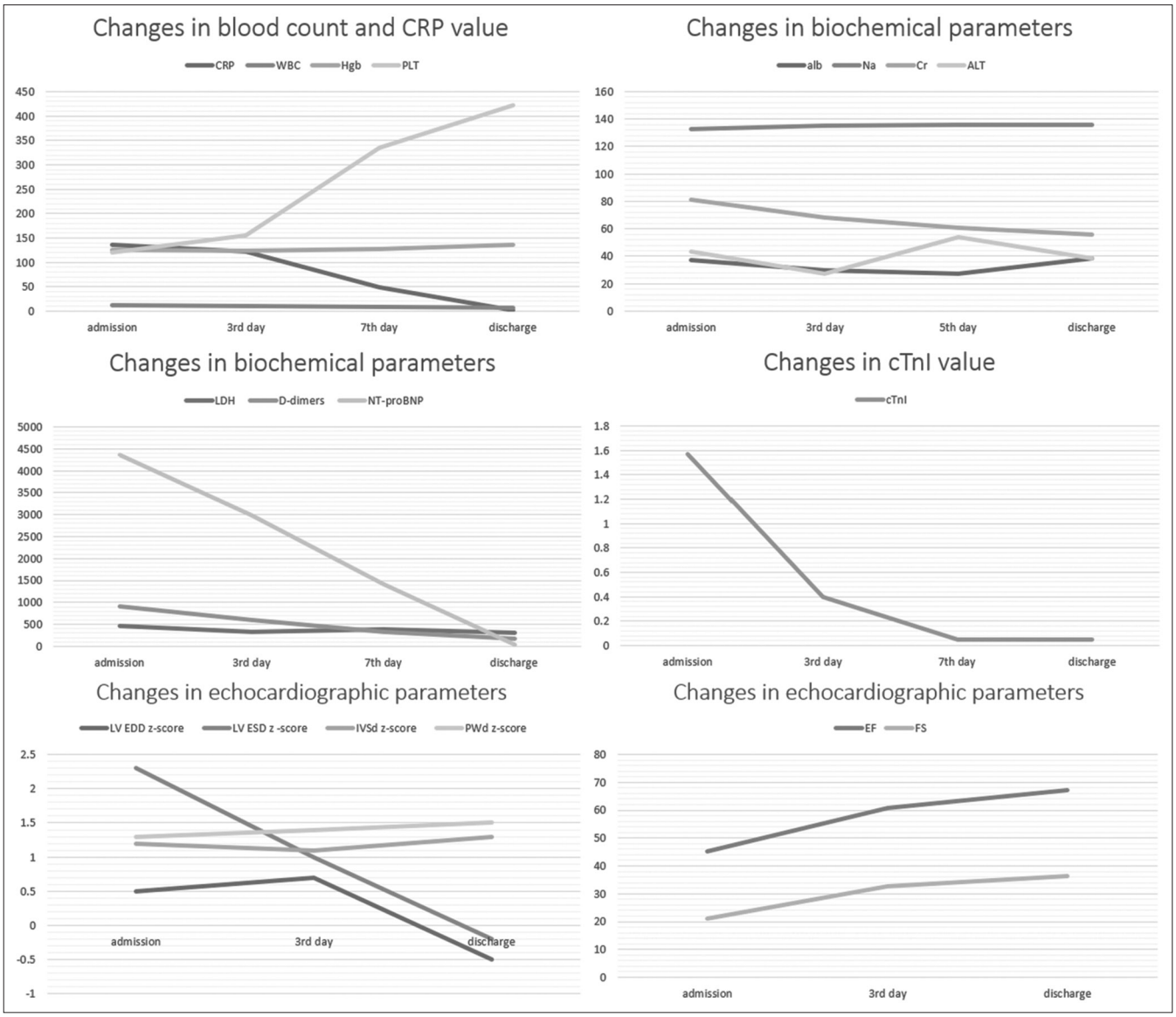

Figure 1: Changes of laboratory and echocardiography parameters during hospitalization. Abbreviations: CRP = C-reactive protein; WBC = White blood cell; Hob = Hemoglobin; Na = sodium; Cr = Creatinine; ALT - Alanine transaminase; LDH - Lactate dehydrogenase; cTnI = Cardiac troponin I; NT-proBNP - N-terminal (NT)-pro hormone B-type natriuretic peptide; LV = Left ventricle, EDD = End-diastolic diameter; ESD = End-systolic diameter; IVSd = Interventricular septum diastolic diameter; PWd = Posterior wall diastolic diameter; EF = Ejection fraction; FS = Fractional shortening

typically developed MIS-C after SARS-CoV-2 infection, and in most cases, only antibodies against SARS-CoV-2 were funded in serum. MIS-C can progress rapidly into shock. Rapid normalization of cardiomyocytolysis markers and echocardiography parameters refer to possible indirect myocardial injury. Early recognition and adequate treatment enable children survival without complications in the short-term follow-up period.

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Conflicts of interest
There are no conflicts of interest.

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