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COVID-19 Associated Multisystem Inflammatory Syndrome in Adults (MIS-A): How Aware Are We?

Erişkinlerde COVID-19 İlişkili Multisistem İnflamatuvar Sendromu: Ne Kadar Farkındayız?

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ABSTRACT

Introduction: *Multisystem inflammatory syndrome-in adults (MIS-A), which occurs as a post-acute syndrome associated with COVID-19, is rarely seen and does not come to mind as in pediatric patients. Therefore, it was aimed to raise awareness that MIS-A, which can occur with different clinical presentations and findings, should be considered in the differential diagnosis with this study.*

Materials and Methods: *Of 4984 patients found positive SARS-COV-2 reverse transcriptase-polymerase chain reaction test (RT-PCR) between March 24, 2020 and June 14, 2021, the files of 370 patients hospitalized within 2-12 weeks after their PCR positivity were investigated retrospectively. Analysis results of six cases meeting the MIS-A criteria defined by the American Center for Disease Control and Prevention were evaluated. The results were analyzed using the SPSS program.*

Results: *Six cases meeting the MIS-A criteria were evaluated. Mean age of the six patients was 44.7 ± 10.2 years. Fever (≥38.0°C) was detected in all patients. Gastrointestinal and cardiovascular systems were the two most commonly involved systems. Two patients had nonpurulent conjunctivitis and mucocutaneous involvement. In laboratory examination, all patients had high inflammatory indicators. Although no patient was diagnosed with MIS-A, it was found that all patients received corticosteroid therapy. Finally, none of the patients were mortal.*

Conclusion: *We think that MIS-A should be included in the differential diagnosis in patients with increased inflammation and coagulation parameters along with multisystemic symptoms. However, we claim that it would be fitting to develop a warning system over hospital automation for cases with appropriate clinical and laboratory data to reduce the possibility of skipping the diagnosis due to the emergence of MIS-A with various clinical and system involvements.*

Key Words: *Multisystem inflammatory syndrome; MIS-A; Complication; COVID-19; Early diagnosis*

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ÖZ

Erişkinlerde COVID-19 İlişkili Multisistem İnflamatuvar Sendromu: Ne Kadar Farkındayız?

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Giriş: *COVID-19 ile ilişkili post-akut sendrom olarak ortaya çıkan multisistem inflamatuvar sendromu (MIS-A) erişkinlerde nadiren görülmekte, pediyatrik hastalarda olduğu kadar akla gelmemektedir. Bu nedenle, bu çalışma ile farklı klinik prezentasyon ve bulgularla ortaya çıkabilen MIS-A'nın ayırıcı tanıda düşünülmesi gerektiği konusunda farkındalık yaratmak amaçlanmıştır.*

Materyal ve Metod: *SARS-COV-2 revers transkriptaz-polimeraz zincir reaksiyonu (RT-PZR) testi 24 Mart 2020 ile 14 Haziran 2021 tarihleri arasında pozitif bulunan 4984 hastadan, PZR pozitifliği sonrası 2-12 hafta içinde hastaneye yatırılan 370 hastanın dosyaları retrospektif olarak incelendi. Amerikan Hastalık Kontrol ve Önleme Merkezi tarafından tanımlanan MIS-A kriterlerini karşılayan altı olgunun analiz sonuçları değerlendirildi. Sonuçlar SPSS programı kullanılarak analiz edildi.*

Bulgular: *MIS-A kriterlerini karşılayan altı vaka değerlendirildi. Altı hastanın yaş ortalaması 44.7 ± 10.2 yıl idi. Tüm hastalarda yüksek ateş (≥38.0°C) tespit edildi. Gastrointestinal ve kardiyovasküler sistemler en sık tutulan iki sistemdi. İki hastada non-pürülan konjonktivit ve mukokutanöz tutulum birlikteliği vardı. Laboratuvar incelemesinde tüm hastalarda yüksek inflamatuvar göstergeleri mevcuttu. Hiçbir hastaya MIS-A tanısı konmamasına rağmen, tüm hastaların kortikosteroid tedavisi aldığı tespit edildi. Son olarak, hiçbir hasta mortal seyretmedi.*

Sonuç: *İnflamasyon ve pıhtılaşma parametreleri artmış, multisistemik semptomları olan hastalarda MIS-A'nın ayırıcı tanıda yer alması gerektiğini düşünüyoruz. Ancak, MIS-A'nın çeşitli klinik ve sistem tutulumlarıyla ortaya çıkması nedeniyle, tanının atlanma olasılığını azaltmak amacıyla, uygun klinik ve laboratuvar verileri olan vakalar için hastane otomasyonu üzerinden bir uyarı sistemi geliştirilmesi de yerinde olacaktır.*

Anahtar Kelimeler: *Multisistem inflamatuvar sendromu; MIS-A; Komplikasyon; COVID-19; Erken tanı*

INTRODUCTION

The disease caused by SARS-CoV-2 was named COVID-19 and the pandemic was declared in March 2020, which marked the start of a global effort to inhibit the spread, clarify the pathogenesis of the disease, and likewise, find successful and reliable treatment and vaccine[1]. However, post-disease consequences for those infected with COVID-19 started to illuminate.

