Original Investigation / *Özgün Araştırma*

DOI: 10.5578/ced.20219605 • *J Pediatr Inf 2021;15(4):e229-e234*

Transient Sinus Bradycardia in Children with Multisystem Inflammatory Syndrome Associated with COVID-19

COVID-19 ilişkili Multisistem İnflamatuvar Sendromlu Çocuklarda Geçici Sinüs Bradikardisi

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Cite this article as: Yalçınkaya R, Polat M, Gümüşer Cinni R, Özdem S, Savaş Şen Z, Kızılkaya MH, et al. Transient sinus bradycardia in children with multisystem inflammatory syndrome associated with COVID-19. J Pediatr Inf 2021;15(4):e229-e234.

Abstract

Objective: Multisystem inflammatory syndrome in children (MIS-C) may cause cardiovascular involvement and dysrhythmia. Although a variety of arrhythmias may be seen, sinus bradycardia was rarely reported. The aim of this study is to determine the frequency and clinical course of bradycardia in children with MIS-C.

Material and Methods: Medical records of patients who were diagnosed with MIS-C between August 2020 and March 2021 were retrospectively evaluated. MIS-C diagnosis was made according to US Centers for Disease Control and Prevention (CDC) criteria. All patients who had sinus bradycardia were included in the study.

Results: Transient sinus bradycardia was observed in 7 of 40 (17.5%) patients (2 girls, 5 boys) with MIS-C. The median age was 10.8 years (range, 5.4-13.8 years). All patients were initially treated with intravenous immunoglobulin (IVIG) and six out of the seven patients also received intravenous methylprednisolone (MPZ). Sinus bradycardia developed a median of four days (range, 2-6 days) after MIS-C diagnosis and continued for a median of four days (range, 2-6 days). In six of the seven patients, bradycardia was detected a median of 42 hours (range, 11-74 hours) after MPZ treatment and resolved a median of 36 hours (range, 20-50 hours) after tapering MPZ dosage. Electrocardiogram (ECG) of patients showed sinus bradycardia. All patients were asymptomatic and awake when bradycardia was observed. No patients had any underlying structural heart defect or electrolyte abnormalities. Bradycardia episodes resolved without any specific intervention.

Öz

Giriş: Çocuklarda multisistem inflamatuvar sendrom (MIS-C), kardiyovasküler sistem tutulumu ve disritmilere neden olabilir. Çeşitli aritmiler görülmesine rağmen sinüs bradikardisi nadiren bildirilmiştir. Bu çalışmada MIS-C nedeni ile izlenen hastalarda bradikardi gelişiminin sıklığı ve klinik özelliklerinin belirlenmesi amaçlandı.

Gereç ve Yöntemler: Ağustos 2020 ile Mart 2021 tarihleri arasında MIS-C tanısı alan hastaların tıbbi kayıtları geriye dönük olarak incelendi. MIS-C tanısı, Amerika Birleşik Devletleri Hastalık Kontrol ve Önleme Merkezleri (CDC) tanı kriterlerine göre konuldu. Sinüs bradikardisi saptanan hastalar çalışmaya dahil edildi.

Bulgular: MIS-C tanılı toplam 40 hastanın 7'sinde (%17.5) (iki kız, beş erkek) geçici sinüs bradikardisi görüldü. Ortalama yaş 10.8 yıl (aralık 5.4-13.8 yıl) olarak saptandı. Tüm hastalar başlangıçta intravenöz immünoglobulin (IVIG) ile tedavi edildi ve altı hastaya ek olarak intravenöz metilprednizolon (MPZ) tedavisi verildi. Sinüs bradikardisi, MIS-C tanısından ortanca dört gün (aralık, 2-6 gün) sonra saptandı ve ortanca dört gün boyunca (aralık, 2-6 gün) devam etti. Yedi hastanın altısında MPZ tedavisinden ortanca 42 saat (aralık, 11-74 saat) sonra bradikardi gelişti ve MPZ dozunun azaltılmasından ortanca 36 saat (aralık, 20-50 saat) sonra düzeldi. Hastaların elektrokardiyogram (EKG) incelemesi sinüs bradikardisi ile uyumlu bulundu. Bradikardi saptandığında tüm hastalar asemptomatikti ve uyanıktı. Hastaların hiçbirinde altta yatan kardiyak anomali veya elektrolit bozukluğu saptanmadı. Tüm bradikardi atakları herhangi bir tedavi veya müdahale olmaksızın düzeldi.

