COVID-19-RELATED MULTISYSTEM INFLAMMATION SYNDROME IN CHILDREN: CARDIOVASCULAR AND CORONARY ASSESSMENT

ÇOCUKLARDA COVID-19 İLIŞKILI MULTISISTEM İNFLAMASYON SENDROMU: KARDIYOVASKÜLER VE KORONER DEĞERLENDIRME

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ABSTRACT

Objective: Despite the global attention directed towards coronavirus-19 (COVID-19) disease, a comprehensive understanding of the condition remains elusive. The cardiovascular implications, pivotal in this disease, are largely derived from case series and reviews, lacking the depth of prospective studies. This single-arm observational study aims to fill this void by examining the coronary arteries and assessing the systolic/diastolic functions of the left ventricle in children diagnosed with "Multisystem Inflammatory Syndrome" associated with COVID-19 (MIS-C).

Material and methods: We conducted a prospective study involving 36 MIS-C patients aged 0-18 years, focusing on cardiovascular involvement and tracking changes in the coronary arteries, as well as the systolic and diastolic functions of the left ventricle during the disease course.

Results: Among the patients, 11.1% exhibited endocarditis, 5.5% myocarditis, 0% pericardial effusion, 16.6% coronary dilation, and 0% coronary aneurysm. Even in patients without cardiovascular involvement, subtle changes were noted, including a decrease in systolic and diastolic left ventricular function and an increase in the z score of the left main coronary artery. Despite these observations, all patients experienced full recovery upon discharge, with no reported deaths or complications.

Conclusion: This study underscores the rarity of cardiovascular manifestations in MIS-C, often following a benign course, particularly with prompt treatment. Even in the absence of clinical symptoms, MIS-C affects the left ventricular function and the left main coronary artery.

Key words: Children, Coronary artery, Left ventricular function, SARS coronavirus

ÖZET

Amaç: COVID-19 hastalığı dünya genelinde büyük ilgi çekmesine rağmen halen tam olarak anlaşılamamıştır. Bu hastalıkta çok önemli olan kardiyovasküler etkiler büyük ölçüde vaka serilerinden ve derlemelerden elde edilmekte olup prospektif çalışmaların derinliğinden yoksundur. Bu tek kollu gözlemsel çalışma, COVID-19 ile ilişkilendirilen "Multisistem İnflamatuar Sendrom" (MIS-C) tanısı konmuş çocuklarda koroner arterleri inceleyerek ve sol ventrikülün sistolik/diyastolik fonksiyonlarını değerlendirerek bu boşluğu doldurmayı amaçlamaktadır.

Materyal ve metot: Yaş aralığı 0-18 yıl olan 36 MIS-C hastasını içeren, kardiyovasküler tutuluma odaklanan ve koroner arterlerdeki değişikliklerin yanı sıra sol ventrikülün sistolik ve diyastolik fonksiyonlarını hastalık seyri boyunca izleyen prospektif bir çalışma yürüttük.

Bulgular: Hastaların %11,1'inde endokardit, %5,5'inde miyokardit, %0'ında perikardiyal effüzyon, %16,6'sında koroner dilatasyon ve %0'ında koroner anevrizma tespit edilmiştir. Kardiyovasküler tutulumu olmayan hastalarda bile, sistolik ve diastolik sol ventrikül fonksiyonlarında azalma, sol ana koroner arterin z skorunda artış gibi belirgin değişiklikler gözlenmiştir. Ancak bu gözlemlere rağmen, tüm hastalar taburcu edildikten sonra tam bir iyileşme hali göstermiş ve herhangi bir ölüm veya komplikasyon durumu bildirilmemiştir.

Sonuç: Bu çalışma, MIS-C'deki kardiyovasküler belirtilerin nadir olduğunu ve genellikle hafif seyir izlediğini vurgulamaktadır. Tedavinin zamanında yapılması, hastalığın olumlu seyrine katkıda bulunmuş olabilir. Klinik belirtiler olmasa bile, MIS-C'nin sol ventrikül fonksiyonu ve sol ana koroner arter üzerindeki etkileri göz önünde bulundurulmalıdır.

Anahtar kelimeler: Çocuklar, Koroner arter, Sol ventrikül fonksiyonu, SARS koronavirüsü

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Introduction

The coronavirus-19 (COVID-19) pandemic has posed unprecedented challenges to global health, with implications reaching every corner of society. Among the diverse impacts, the effect of the virus on pediatric populations has garnered considerable attention. As the world collectively navigates this public health crisis, insights into the specific nuances of COVID-19 infection in children have become increasingly crucial.