SARS-CoV-2 infection, which had critical importance at the beginning of the pandemic due to its high contagiousness, mortality, and morbidity, has gained even more significance with the emergence of manifestations with severe post-COVID sequelae in the following days. As the pandemic has gradually proceeded, the incidence of a new multisystem inflammatory syndrome (MIS-C) with clinical features similar to Kawasaki Disease in children has been reported to increase in Europe and the United States[2-4]. Afterwards, life-threatening hyperinflammatory condition has been observed in the next 2-6 weeks after the primary COVID-19 infection in adults. Multisystem Inflammatory Syndrome-in Adults (MIS-A) has been defined as a post-COVID complication in adults with similar characteristics. The Centers for Disease Control and Prevention (CDC) notes that MIS-A cases have been reported since June 2020[5]. In the report, in which 16 adult patients diagnosed with MIS-A in the United Kingdom and the USA evaluated, it was seen that almost all of the patients had findings of cardiovascular system pathology[6,7]. Both MIS-A and MIS-C are characterized by multi-organ involvement as a result of an impaired immune response, with serological/molecular evidence of COVID-19, 2-6 weeks prior to the diagnosis. The diagnosis rate of MIS-A is lower than MIS-C since the clinical picture is presented with different system

involvements, and these symptoms and signs are not considered as they are frequently seen in adult patients.

Therefore, this study aimed to raise awareness of MIS-A to promote its likeliness as a preliminary diagnosis. Additionally, we revealed MIS-A clinical and laboratory findings and outcomes.

MATERIALS and METHODS

Study Design and Patient Selection

This retrospective observational study consisted of adult patients aged 21-90 years who were found as positive for the SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) test between March 24, 2020 and June 14, 2021 and met the MIS-A criteria defined by the CDC within 2-12 weeks after PCR positivity[8].

Inclusion criteria

- Clinical criteria

- Age≥ 21
- Patients with subjective or documented fever (≥38.0°C) ≥24 hours before admission or within three days of hospitalization;
- At least three of the following clinical criteria, of which at least one is the primary clinical criterion, occur before or within the first three days after hospitalization:

A. Primary clinical criteria

1. Serious cardiac disease (myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (LVEF< 50%), degree 2/3 AV block or ventricular tachycardia (Cardiac arrest alone does not meet the criteria.)

2. Rash and nonpurulent conjunctivitis

B. Secondary Clinic criteria

1. New-onset neurological signs and symptoms (peripheral neuropathy including encephalopathy, seizure, meningeal signs, or Guillain-Barré syndrome without prior cognitive impairment)

2. Shock or hypotension independent of medical treatment

3. Abdominal pain, vomiting, or diarrhea

4. Thrombocytopenia (<150000/μL)

- Laboratory criteria

Increase in at least two inflammatory markers: C-reactive protein (CRP), ferritin, interleukin-6 (IL-6), erythrocyte sedimentation rate, procalcitonin

SARS-CoV-2 PCR/Antigen/Antibody positivity

Exclusion criteria

- Patients in whom bacterial infection/sepsis could not be excluded,
- Patients with positivity in any microbiological culture,
- Patients who had an alternative diagnosis to MIS-A.

Data Collection

Data regarding patients' epidemiological, clinical, radiological, and other imaging characteristics, comorbid status, laboratory findings, symptoms, treatments, and outcomes were obtained by retrospective electronic patient records review. The lowest levels of serum lymphocyte, thrombocyte, and the peak levels of other tests were recorded.

Statistical Analyses

Data were analyzed using SPSS Statistics version 22.0 software (IBM Corp, Armonk, NY, USA). Continuous variables were evaluated for normal distribution using the Shapiro-Wilk test. Categorical variables were expressed as frequency (n) and percentage (%), continuous variables that met the assumptions for parametric tests were presented as mean and standard deviation (SD), and those that did not were presented as median, minimum, and maximum values.

RESULTS

Between March 24, 2020 and June 14, 2021, out of 4984 cases with positive SARS-CoV-2 RT-PCR test, 370 cases were hospitalized within 2-12 weeks after PCR positivity, and in a retrospective analysis, six of them were found to meet the MIS-A criteria defined by CDC (Figure 1). Our hospital is a tertiary training and research hospital with 1500 beds and a COVID-19 follow-up and treatment center.

