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Original Research

Cardiac Evaluation in Children with Multisystem Inflammatory Syndrome Associated with SARS-CoV-2

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Abstract

Objectives: The heart is one of the organs frequently affected by the multisystem inflammatory syndrome in children (MIS-C), associated with severe acute respiratory syndrome coronavirus 2 infection. Cardiac involvement in patients with MIS-C was evaluated with physical examination findings, biochemical test, and cardiological imaging tests. We reported the degree of cardiac involvement in patients with MIS-C.

Methods: In this retrospective study, the complaints, physical examination, and cardiac findings of patients with MIS-C were evaluated.

Results: Sixteen patients (four males and 12 females) with MIS-C were included in the study. The median age was 6 (5–17) years. In patients, palpitations (6%), chest pain (12%), ECG changes (50%), valve insufficiency (50%), low ejection fraction (6%), coronary dilatation (6%), troponin (38%), and d-dimer (88%) elevation were detected. One patient died. Valve insufficiency persisted in 5 (31%) patients.

Conclusion: Severe cardiac involvement can be seen in MIS-C patients. Due to its serious effects on mortality and morbidity, cardiac involvement should be evaluated with cardiac imaging tools such as echocardiography and ECG in all MIS-C patients.

Keywords: MIS-C and heart, COVID-19, Multisystem inflammatory syndrome in children, Myocarditis

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The novel virus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly around the world since December 2019, caused a pandemic. According to preliminary information, this disease, called coronavirus disease 19 (COVID-19) by the World Health Organization (WHO) On February 11, 2020, had been a milder course in children compared to adults.[1] However, in the following months, a Kawasaki-like disease began to be reported in some pediatric patients with a history of COVID, first in United Kingdom and then in some European countries and in United State of America.[2-5] These studies demonstrated that this multisystem inflammatory syndrome in children (MIS-C), which progressive inflammation and multiple organ involvement, was associated with SARS-CoV-2. In the following period, certain diagnostic criteria were defined by the WHO and the Centers for Disease Control and Prevention (CDC) for MIS-C patients. The diagnostic criteria determined by the CDC include <21 years age, history of

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fever >38.0°C for ≥24 h or subjective fever lasting ≥24 h, laboratory evidence of 1 or more inflammation (CRP, ESR, d-dimer, procalcitonin, ferritin, fibrinogen, LDH, IL6, neutrophil elevation and/or lymphopenia, and hypoalbuminemia), severe illness requiring hospitalization with multisystem (>2) organ involvement (heart, kidney, respiratory, hematological, gastrointestinal, dermatological, or neurological), demonstrated COVID-19 association (positive by PCR and/or positive by serology and/or positive by antigen test and/or COVID-19 exposure within prior 4 weeks), and no alternative plausible diagnoses.[6]

Much more severe clinical conditions were encountered in COVID-19 patients with MİS-C. One of the most serious clinical effects was seen on the heart. Signs of myocardial depression ranging from mild circulatory failure to circulatory shock were demonstrated in affected many patients.[7] In this single-center retrospective study, we aimed to demonstrate the effects of MIS-C on the heart in patients associated with SARS-CoV-2.

Methods

This retrospective study was approved by the Local Ethics Committee of our institution. Sixteen patients who were followed up and treated with the diagnosis of MIS-C according to CDC criteria[6] in the pediatric health and diseases clinic of Hamidiye Etfal Training and Research Hospital between November 2020 and April 2021 were included in the study. All clinical data about patients were obtained retrospectively from hospital file archives.

Demographic characteristics of the patients, comorbid diseases, physical examination findings, arterial blood pressure measurements, cardiac symptoms, and findings such as murmur, palpitation, and chest pain were noted. From the biochemical tests of the patients, the measurements of high sensitivity Troponin I, NT-proBNP, D-dimer, and Creatinine Kinase were recorded at the time of admission and follow-up. Initial admission and follow-up electrocardiogram (ECG) and transthoracic echocardiography reports of the patients were reviewed. Ventricular and supraventricular arrhythmic findings, ST-, and T-wave changes detected in the ECG were recorded. Transthoracic echocardiography reports of the patients were evaluated for the presence of coronary artery dilatation (z score >2), ventricular dilatation, left ventricular ejection fraction, segmental hypokinesia, and valvular insufficiency. In addition, support treatment needs such as inotropic, antiarrhythmic, corticosteroid, immunoglobulin, and anticoagulation were questioned during the follow-up of the patients.