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Received: 12.05.2021 **Accepted:** 30.06.2021 **Available Online Date:** 29.12.2021

Conclusion: Sinus bradycardia may occur due to the cardiac involvement of MIS-C itself or as a possible side effect of MPZ therapy, which can resolve without any specific treatment.

Keywords: Bradycardia, child, methylprednisolone, SARS-CoV-2

Sonuç: Sinüs bradikardisi, MIS-C'nin kardiyak tutulumuna bağlı olabileceği gibi MPZ tedavisinin bir yan etkisi de olabilir ve herhangi bir tedaviye gerek olmadan kendiliğinden düzelebilir.

Anahtar Kelimeler: Bradikardi, çocuk, metilprednizolon, SARS-CoV-2

Introduction

Multisystem inflammatory syndrome in children (MIS-C) is diagnosed when fever, systemic inflammation, at least two signs of multisystem involvement, and evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or previous exposure is present (1). Cardiovasculary involvement may be seen in a wide spectrum including myocarditis, coronary artery dilatation, ventricular dysfunction, and arrhythmia. Arrhythmias were reported in 7–60% of the patients with MIS-C (2). Although a variety of arrhythmias may be seen such as heart block, atrial or ventricular tacychardia, ST segment changes, QT prolongation; sinus bradycardia was rarely reported. The aim of this study is to determine the frequency and clinical course of sinus bradycardia in children with MIS-C.

Materials and Methods

Medical records of 40 patients who were diagnosed with MIS-C between August 2020 and March 2021 were retrospectively evaluated. Seven patients who had sinus bradycardia were included in the study. Patients' demographic and clinical features, laboratory parameters, bradycardia related characteristics (timing and duration of bradycardia, resolving time of bradycardia, association between the bradycardia and the treatments utilized, heart rate, and electrocardiographic (ECG) findings) were recorded. MIS-C diagnosis was made according to US Centers for Disease Control and Prevention (CDC) criteria when all these 4 criteria were present:

1. Age <21 years
2. Clinical presentation consistent with MIS-C, including all of the following:
    a. Fever ≥38.0°C for ≥24 hours
    b. Laboratory evidence of inflammation (Including but not limited to one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase (LDH), interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin)
    c. Multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)
    d. Evidence of clinically severe illness requiring hospitalization
3. No alternative plausible diagnoses
4. Positive for current or recent SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR), serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the four weeks prior to the onset of symptoms (1).

All patients were initially treated with intravenous immunoglobulin (IVIG, 2 gr/kg). Intravenous methylprednisolone (MPZ) was added to treatment (2 mg/kg/day in 2 doses) if fever persisted and/or clinical and laboratory deterioration continued despite the IVIG therapy. The MPZ treatment was utilized in 24 (60%) out of 40 patients. The MPZ dose was tapered at intervals of five days, starting from 2 mg/kg/day, reduced to 1 mg/kg/day, and finally to 0.5 mg/kg/day when patients improved clinically.

Bradycardia was defined as having a heart rate (HR) below the 10th percentile for age in the awake state (3). Any bradycardia that developed during sleep was not recorded. When bradycardia was observed, ECG and 24-hour ECG Holter monitoring were performed. All ECGs were recorded at 25 mm/second paper speed, PR intervals were recorded, and QTc was calculated with Bazett's formula (QTc = QT/√RR interval). All children were closely monitored in terms of vital signs which was recorded at least 12 times a day.

The statistical analyses of this study were performed via the SPSS software (version 22.0) for the Windows operating system. Normality of distribution in continuous variables was assessed with Q-Q plots and the Shapiro Wilk test. Given the presence of normal distribution, comparisons between groups were performed with the Student's t-test; whereas, the Mann-Whitney U test was used to compare variables without normal distribution. The distributions of categorical characteristics in the two groups were compared with Chi-squared tests. Any p-value lower or equal to 0.05 was accepted to demonstrate statistical significance.

Ethical approval was obtained from the Ethics Committee of our institution (E-20/12-044).

