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Original Article

Electrocardiographic Findings in Pediatric MIS-C Patients

Pediatrik MIS-C Hastalarında Elektrokardiyografik Bulgular

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ABSTRACT

Objective: This study investigates electrocardiographic (ECG) findings in pediatric patients diagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C) during the coronavirus disease-2019 pandemic, offering valuable insights into the diagnostic process.

Method: Demographic, clinical, and laboratory data of 71 MIS-C cases and 27 Kawasaki disease cases between January 2019 and December 2021 were retrospectively collected from hospital records, following ethics committee approval. MIS-C diagnosis adhered to World Health Organization criteria, and Kawasaki disease diagnosis followed American Heart Association guidelines.

Results: Seventy one MIS-C cases and 27 Kawasaki disease cases were included. MIS-C patients exhibited a significantly shorter duration of fever, higher C-reactive protein levels, and elevated serum cardiac troponin T troponin values compared to Kawasaki disease cases. Transthoracic echocardiographic evaluation revealed specific cardiac abnormalities in MIS-C patients, including mitral regurgitation and aortic regurgitation. ST segment changes, T-wave negativity, and QRS changes were observed significantly in MIS-C patients.

Conclusion: Results provide crucial information about the ECG profile of MIS-C cases. Particularly, indicators such as ST segment changes and T-wave negativity play a critical role in distinguishing MIS-C from other similar conditions and understanding its cardiac effects. These data offer valuable clinical markers that can be utilized in the diagnosis and treatment of MIS-C.

Keywords: Electrocardiography, pediatrics, MIS-C, Kawasaki disease

ÖZ

Amaç: Bu çalışma, koronavirüs hastalığı-2019 pandemisi sırasında Multisistem Enflamatuvar Sendromu olan Çocuklarda (MIS-C) elektrokardiyografik (EKG) bulguları araştırarak, tanı sürecine değerli bir bakış sunmayı amaçlamaktadır.

Yöntem: Ocak 2019 ile Aralık 2021 tarihleri arasında 71 MIS-C olgusu ve 27 Kawasaki hastalığı olgusunun demografik, klinik ve laboratuvar verileri, etik kurul onayı sonrasında hastane kayıtlarından retrospektif olarak toplandı. MIS-C tanısı, Dünya Sağlık Örgütü kriterlerine uygun olarak yapılırken, Kawasaki hastalığı tanısı Amerikan Kalp Derneği kılavuzlarına göre yapıldı.

Bulgular: Yetmiş bir MIS-C olgusu ve 27 Kawasaki hastalığı olgusu dahil edildi. MIS-C hastaları, Kawasaki hastalığı olgularına göre belirgin olarak daha kısa süreli ateş, daha yüksek C-reaktif protein seviyeleri ve yüksek cTnT troponin değerleri sergiledi. Transtorasik ekokardiyografik değerlendirme, MIS-C hastalarında özel kardiyak anormallikleri, mitral ve aort regürjitasyonunu içeren belirli kardiyak patolojileri ortaya çıkardı. ST segment değişiklikleri, T dalga negatifliği ve QRS değişiklikleri MIS-C hastalarında belirgin olarak gözlemlendi.

Sonuç: Sonuçlar, MIS-C olgularının EKG profil hakkında önemli bilgiler sağlamaktadır. Özellikle, ST segment değişiklikleri ve T dalga negatifliği gibi göstergeler, MIS-C'yi diğer benzer durumlardan ayırmada ve kardiyak etkilerini anlamada kritik bir rol oynamaktadır. Bu veriler, MIS-C'nin tanı ve tedavisinde kullanılabilecek değerli klinik işaretler sunmaktadır.

Anahtar kelimeler: Elektrokardiyografi, pediatrik, MIS-C, Kawasaki hastalığı

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INTRODUCTION

While the disease process was asymptomatic in childhood at the beginning of the coronavirus disease-2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2, in April 2020, the United Kingdom Pediatric Intensive Care Association

published an article on one deceased and seven survived patients with severe gastrointestinal system symptoms, toxic shock, high fever associated with COVID-19 that presented with a clinical picture similar to atypical Kawasaki disease with severe myocardial involvement[1]. This clinical condition was named "multisystem inflammatory syndrome in children (MIS-C)" by the World Health Organization (WHO) after similar case reports came from other countries.