Available findings were given as median with the quartile range or percentage ratio using the SPSS 21 software (SPSS Inc., Chicago, IL, USA).

Results

A total of 16 patients, four males and 12 females, who were hospitalized according to MIS-C diagnostic criteria were included in the study. The demographic characteristics and cardiac signs of the patients are summarized in Tables 1 and 2. The median age was 6 (5–17) years, and none of

Table 1. Patient characteristics

Characteristics	n (%)
Age, year	
Median	6
Distribution	
<1 year	0
1–5 year	1
6–10 year	11
11–18 year	4
Sex, n (%)	
Male	4 (25)
Female	12 (75)
Comorbidity, n (%)	2 (13)
Leukemia	1
Overweight (body mass index >25 kg/m^2)	1

Available findings were given as median (interquartile range) or n (%). n is the number of patients with complete data in the total patients.

Table 2. Cardiac signs of the patients

Characteristics	n (%)
Clinical Signs	
Palpitation	1 (6)
Chest Pain	2 (13)
Murmur	1(6)
Hypotension at admission (blood pressure, percentile <5th)	2 (13)
ECG	
Sinus tachycardia	3 (19)
T-wave inversion	2 (13)
ST-elevation	1 (6)
Ventricular arrhythmia	1 (6)
Supraventricular arrhythmia	1 (6)
Echocardiography	
Coronary artery dilatation (z score >2)	1 (6)
Ventricular dilatation	2 (13)
Left ventricular ejection fraction	
<55%	1 (6)
>55%	14 (94)
Segmental hypokinesia	2 (13)
Valvular insufficiency	8 (50)

Available findings were given as median (interquartile range) or n (%). n is the number of patients with complete data in the total patients.

the patients had a history of underlying heart disease. Only two patients had comorbidity included as 1 leukemia and 1 overweight. Cardiac complaints and physical signs at admission were limited. Only one of the patients had palpitations, two had chest pain. On physical examination of the patients revealed heart murmur in one, and hypotension in two. At admission and/or follow-up of eight patients (50%) with MIS-C, non-specific ECG changes such as sinus tachycardia, ST elevation, T inversion, ventricular, and supraventricular arrhythmias were detected. Except the prominent valve insufficiencies (50%) in the echocardiographic examination of the patients, other cardiac signs including low ejection fraction (6%), ventricular dilatation (6%), and segmental hypokinesia (13%) were limited. Coronary dilatation was determined in only one patient. Significant changes were observed in some laboratory tests, as shown in Table 3. At admission, 38 % of the patients diagnosed with MIS-C had moderate troponin elevation. On the other hand, 88 %of the patients had a remarkable increase in D dimer values. Nt-ProBnp could only be studied in four patients. Two (50%) of patients had high Pro-Bnp level at admission. Moreover, remarkably, high mean values were detected in the relevant patients. Various treatment methods were applied to the patients with MIS-C depending on the severity of the disease. Almost all patients received intravenous immunoglobulin, steroid, and anticoagulant treatment in addition to other supportive therapies. In only three patients, IVIG treatment was not required. Inotropic drug support was provided to three patients with circulatory disorders. Antiarrhythmic therapy was required in one patient due to ventricular arrhythmia (Table 4).

Despite all the supportive care required, one of the patients with comorbidity due to leukemia died. At the same time, cardiogenic shock and circulatory collapse at the venoarterial extracorporeal membrane oxygenation treatment limit was observed in another patient with obesity. Moreover, moderate valvular insufficiency persisted in the early follow-up of 5 (31%) patients after discharge (Table 5).

Table 4. Treatment of the patients

	n (%)
Inotropic or vasopressor support	3 (19)
Antiarrhythmic therapy	1 (6)
Intravenous corticosteroids	15 (94)
Immunoglobulin infusion	13 (81)
Anticoagulation	15 (94)
Venoarterial extracorporeal membrane oxygenation	0

Available findings were given as median (interquartile range) or n (%). n is the number of patients with complete data in the total patients.