Results

A total of 40 patients with MIS-C of whom 36 (90%) had cardiac involvement were evaluated in our clinic. Of these, 24 (%60) were treated with MPZ. Transient sinus bradycardia was observed in 7 of 40 (17.5%) patients (two girls, five boys). The median age was 10.8 years (range, 5.4-13.8 years). All seven patients received IVIG therapy and six of them were also treat-

ed with MPZ. Sinus bradycardia developed after a median of four days (range, 2-6 days) after MIS-C diagnosis, continued for a median of four days (range, 2-6 days). Bradycardia was first detected after a median of 46 hours (range, 26-106 hours) after completion of IVIG infusion. In six of the seven patients, bradycardia was detected a median of 42 hours (range, 11-74 hours) after MPZ treatment and resolved a median of 36 hours (range, 20-50 hours) after tapering MPZ dosage. The demographic and clinical findings of patients and bradycardia related characteristics are shown in Table 1. The follow-up data of each patient, including the mean and lowest HR, bradycardia episodes, and treatments are also shown in Figure 1.

Table 1. Clinical features of patients with MIS-C who had transient sinus bradycardia

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (years)	5.4	6.2	9	10.8	11.6	12.5	13.8
Gender	M	M	F	M	F	M	M
Reference HR values by age, 10th percentile*	81 bpm	74 bpm	67 bpm	67 bpm	67 bpm	62 bpm	62 bpm
Reference HR values by age, 1st percentile*	65 bpm	59 bpm	52 bpm	52 bpm	52 bpm	47 bpm	47 bpm
Bradycardia related characteristics							
Timing of bradycardia							
From diagnosis, days	5 d	3 d	6 d	6 d	4 d	4 d	2 d
From initiation of steroids, hours	36 h	22 h	64 h	Not treated with steroids	48 h	74 h	11 h
From completion of IVIG infusion, hours	70 h	26 h	106 h	74 h	41 h	46 h	27 h
Time of day	7 AM	8 AM	7 AM	8 AM	8 AM	10 PM	7 AM
Duration of bradycardia, days	4 d	5 d	4 d	2 d	5 d	4 d	6 d
Lowest HR	62 bpm	52 bpm	50 bpm	60 bpm	56 bpm	54 bpm	42 bpm
Mean HR	72.9 bpm	59.6 bpm	72.5 bpm	73.3 bpm	71.5 bpm	69 bpm	58 bpm
ECG rhythm	Sinus bradycardia	Sinus bradycardia	Sinus bradycardia	Sinus bradycardia	Sinus bradycardia	Sinus bradycardia	Sinus bradycardia
24-hour Holter ECG monitoring	Not performed	Normal	Normal	Normal	Not performed	Not performed	Normal
PR interval (sec)	0.14 s	0.18 s	0.14 s	0.12 s	0.18 s	0.16 s	0.18 s
Corrected QT (QTc) (sec)	0.41 s	0.40 s	0.41 s	0.42 s	0.39 s	0.37 s	0.40 s
Symptoms	None	None	None	None	None	None	None
Resolving time of bradycardia							
From tapering the steroid dose to 1 mg/kg/day, hours	20 h	50 h	28 h	Not treated with steroids	27 h	31 h	41 h
Echocardiographic findings	MR, TR, depressed LV function	MR, depressed LV function	MR, depressed LV function	MR, depressed LV function	MR, depressed LV function	Coronary artery dilatation, MR, TR, depressed LV function	MR
Abnormal serum electrolytes	None	None	None	None	None	None	None
Mean HR before discharge	100 bpm	92 bpm	96 bpm	96 bpm	92 bpm	82 bpm	78 bpm

ECG: Electrocardiography, F: Female, HR: Heart rate, IVIG: Intravenous immunoglobulin, LV: Left ventricle, M: Male, MIS-C: Multisystem inflammatory syndrome in children, MR: Mitral valve regurgitation, TR: Tricuspid valve regurgitation
*Data taken from reference 3.

All patients were asymptomatic and awake; all bradycardia episodes were mostly observed in morning hours. Electrocardiogram of patients showed sinus bradycardia without prolonged PR or QT intervals. None of the patients had any conditions that might have caused the bradycardia, including structural/congenital heart defects and electrolyte abnormalities.

Bradycardia developed in 6 (25%) of 24 patients treated with MPZ. In those who did not receive MPZ treatment (n= 16), bradycardia development was present in only 1 (6.2%) patient. When the patients with MIS-C were compared in terms of bradycardia, there was no significant difference between those who received and did not receive MPZ treatment (p= 0.126).