Kawasaki disease in the differential diagnosis of MIS-C is a frequently confused clinical picture. Although the diagnostic criteria are mostly sufficient to establish a definitive diagnosis and treatment planning, in some cases making an accurate differential diagnosis is almost impossible. Overlapping clinical manifestations are frequently encountered. For the administration of human immunoglobulin and acetylsalicylic acid, which are the first treatment options in Kawasaki disease, a febrile period persisting up to 9 days is an acceptable indication. Since rapid clinical deterioration and shock are more prominent features in MIS-C, early diagnosis, and effective treatment carry vital importance[2].

In this study, we aimed to examine the conventional 12-lead electrocardiographic (ECG) changes detected at the time of admission of MIS-C cases diagnosed and followed up in our clinic during the COVID-19 pandemic.

MATERIALS and METHODS

Demographic, clinical, and laboratory information of cases diagnosed with MIS-C (n=71) and Kawasaki disease (n=27) between January 2019 and December 2021 were retrieved from hospital records after obtaining the necessary ethics committee approval. Ethics committee approval was obtained from the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee (decision no: 2022/11-06, date: 09.06.2022).

MIS-C was diagnosed according to the WHO criteria[3]. Patients between the ages of 0-19 years with ≥3 days of fever with at least two of the following diagnostic criteria; rash, conjunctivitis or mucocutaneous lesion, hypotension or shock, cardiac involvement (myocardial dysfunction, pericarditis, valvulitis or coronary artery anomaly), coagulopathy, increased sedimentation rate, C-reactive protein (CRP), and procalcitonin levels with

Table 1. Comparative evaluation of demographic, clinical, electrocardiographic findings, and serum cardiac troponin T levels of the patients

	Multiple systemic inflammatory syndrome	Kawasaki disease	p-value
Gender			
Male, n (%)	52 (73)	13 (48.1)	<0.05
Female, n (%)	19 (26.7)	14 (51.7)	<0.05
Transthoracic echocardiographic findings			
Mitral regurgitation (1-2 degrees), n (%)	19 (26.7)	4 (19)	
Aortic regurgitation, n (%)	4 (5.6)	1 (4.7)	
Pericardial effusion, n (%)	2 (2.8)	0	
LVSD, n (%)	9 (9.1)	0	
Coronary aneurysm, n (%)	0	1 (4.7)	
Normal, n (%)	46	21	
Electrocardiographic findings			
QRS change, n (%)	5 (7)	0	
T-wave change, n (%)	6 (8.4)	0	
ST segment change, n (%)	6 (8.4)	0	
Normal, n (%)	54 (76.2)	27	
Serum cardiac troponin T levels			
1-5 x ULN	6 (6)	1	0.02
5-10 x ULN	2 (2.8)	0	
10 x ULN	17 (23.9)	0	

LVSD: Left ventricular systolic dysfunction, ULN: Upper limit of normal

acute gastrointestinal symptoms were included in the MISC group.

American Heart Association (AHA) guidelines were used for the diagnosis of Kawasaki disease[4]. The diagnosis of Kawasaki disease was based on the presence of ≥5 days of fever and the presence of ≥4 of the 5 principal clinical features including extremity changes, rash, conjunctivitis, oral lesions, and servical lymphadenopathy.

ECG data were obtained retrospectively from conventional standard 12-lead ECG recordings (Philips Medical Systems, Andover, MA, USA) taken at 25 mm/s and 10 mm/mV at admission. PR interval, QRS, and RR measurements were calculated electronically from ECG recordings, and corrected QT interval (QTc) was estimated manually from leads D2 and V5 using Bazett's formula. T-wave amplitude was evaluated from leads D1 and V6, and R and S wave amplitudes were measured manually from leads V1, V4, and V6.