Table 5. Responses of clinical status of the patients

	n (%)
Persistent valvular insufficiency	5 (31)
Cardiogenic shock	1 (6)
Death	1 (6)

Available findings were given as median (interquartile range) or n (%). n is the number of patients with complete data in the total patients.

Discussion

Due to insufficient case definitions and lack of specific supportive laboratory criteria, it might be difficult to distinguish MIS-C from diseases with similar clinical condition such as acute severe COVID-19 and Kawasaki disease.[2,8]

Cardiac MR findings in MIS-C patients revealed that the event is mostly a post infectious condition and is similar to the involvement in Kawasaki disease.[9] MIS-C is clinically similar to Kawasaki disease too. However, there are differences in terms of age and coronary involvement. Although coronary involvement is observed in up to 33% of patients with Kawasaki in the acute phase, this rate is between 9 and 18% in patients with MIS-C as shown in various studies.[2,10-12] Kawasaki disease is common in children under the age of 5.[13] However, as shown in our study too, MIS-C disease is often more prevalent in children over 5 years of age

Table 3. Laboratory findings of the patients

	n	Rate of high values at admission n (%)	Baseline	Monitoring values, Day (No. Of patient)		Normal Values
				Day 1 (10)	Day 7 (10)	
High sensitivity troponin I, ng/L	16	6 (38)	5.95 (3–19844)	8 (7–11)	8 (3–32)	<14
Creatinine kinase, U/L	15	4 (25)	67 (52–181)			<171
NT-proBNP, pg/mL	4	2 (50)	2954 (147–8445)			<300
D-dimer ug/L	16	14 (88)	1387 (685–2807)			<500

Available findings were given as median (interquartile range) or n (%). n is the number of patients with complete data in the total patients.

(average 8–10 years) who have previously had SARS-CoV-2 infection.[8]

Although COVID-19 seems to be a smaller problem clinically due to a mild course in children and low mortality rate of 0.1%; unfortunately, MIS-C associated with COVID-19 has become a major health problem with the severity of the disease and death rate of % 1.8–2.[2,12,14] Another remarkable point is that although respiratory system involvement is common in COVID-19, cardiovascular system involvement is more common in MIS-C associated with COVID-19.[12,15]

Various hypotheses were raised regarding cardiac injury. It was thought that cardiac damage due to direct virus invasion and immunity against myocyte cells as a result of this damage may be responsible for this destruction.[8,9] However, positivity of serological tests rather than PCR tests (that reveal the presence of live viruses in MIS-C patients), cytokine storm and multiorgan involvement suggest that the event occurs as a result of the destructive effect of the hyperinflammatory response rather than direct viral invasion. Cytokine storm and macrophage activation with high D-dimer levels demonstrated in MIS-C patients who underwent cardiogenic shock.[11] In addition, rapid and effective response to IVIG and steroid therapy as immunomodulator and immunosuppression might support the systemic excessive immune response mechanism in MIS-C.[16,17]

Cardiovascular involvement might be encountered in a variable spectrum from serious conditions such as myocarditis, arrhythmia, valve insufficiency, coronary-artery aneurysm, and cardiogenic shock to isolated troponin elevation.[11,12]

In various studies, the rate of myocarditis in patients with MIS-C was determined as 22–52%.[2,12] Dufort et al.[2] determined that myocarditis cases increase with age in MIS-C patients. Moreover, the highest rate was detected in the adolescent group as 73%. In studies conducted on rats with myocarditis, it was concluded that inflammatory cytokines such as IL-6 and TNF-alpha could cause heart damage by generating reactive oxygen species. IL-6 and similar cytokines have been shown to be intensely secreted in MIS-C patients.[18,19]

Non-specific ECG changes such as sinus tachycardia, ST-elevation, t-inversion, ventricular, and supraventricular arrhythmias frequently accompany MIS-C patients. ST-T-wave changes in ECG are expected in patients with increased troponin as an indicator of cardiac damage. However, this situation alone is insufficient to explain other abnormal rhythm mechanisms. In the modeling of immune-mediated myocarditis in rats, it was shown that cytokines such as tumor necrosis factor-α and interleukin-6, which are increased by inflammation, can cause Ca^{+2}/calmodulin Protein Kinase II (CaMKII) activation. It was concluded that such a situation, which may cause regional Ca^{+2} transition heterogeneity, is responsible for arrhythmia.[19,20] In our two patients with ventricular and supraventricular arrhythmias without troponin elevation, the improvement of the arrhythmia simultaneously with the suppression of inflammation also supports this situation.