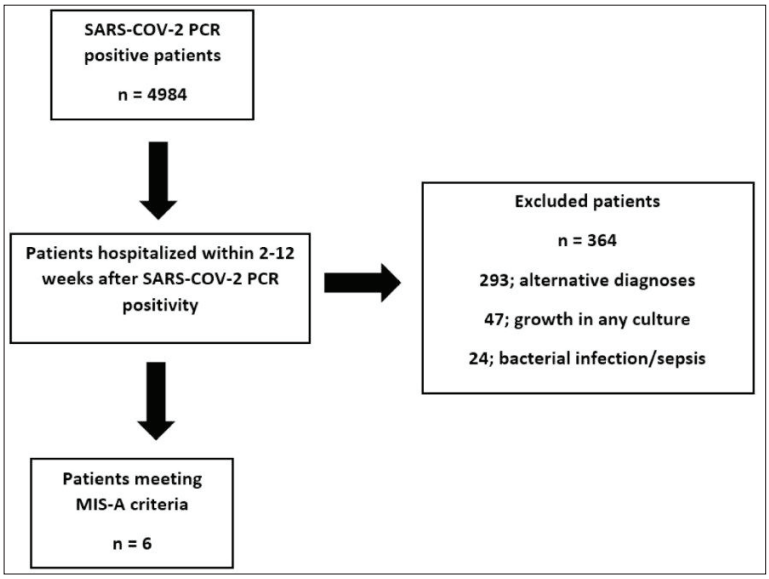

Figure 1. Flowchart of patient selection.

Demographic, clinical, imaging, and laboratory features of the cases are shown in Table 1. Six patients with MIS-A had a mean age of 44.7 ± 10.2, and 4 (66.7%) of the patients were females. The time between PCR positivity and MIS-A symptoms was 25.5 ± 5.1 days, and the hospitalization period after to diagnosis of MIS-A was 14.8 ± 3.1 days. Four of the patients had no comorbid disease. Patients had not received the COVID-19 vaccine.

The clinic that all patients applied to when they met the MIS-A criteria was the emergency department. All of the patients had a subjective fever. All patients had a high fever at admission to the hospital. Gastrointestinal system involvement was the most common (n= 5, 83.3%) and the cardiovascular system was in second place. All patients with cardiac involvement (n= 4, 66.7%) had congestive heart failure and dyspnoea secondary to myocarditis/ myopericarditis. It was determined that all patients with cardiovascular system involvement and heart failure received oxygen support, and one of these patients was followed up with mechanical ventilation. While one of six patients was in shock, he was provided vasoactive treatment. Two patients were found to have mucocutaneous rash and nonpurulent conjunctivitis. The patients' demographical, clinical, laboratory, and imaging features, and complications are shown in Table 1. A concomitant encephalopathy clinic was found in two patients. One of these patients -a 54-year-old female patient- was observed to have encephalopathy presentation with multiple cranial nerves involvement on physical examination. Additionally, the patient had nonpurulent conjunctivitis in the left eye and limited gaze in all directions, and involvement of three, four, five, six, seven, and 8th cranial nerves accompanied by left facial paralysis. No cells were detected in the cerebrospinal fluid (CSF) in the lumbar puncture performed to rule out central nervous system (CNS) infection and other diseases involving the CNS. At the same time, CSF oligoclonal immunoglobulin band electrophoresis, mycobacterial and viral panel PCR, Brucella, serum autoimmune panel, and Brucella tests were negative. Serum IgG and IgM values were observed to be within normal limits. Lastly, it was reported that the patient was discharged with right hemiplegia and permanent blindness.

When the laboratory findings of the patients were examined, it was seen that inflammation indicators such as serum leukocyte, polymorphonuclear leukocyte (PMNL), ferritin, CRP, and procalcitonin were higher than the values observed during patients were going