A valuable starting point in understanding COVID-19 infection from a pediatric perspective is provided, emphasizing the unique considerations and challenges in managing cases involving children (1). As critical cases among children have been documented, a comprehensive narrative review sheds light on the experiences of critically ill children affected by COVID-19, thereby contributing to our understanding of the disease's impact on this demographic (2).

Recognizing the complexity of COVID-19's effects on the cardiovascular system, a systematic review was conducted, focusing specifically on the cardiovascular implications of the virus in children (3). This report elucidates the multifaceted nature of cardiovascular involvement and serves as a pivotal reference in understanding this aspect of the disease. To further enrich our understanding of the clinical characteristics and outcomes in pediatric COVID-19 cases, a systematic review and meta-analysis were conducted (4). This study provides a comprehensive synthesis of available data, helping to guide clinical practices and inform future research directions in pediatric COVID-19 management.

In this context, our study has investigated cardiovascular changes in COVID-19-associated Multisystem Inflammatory Syndrome in Children (MIS-C). Acknowledging the limited prospective studies in this area, we focus on evaluating coronary arteries and the systolic/diastolic functions of the left ventricle in MIS-C cases associated with COVID-19. By addressing this critical knowledge gap, our research aims to contribute valuable insights to the broader discourse on pediatric COVID-19 manifestations, aligning with the collective global effort to comprehend and combat the ongoing pandemic.

Material and methods

This prospective single-arm observational study was conducted in 36 children with multisystem inflammatory syndrome in children, between November 2020 and March 2021. The study protocol was approved by the local ethic committee (protocol number: 2020/623). Written informed consent was obtained from all parents participating in the study.

Multisystem inflammatory syndrome in children (MIS-C) is diagnosed based on the criteria outlined by the "Centers for Disease Control and Prevention" (CDC). The CDC introduced a case definition for MIS-C in May 2020, defining it as the presence of fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization. The criteria include multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic), the absence of plausible alternative diagnoses, and positive testing for current or recent SARS-CoV-2 infection by PCR, serology, or antigen test, or coronavirus-19 disease exposure within the 4 weeks before the onset of symptoms (1). The exclusion criteria were chronic diseases (inflammatory or autoimmune, renal, hepatic, cardiac) and immune deficiencies. Treatment considerations based on presentation. In case of coronary artery dilation/aneurysm and symptoms mimicking Kawasaki disease, intravenous immune globulin, glucocorticoids, and acetylsalicylic acid were given. Inotropes (epinephrine, norepinephrine, dobutamine, milrinone) were used for left ventricular dysfunction. Interleukin 1 inhibitor (anakinra) was used for cases that were refractory to glucocorticoids.Demographic data, symptoms, vital signs, and physical examination findings were systematically recorded in our study.A comprehensive array of laboratory tests was conducted, encompassing complete blood count, blood chemistry (including liver and renal function tests, cardiac enzymes), blood gas analysis (lactate levels), acute phase reactants (such as erythrocyte sedimentation rate,C-reactive protein, procalcitonin, fibrinogen, ferritin, and d-dimer)and coagulation tests (prothrombin time and international normalized ratio).

Additionally, all patients underwent chest roentgenogram and 12-lead electrocardiography assessments. Echocardiographic examinations were conducted at admission before the initiation of treatment and at the end of the treatment by the same experienced pediatric cardiologist. "General Electric Vivid 7" cardiac ultrasound machine, employing sector probes tailored to the age and weight of the patients was used for echocardiographic assesment. Echocardiographic measurements were assessed according to the American Echocardiography Association Pediatric Echocardiography Guideline (5). Pathologic valvular insufficiency related to endocarditis was assessed using color Doppler imaging. Systolic function parameters of the left ventricle, including ejection fraction and shortening fraction, were calculated through M-mode assessment immediately distal to the tips of the mitral valve leaflets in the parasternal long-axis view. Diastolic function parameters of the left ventricle were determined using pulsed-wave Doppler of mitral inflow velocity (mitral E, mitral A, mitral E/A, and mitral deceleration time) in the apical four-chambers view. The sample volume was positioned between the mitral leaflet tips, and color Doppler imaging was utilized to visualize the flow direction through the mitral valve.