A large study by Godfred-Cato et al.[12] in patients with MIS-C, mitral regurgitation, and pericardial effusion were detected with frequency of 25.5% and 23.9%, respectively. Valvular insufficiency seems to be due to possible cardiac edema and ring dilatation. However, persistence of multiple valve insufficiency in the late follow-up of our patients suggests that endocarditis may be responsible for valve damage. Therefore, the effect of MIS-C on the heart may be in the form of pan-carditis together with myocarditis, pericarditis, endocarditis. However, histopathological examinations are needed to determine this definitively.

Conclusion

Severe cardiac involvement can be seen in MIS-C patients. Due to its serious effects on mortality and morbidity, cardiac involvement should be evaluated with cardiac imaging tools such as echocardiography and ECG in all MIS-C patients.

Disclosures

Ethics Committee Approval: This study approval Hamidiye Etfal Ethical Committee (Reference number: 30.03.2021/3211).

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References

1. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics 2020;145:e20200702.
2. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al; New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383:347–58. [CrossRef]
3. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, et al. COVID-19 and Kawasaki Disease: novel virus and novel case. Hosp Pediatr 2020;10:537–40. [CrossRef]
4. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020;395:1607–8. [CrossRef]
5. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda

M, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395:1771–8. [CrossRef]

6. Centers for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). Available at: https://www.cdc.gov/mis/mis-c/hcp/index.html. Accessed Apr 06, 2022.
7. Kaushik S, Aydin SI, Derespina KR, Bansal PB, Kowalsky S, Trachtman R, et al. multisystem inflammatory syndrome in children associated with severe acute respiratory syndrome coronavirus 2 infection (MIS-C): a multi-institutional study from New York City. J Pediatr 2020;224:24–9. [CrossRef]
8. Kohli U, Lodha R. Cardiac involvement in children with COVID-19. Indian Pediatr 2020;57:936–9. [CrossRef]
9. Blondiaux E, Parisot P, Redheuil A, Tzaroukian L, Levy Y, Sileo C, et al. Cardiac MRI in children with multisystem inflammatory syndrome associated with COVID-19. Radiology 2020;297:E283–8.
10. Advani N, Sastroasmoro S, Ontoseno T, Uiterwaal CS. Long-term outcome of coronary artery dilatation in Kawasaki disease. Ann Pediatr Cardiol 2018;11:125–9. [CrossRef]
11. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation 2020;142:429–36. [CrossRef]
12. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al; California MIS-C Response Team. COVID-19-associated multisystem inflammatory syndrome in children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep 2020;69:1074–80. [CrossRef]
13. Şahin A, Şahin L, Karabulut M, Dalgıç N. Clinical and epidemiological characteristics of cases monitored by the diagnosis of Kawasaki disease. J Pediatr Inf 2018;12:87–92. [CrossRef]
14. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr 2020;109:1088–95. [CrossRef]
15. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet 2020;395:1014–5. [CrossRef]
16. Barshes NR, Goodpastor SE, Goss JA. Pharmacologic immunosuppression. Front Biosci 2004;9:411–20. [CrossRef]
17. Sewell WA, Jolles S. Immunomodulatory action of intravenous immunoglobulin. Immunology 2002;107:387–93. [CrossRef]
18. Gruber CN, Patel RS, Trachtman R, Lepow L, Amanat F, Krammer F, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell 2020;183:982–95. [CrossRef]
19. Park H, Park H, Lee D, Oh S, Lim J, Hwang HJ, et al. Increased phosphorylation of Ca(2+) handling proteins as a proarrhythmic mechanism in myocarditis. Circ J 2014;78:2292–301. [CrossRef]
20. Tse G, Yeo JM, Chan YW, Lai ET, Yan BP. What is the arrhythmic substrate in viral myocarditis? Insights from clinical and animal studies. Front Physiol 2016;7:308. [CrossRef]