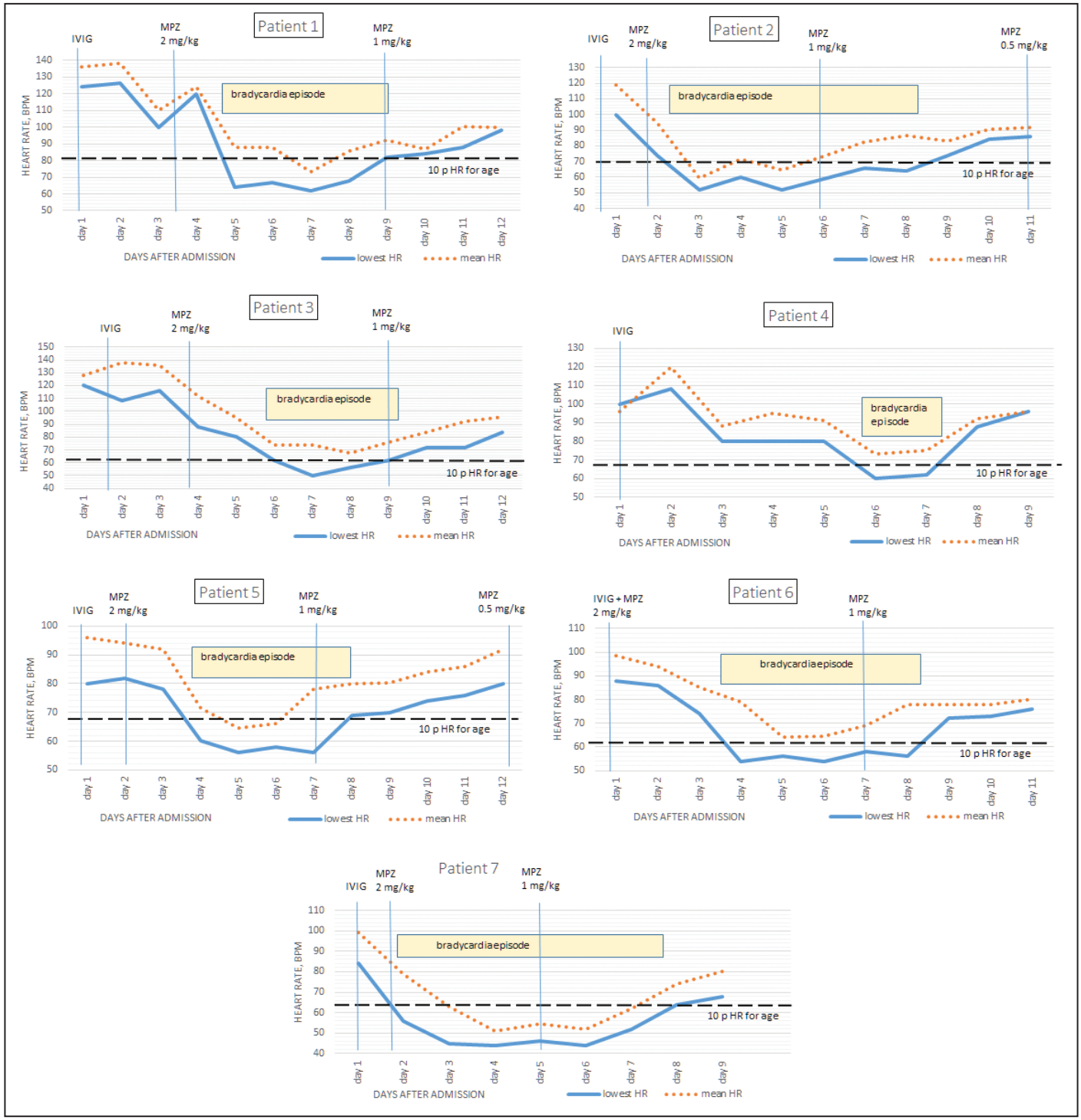

Figure 1. The follow-up data of each patient, including the mean and lowest HR, bradycardia episodes, and treatments.
HR: Heart rate, IVIG: Intravenous immunoglobuline, MPZ: Methylprednisolone, p: Percentile.