Furthermore, coronary arteries were visualized in the parasternal short-axis view. Any dilation or aneurysms were meticulously measured and recorded. The proximal right coronary artery and left main coronary artery were specifically measured, and z scores were documented in accordance with the body weight of healthy children, providing a comprehensive assessment of cardiovascular health in the pediatric population (6).

Statistical analysis

Data collected were checked and analyzed by using the Statistical Package for Social Sciences Program (SPSS) version 17. This was followed by the relevant data analysis and assessment. Quantitative variables are expressed as median values and interquartile ranges as measures of central tendency. Comparison of continuous quantitative variables was performed using paired sample t-test and independent t-test. One-way ANOVA was used to compare more than two groups. In cases where variance homogeneity could not be achieved, the K independent nonparametric test was used. The study was performed with the ethical approval of the institutional review board of Ondokuz Mayıs University (Protocol number: 2020/623), and the Provincial Health Directorate of Samsun. In accordance with the principles of the Declaration of Helsinki with written informed consent obtained from the parents.

Results

Presenting clinical and laboratory characteristics

The study included group 24 girls (66.7%) and 12 boys (33.3%). The mean age of the patients, body weight and body mass index were 9±4 years, 32±17 kg and 20.8±1, respectively. The most common symptoms were fever (100%), fatigue (88.8%), abdominal pain (63.8%), diarrhea (63.8%), nausea-vomiting (61.1%), rash (58.3%), myalgia (47.2%), headache (33.3%) and cough (16.6%). Hypotension and prolonged capillary filling time was observed in 25% and 13.8% of the cases.

The mean body temperature of the patients at admission was 38.8±0.5 °C, heart rate 113±20/min, respiratory rate 24±4/min, oxygen saturation (SpO2) 96±2%, systolic and diastolic blood pressure 105±8 and 67±6 mmHg. The mean duration of fever was 4.5±1.7 days. Laboratory data of the cases are given in Table 1.

Table 1. Laboratory data of the cases

Laboratory findings (reference range)	Mean±SD	Laboratory findings (reference range)	Mean±SD
Complete blood count		**Blood Chemistry & Lactate**	
Hemoglobin (g/dL) (11.5 to 15.5)	11.1±1.2	ALT (U/L) (0 to 34)	62±150
WBC (x109/L) (4.3 to 11.0)	9.3±3.9	AST (U/L) (0 to 40)	87±214
Thrombocytes (x109/L) (150 to 400)	189±121	GGT (U/L) (0 to 60)	53±77
Lymphocytes (x109/L) (1.5 to 4.0)	1.4±0.9	LDH (U/L) (0 to 975)	398±308
Neutrophils (x109/L) (1.5 to 7.0)	7.3±3.5	Albumin (g/dL) (3.5 to 5)	3.4±0.5
Acute phase reactants		Urea (mg/dL) (5 to 18)	10±4
CRP (mg/L) (0 to 10)	148±99	Creatinine (mg/dL) (0.4 to 1.4)	0.4±0.2
Procalcitonin (ng/mL) (0.0 to 0.1)	7.4±9.9	Troponin I (µg/L) (0 to 0.15)	0.19±0.20
ESR (mm/h) (0 to 20)	47±32	Lactate (U/L) (0.4 to 2)	1.3±0.4
Fibrinogen (mg/dL) (200 to 400)	294±217	**Coagulation parameters**	
Ferritin (ng/mL) (13.7 to 78.0)	846±1777	PT (seconds) (9.4 to 12.5)	13.3±1.6
D-dimer (µg/mL) (0.1 to 0.56)	5.4±3.0	PT-INR (0.85 to 1.15)	1.16±0.2

Cardiological evaluation

Cases were evaluated by echocardiography during the course of the disease 2.3±1.5 times. Four patients (11.1%) had signs of endocarditis (mild mitral regurgitation), two patients (5.5%) had myocarditis (decreased ejection fraction and/or shortening fraction), 6 patients (16.6%) had coronary dilatation (left in four, right in one, and left&right in one). Coronary aneurysm was not observed.

There were no patients who died or developed complications. All patients were discharged after 7.3±3.2 days of treatment. Echocardiography at discharge showed an increase in left ventricular systolic (ejection fraction and shortening fraction), diastolic functions (mitral E, mitral E/A) and higher left main coronary artery z score at the end of treatment (Table 2).