The ECG interpretation was performed according to the guideline published by the AHA Electrocardiography and Arrhythmias Committee[5]. Accordingly, cases with PR >98% according to age and gender were considered to have first-degree AV block. Age-, and gender-adjusted QRS, and QTc intervals >98 were defined as prolonged QRS, and QTc intervals, respectively. ST segment depression was diagnosed when ≥0.05 mV decrease in two or more contiguous leads was observed. ST-segment elevation was defined as ≥0.2 mV in V2/V3, and ≥0.1 mV increase in other leads. T-wave inversion was defined as ≥0.1 mV negativity in any lead, and T-wave negativity between V1-3 was defined as a juvenile pattern (if it was observed in the pediatric age group) was not considered as a pathological finding.

Statistical Analysis

For statistical analysis SPSS 18.0 software (SPSS Inc., Chicago, IL, USA) was used. To check for homogeneous distribution of data coming from two independent groups Kolmogorov-Smirnov test was used. Student's t-test was employed to compare homogeneously distributed data, and Mann-Whitney U test to compare data that did not show homogeneous distribution. The chi-square test was used to compare observed results with expected results.

RESULTS

Seventy-one cases with MIS-C (mean age: 8.5±5.1 years) and 27 patients diagnosed with Kawasaki disease (mean age: 2.4±2.1 years) in the same study period were included in the study ($p<0.05$). The MIS-C group consisted of 52 boys (73%), 19 girls (26.7%), and Kawasaki disease group included 13 boys (48.1%) and 14 girls (51.8%) ($p<0.05$).

The febrile period in the MIS-C group was significantly shorter than the Kawasaki disease group monitored during the same study period (4.76 vs. 6.6 days).

CRP levels were higher in MISC patients than those with Kawasaki disease (10.91 vs. 6.02) (CRP normal value <0.5 mg/dL).

Serum cardiac troponin T (cTnT) values increased 10 times the upper limit of normal (ULN) in 17 (23.9%), 5-10 times the ULN in 2 (2.8%), and 1-5 times the ULN in 6 (6%) patients (cTnT n<0.014 ng/dL). The cTnT levels increased in 7 (77.7%) of 9 patients with systolic dysfunction and ECG changes. Only one (4%) Kawasaki patient had a cTnT value between 1-5 times the ULN ($p<0.042$). The cTnT values of MIS-C patients were statistically significantly higher than those with Kawasaki disease ($p=0.02$).

In the transthoracic echocardiographic evaluation of MIS-C patients, mitral regurgitation (1-2 degrees) was found in 19 patients (26.7%), and aortic regurgitation in 4 patients (5.6%). Pericardial effusion was detected in 2 (2.8%) cases. Coronary artery aneurysm (left coronary artery, z+1.6) was detected in 1 (3.5%) Kawasaki disease patient. Left ventricular systolic dysfunction was detected in 9 (9.1%) patients. All patients with left ventricular systolic dysfunction were in the MIS-C group.

Seventeen (23.9%) MIS-C patients including the cases with ST segment changes (n=6; 8.4%), T-wave negativity (n=6; 8.4%), and QRS changes (n=5; 7%) received positive inotropic therapy. QRS fragmentation was observed in one of the patients with ST-segment changes. QRS changes were detected in 2, T-wave changes in 1, and ST segment changes in 4 patients who received positive inotropic therapy. Among 54 patients (76.1%) who did not need positive inotropic therapy alterations in QRS complexes (n=3), T-waves (n=1), and ST segments (n=5) were observed. No pathological ECG changes were detected in patients diagnosed with Kawasaki disease.

DISCUSSION

Although the pathophysiology of MIS-C is not known precisely, the alteration in T cell response after contact with COVID-19, ACE2 receptor-related pathologies, and hyperinflammatory clinical manifestations due to exaggerated interleukin response have been indicated

in its pathogenesis. Unlike Kawasaki disease, in some MIS-C patients, decreased number of naive CD4+ T cells, decreased follicular T helper cell expression, lower IL17A levels, and increased macrophage activation syndrome precursor interferon-γ levels have been detected[6-9]. The clinical findings of MIS-C syndrome, which are observed in clinical practice with the onset of COVID-19 pandemic, show similarities to those of Kawasaki disease[10]. Although history of COVID-19 infection or contact with infected persons is an indispensable diagnostic criterion for MIS-C syndrome, due to its clinical similarity, it is an obvious fact that the physicians caring for these patients need parameters that will help in the decision-making process and arriving at a differential diagnosis.