Discussion

MIS-C has emerged as a condition that is associated with cardiovascular involvement and dysrhythmia. Abnormal cardiac rhythms have been reported at a frequency from 7% to 60% in patients. The most commonly reported abnormal ECG findings were ST-segment changes, QTc prolongation, and premature atrial or ventricular beats (2). In a study that described ECG findings of 63 MIS-C patients, the authors found that 13 (21%) had arrhythmia. Among these, 11 had transient bradyarrhythmia of which four were identified to have first-degree atrioventricular block (AVB) (4). Another report of 25 children with MIS-C showed ECG abnormalities in 14 patients (56%), 6 (19%) of those had first-degree AVB, and 7 (28%) had QTc prolongation (5). However, sinus bradycardia was not reported in any of these studies (4,5). In this study, sinus bradycardia was observed in 17.5% of MIS-C patients in the first week of diagnosis.

In children, the most common reasons for bradycardia is known as follows: sleep, medications, hypoxia, hypothermia, hyperkalemia. Mild bradycardia is commonly asymptomatic; however, fatigue, dizziness, and syncope may be seen. Our patients' body temperature, blood pressure, and oxygen saturation were all normal throughout bradycardia episodes. All patients were in an awake state and none had any complaints. Considering the lack of any particular cause for the bradycardia and the fact that all other possible causes were excluded, we believe it is feasible to associate these patients' bradycardia with either MIS-C itself or the medications being used for its treatment.

The treatment regimen of MIS-C includes IVIG and steroids. Cardiac side effects of IVIG are uncommon. A single case report described sinus bradycardia in an adult patient after IVIG infusion, which resulted in the lowest HR of 30 bpm (6); however, to our knowledge, no pediatric cases of IVIG-related bradycardia have been reported. Methylprednisolone is known as a potential cause of bradycardia in children, albeit infrequently. The exact mechanism of bradycardia is unknown; however, a single dose of MPZ was shown to cause a depression of cardiovascular β receptor sensitivity in animal studies (7). In a recent study that included patients with severe KD, the authors compared patients treated with only IVIG to those treated with IVIG plus prednisolone. The HR of patients in the IVIG plus prednisolone group was significantly lower than the IVIG group. They suggested that a standard dose of prednisolone might be associated with bradycardia (8). A similarity to this report was the fact that all cases of bradycardia were resolved without any additional intervention.

Preliminary data shows that the HR returns to normal when steroid therapy is discontinued or when the dose is reduced in patients diagnosed with steroid-related bradycardia (9). In the current study, MPZ therapy was continued with the standard protocol tapering in 5-day intervals, and no specific treatment was applied to correct bradycardia. As a result of close HR monitoring, we noticed that most of the bradycardia episodes resolved median 36 hours after tapering the dose to 1 mg/kg/day in our patient group. The dose of steroid that caused bradycardia showed variety in the reports. In one report that evaluated two children with epileptic spasms, the authors observed bradycardia with 3.8 mg/kg/day and 8 mg/kg/day dosage of oral prednisolone (9). Another report suggested that bradycardia was observed in five children with rheumatic diseases after treating with pulse MPZ and the dosage was 30 mg/kg/day (10). All MIS-C patients in our report were treated with the dosage of 2 mg/kg/day of intravenous MPZ, which seems a lower dosage than previously reported cases; even so, bradycardia occurred.

As conclusion, clinicians should be aware of the development of sinus bradycardia which may be a result of either cardiac involvement of MIS-C or the possible adverse effect of MPZ treatment.

Ethics Committe Approval: The study was approved by the Dr. Sami Ulus Children's Health and Diseases Training and Research Hospital Clinical Research Ethics Committee (Decision no: E-20/12-044, Date: 03.12.2020).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - RY, MP, FNÖ, GT; Design - RY, MP, FNÖ; Supervision - RY, MP, FNÖ, GT; Resource - All of authors; Data Collection and/or Processing - All of authors; Analysis and/or Interpretation - RY, RGC, SÖ, ZSŞ, MHK; Literature Search - RY, RGC, SÖ, ZSŞ; Writing - RY, MP, FNÖ; Critical Review - MP, FNÖ, GT.

Conflict of Interest: All authors declare that they have no conflicts of interest or funding to disclose.

Financial Disclosure: The authors declared that this study has received no financial support.

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