Table 2. Echocardiographic data of the cases at admission (first) and follow-up (last)

		Mean±SD	p*			Mean±SD	p*
EF (%)	**First** **Last**	61.7±6.8 69.7±4.2	0.029	**Mitral E (m/s)**	**First** **Last**	100±8 112±8	**0.001**
SF (%)	**First** **Last**	32.6±4.8 38.8±3.8	0.023	**Mitral A (m/s)**	**First** **Last**	62±7 62±4	0.068
LMCA z score	**First** **Last**	1.31±2.72 -0.64±1.45	0.037	**Mitral E/A**	**First** **Last**	1.64±0.16 1.80±0.13	**0.032**
PRCA z score	**First** **Last**	-0.20±1.91 -1.06±1.79	0.300	**DT (ms)**	**First** **Last**	118±33 118±18	0.059

EF=Ejection fraction; SF= Shortening fraction; LMCA= Left main coronary artery; PRCA= Proximal right coronary artery; DT= Deceleration time; *two-tailed p value according to the Paired-Samples T test

The association between age, gender, body weight, vital signs, laboratory tests, chest roentgenogram pathologies, and the echocardiographic data (ejection fraction, shortening fraction, mitral E, mitral E/A, left main coronary artery z score) were examined (Table 3).

Table 3. Echocardiographic data and clinical, laboratory and radiological findings

	EF	SF	Mitral E	Mitral E/A	LMCA z score
Bodyweight	**0.043**	**0.017**	0.589	0.798	0.533
Body temperature	0.930	0.856	**0.039**	0.955	0.855
BP (systolic)	0.200	0.381	**0.030**	0.721	0.467
BP (diastolic)	0.772	0.975	**0.028**	0.924	0.513
SpaO2	**0.018**	**0.040**	**0.048**	0.232	0.616
Urea	**0.018**	**0.022**	0.263	0.648	0.906
Creatinine	**0.032**	**0.003**	0.031	0.762	0.896
LDH	0.716	0.499	0.330	0.310	**0.037**
Troponin	0.073	0.090	0.061	**0.014**	0.375
PT-INR	0.356	0.240	0.229	0.360	**0.011**
Ferritin	0.733	0.661	0.042	0.460	0.235
Fibrinogen	**0.011**	**0.031**	0.714	0.739	0.219
Chest X-ray	**0.042**	**0.029**	0.718	0.893	**0.012**

Only those with statistically significant correlations, according to the One-way ANOVA, are shown.
BP= Blood pressure; SpaO2= Arterial oxygen saturation; LDH= Lactate dehydrogenase; EF=Ejection fraction; SF= Shortening fraction; LMCA= Left main coronary artery

Discussion

Most children with coronavirus-19 disease are asymptomatic or have mild symptoms (1). Severe clinical manifestations and death were rarely reported in children (7). A multisystemic presentation of the disease, multisystem inflammatory syndrome in children was defined in May 2020. Due to overlapping features with Kawasaki disease, there are debates about whether multisystem inflammatory syndrome in children was a variant form of acute coronavirus disease 2019, or an exacerbation of inflammatory syndromes (8). The recent information about the severe manifestations of multisystem inflammatory syndrome in children is limited (9, 10). Knowledge about multisystem inflammatory syndrome in children needs to be improved because coronavirus-19 disease seems to continue to be on the world agenda as global vaccination will not be completed soon. In the review of 16 studies, 56.8% of children with multisystem inflammatory syndrome in children were male in Europe and North America (3). In a multicenter study, 66.7% of multisystem inflammatory syndrome in children were male (11). In another review, the sex distribution of the multisystem inflammatory syndrome in children cases was 1:1 (5). In our study, a slightly female predisposition (66.7%) was found. We think that gender is not a prominent factor in multisystem inflammatory syndrome in children.

The mean age (7.3-11 years) for multisystem inflammatory syndrome in children is higher than Kawasaki disease and was 9±4 years in our study (4, 8, 12). Obesity was reported as a comorbidity in children with coronavirus-19 disease (4, 8). The mean body mass index was normal in our study. We think that multisystem inflammatory syndrome in children has a tendency to affect nonobese patients, unlike acute coronavirus-19 disease. A wide range of cardiovascular events is reported in children with multisystem inflammatory syndrome in children (13). Most common cardiovascular symptoms include congestive cardiac failure, tachyarrhythmia, coronary artery dilation, and cardiogenic shock (8, 11, 12, 14). The exact pathogenesis of cardiovascular involvement in multisystem inflammatory syndrome in children remains unclear. Angiotensin-converting enzyme-2 receptor is the main receptor for coronavirus-19 disease.Therefore, key point of cardiovascular manifestations is probably the expression level of angiotensin-converting enzyme-2 receptor in the heart (1). After the coronavirus binds to