While Kawasaki disease is typically seen in early infancy (<5 years), MIS-C can be seen at any age, and it is significantly more common in men. Febrile period is shorter in MIS-C patients (4.76 vs. 6.6 days, $p<0.05$) compared to those with Kawasaki disease. In MIS-C patients, left ventricular systolic dysfunction and mitral valve regurgitation were detected by echocardiography at a significantly higher rate compared to Kawasaki disease, and greater number of patients required inotropic treatment and monitoring in pediatric intensive care unit ($p<0.05$). Higher cTnT levels, and more intense inflammation have been detected in MIS-C patients[11], but there was no coronary artery involvement in echocardiographic evaluation, unlike reported by Sperotto et al.[12] in a multicenter study. ST segment changes and T-wave polarization changes were much more frequently detected in our MIS-C patients compared to our patients with Kawasaki disease, which shares similar clinical and biochemical characteristics with MIS-C. We linked the relevant ECG changes to the presence of more extensive systemic involvement and metabolic stress due to the severe inflammatory process in MISC which would increase the possibility of cardiac involvement. We found that the cTnT levels were higher in patients with ST-segment changes and T-wave depolarization disorders detected on ECG. Systolic dysfunction was observed only in MIS-C patients. Cardiac troponin T levels of these patients were significantly higher. However, although few of these MIS-C patients (6%) had troponin positivity and needed inotropic therapy, any pathological change was not observed in ECG. cTnT values were elevated in all patients who needed IV inotropic therapy.

Since our study patients were admitted to our clinic during the pandemic period, the data we obtained during COVID-19 outbreak were of great benefit when evaluating the patients in terms of their exposure to COVID-19 or clinical discrimination of patients with negative COVID-19 IG-G antibodies. In contrast to the case series of Villacis-Nunez et al.[13] in which they detected giant coronary artery aneurysms, coronary artery aneurysms were not detected in any of our MIS-C patients, thanks to the early initiation of medical treatment in our patients diagnosed with MIS-C. The rate of correct diagnosis increased thanks to our criteria for differential diagnosis between MIS-C, and Kawasaki disease which based on number of febrile days, increased CRP, and cTnT levels, presence of systolic dysfunction, and ECG changes. Detecting ECG findings in MIS-C patients that we did not expect to see in cases with Kawasaki disease facilitated our diagnostic process[14].

Study Limitations

The study was conducted in a single clinic, possibly limiting the external validity of the results, as the population characteristics may not represent the broader demographic diversity. The study was conducted during the COVID-19 pandemic, and the unique circumstances of the healthcare system during this period could introduce confounding variables that may impact the internal validity of our study findings.

CONCLUSION

This study delves into the ECG findings in pediatric patients diagnosed with MIS-C during the COVID-19 pandemic, offering valuable insights into the diagnostic process and highlighting differences from Kawasaki Disease. The MIS-C group exhibited distinct clinical characteristics, including a shorter duration of fever, higher CRP levels, and significantly elevated cTnT values. Echocardiographic evaluations revealed more frequent left ventricular systolic dysfunction in MIS-C patients. Importantly, ECG abnormalities, such as ST segment changes and T-wave polarization disorders, were more prevalent in MIS-C, emphasizing the potential for cardiac involvement in this syndrome. The study underscores the significance of considering ECG changes as diagnostic aids in differentiating MIS-C from Kawasaki disease in pediatric populations. The findings contribute to the understanding of unique ECG profile of MIS-C, aiding clinicians in the timely and accurate diagnosis of this syndrome during the ongoing pandemic.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and

Surgery Training and Research Hospital Ethics Committee (decision no: 2022/11-06, date: 09.06.2022).

Informed Consent: Retrospective study.

Author Contributions

Surgical and Medical Practices: M.M.B., Concept: M.M.Y., G.V., Design: M.M., C.D., Data Collection or Processing: C.K., Analysis or Interpretation: M.M.Y., Literature Search: T.M., Writing: M.M.B.

Conflict of Interest: The authors have no conflict of interest to declare.

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