angiotensin-converting enzyme-2 via a surface glycoprotein (spike) and enters the host cell, cytokine storm and immune dysregulation result in myocardial fiber distention, rather than direct damage (13, 15). The high troponin I level is the main marker of cardiac injury (16). The clinical interpretation of lactate dehydrogenase is challenging. Until hemolysis or myocardial damage occurs, lactate dehydrogenase is normal in multisystem inflammatory syndrome in children (11). In our study, lactate dehydrogenase was normal, troponin I was slightly high and normalized in a short time. We think that if lactate dehydrogenase is normal despite troponin increases, myocardial injury is mild and reversible in multisystem inflammatory syndrome in children. The most common noncoronary findings on echocardiography are myocarditis (41-61%) and pericardial effusion (21-34%) (11-13). In our study, endocarditis and myocarditis were found in 11.1% and 5.5% of the cases. Pericardial effusion was not observed. Echocardiographic evaluation was repeated 2.3±1.5 times during follow-up. Significant differences were detected in systolic (ejection fraction, shortening fraction) and diastolic functions (mitral E/A) of the left ventricle on admission compared to discharge. The autopsy series revealed the most likely localization of SARS-CoV-2 is the interstitial cells of the myocardium (17). The systolic and diastolic functions depend on cardiomyocytes as well as healthy interstitial cells. Therefore, systolic and / or diastolic functions of the left ventricle are expected to be affected in multisystem inflammatory syndrome in children even if cardiomyocyte injury was absent. Our results showed that systolic and diastolic functions of the left ventricle were decreased in multisystem inflammatory syndrome in children even if they were within normal limits. Coronary artery dilation or aneurysms were described in 6-24% of patients (11, 12, 18). In our study, coronary artery dilation was observed in 16.6% of cases (11.1% left main coronary artery, 2.7% proximal right coronary, 2.7% left and right coronary). he mean coronary artery z scores of the patients whose coronary arteries were not dilated were evaluated. There was not a significant difference for right proximal coronary artery. The mean left main coronary artery z score was within normal limits but a significant decrease was observed after the standard treatment of multisystem inflammatory syndrome in children was completed. This result may be associated with fever and acute inflammation. However, the z-score height being unilateral suggests an isolated effect of coronavirus-19 disease on the left main coronary artery or more severe inflammation in the reflected left ventricle in the left main coronary artery.Coronary artery aneurysms could develop after acute phase of disease (19). Coronary aneurysm was not observed in the acute phase and during follow-up of 68±39 days. Despite this favourable result, careful follow-up of these patients is necessary due to the probability of a late coronary aneurysm. The course of this syndrome is relatively favourable in children compared to adults. The mortality rate in multisystem inflammatory syndrome in children is 2% in all cases and 0-4% in those who need intensive care (1, 3). In our study, ventilation was used in 13.5% of cases (non-invasive in 10.8% and mechanical ventilation in 2.7%). There were no patients who died or developed complications. Although the reason for the better prognosis of this disease in children is not known, there are some theories like lower angiotensin-converting enzyme-2 receptor expression and presence of other microorganisms in the epithelial lining of the lungs (20). In our study, treatment of the patients was begun immediately after a detailed work-up. We think that immediate diagnostic studies are very important in preventing the development of severe complications such as cardiogenic shock. Young age (esp <12 months), male gender, and having cardiac involvement are related to a higher mortality rate (4, 12). In our study, lower body weight, lower SpO2, decreased renal function, increased fibrinogen, and chest roentgenogram findings were found to be with decreased left ventricle systole function Troponin elevation was found to be associated with decreased left ventricle diastole function. According to our literature search, this is the first study in which the association between clinical, laboratory radiological findings, and systolic/diastolic functions of the left ventricle and coronary involvement were evaluated prospectively.

Conclusion

Given the smaller numbers of pediatric cases, there is still scarce data about the cardiovascular involvement in multisystem inflammatory syndrome in children. Recent data in this study suggest that cardiovascular involvement is not very frequent in children and cardiac manifestations have a good course with early management of cases. Although they remain within normal limits, the left main coronary artery, and the systolic and diastolic functions of the left ventricle are affected in multisystem inflammatory syndrome in children. Our current knowledge of the underlying factors of cardiac involvement in multisystem inflammatory syndrome in children is limited and future in-depth rigorous studies are warranted.

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Conflict of interest

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