Table 1. Demographic, clinical, and laboratory characteristics of the patients

Patient	Age Sex Comorbidity	Time from PCR positivity to the clinic (day)	Clinical features	Imaging findings	Laboratory findings	Treatment	Complications
1	26 Female No comorbidity	25	Chest pain, fever (38.2°C), dyspnoea, vomiting, palpitation, presyncope	ECG: ST segment change, myopericarditis Echocardiography: EF: 30%, LV systolic dysfunction, pericardial effusion, pericardial thickening Chest CT: Pulmonary edema, pleural effusion	WBC: 11600/µL Platelet: 126 x 10^3/µL Ferritin: 1120/µg/L CRP: 72 mg/L Procalcitonin: 0.16 µg/L Troponin I: 3808 ng/L	HFNO Corticosteroid Colchicum dispert LMWH	Congestive heart failure, arrhythmia, myopericarditis
2	48 Female No comorbidity	26	Fever (38.6°C), dyspnoea, chest pain, abdominal pain, vomiting, diarrhea	ECG: ST segment change, abnormal T wave Echocardiography: EF: 40%, Apex and apical septum anterior midapical akinetic-aneurysmatic Chest CT: Bilateral ground glass opacity, pulmonary edema, pleural effusion	WBC: 16000/ µL Platelet: 212 x 10^3/µL Ferritin: 624 µg/L CRP: 153 mg/L Procalcitonin: 0.25 µg/L Troponin I: 3477 ng/L	HFNO Corticosteroid Colchicum dispert LMWH Antiplatelet medication	Congestive heart failure, arrhythmia, myocarditis
3	41 Male No comorbidity	17	Shock, dyspnoea, fever (38.3°C), abdominal pain, diarrhea, encephalopathy	ECG: Sinus tachycardia, abnormal T wave Echocardiography: EF: 15%, global hypokinesia Chest CT: Pleural effusion	WBC: 34000/µL Platelet:118 x 10^3/µL Ferritin: 883 µg/L CRP: 172 mg/L Procalcitonin: 0.72 µg/L Troponin I: 391 ng/L	Mechanical ventilation Vasoactive agents Corticosteroid Colchicum dispert	Congestive heart failure, arrhythmia, myocarditis
4	54 Female Hypertension	24	Fever (38.2°C), headache, myalgia, vision loss, encephalopath, conjunctivitis, mucocutaneous lesions, cranial nerve involvement (3-4,5,6,7,8)	ECG: Nonspecific ST segment change Echocardiography: EF: 70% Chest CT: Bilateral ground glass opacity and nodular infiltrates Brain MRI: Edema in the left frontoparietal region and diffusion restriction MR venography: No pathology	WBC: 16700/µL Platelet: 206 x 10^3/µL Ferritin: 377 µg/L CRP: 77 mg/L Procalcitonin: 0.18 µg/L	Nasal oxygen Corticosteroid LMWH Antiplatelet medication	Encephalitis, right hemiplegia, blindness

Table 1. Demographic, clinical, and laboratory characteristics of the patients (continue)

Patient	Age Sex Comorbidity	Time from PCR positivity to the clinic (day)	Clinical features	Imaging findings	Laboratory findings	Treatment	Complications
5	47 Female Diabetes mellitus	32	Fever (38.1°C), headache, conjunctivitis, left lower and upper extremity muscle weakness and sensory loss, vomiting, altered consciousness, mucocutaneous lesions	ECG: No pathology Echocardiography: EF: 65% Brain MRI: Hypodense area consistent with edema in the posterior of the right parietal lobe Chest CT: Bronchial enlargement and nodular infiltrates	WBC: 15100/µL Platelet: 279 x 10^3/µL Ferritin: 1058 µg/L CRP: 15 mg/L Procalcitonin: 3 µg/L	Nasal oxygen Corticosteroid LMWH Antiplatelet medication	Left hemiplegia
6	52 Male No comorbidity	29	Fever (38.0°C), chest pain, dyspnoea, vomiting, abdominal pain, palpitation, presyncope	ECG: Sinus tachycardia, Abnormal QRS wave complex, AV-block Echocardiography: EF: 30%, LV systolic dysfunction Chest CT: Ground glass opacity	WBC: 11500 /µL Platelet: 366 x10^3/µL Ferritin: 1066 µg/L CRP: 125 mg/L Procalcitonin: 0.17 µg/L Troponin I: 2727 ng/L	HFNO Corticosteroid Colchicum dispert LMWH	Congestive heart failure, arrhythmia, myocarditis

ECG: Electrocardiography, EF: Ejection fraction, LV: Left ventricle, CT: Computed tomography, WBC: White blood cell, CRP: C-reactive protein, HFNO: High flow nasal oxygen, LMWH: Low molecular weight heparin, MRI: Magnetic resonance imaging, AV: Atrioventricular.

Table 2. Laboratory findings of the patients at the time of diagnosis of COVID-19 (Period 1) and when they met MIS-A criteria (Period 2)

Laboratory findings	Period 1	Period 2
Serum leukocyte count/μL	6116 ± 1274	*15550 (11500-34000)
PMNL/μL	4583 ± 1184	1367 ± 4531
Serum lymphocyte count/μL	1133 ± 121.1	1750 ± 672
Thrombocyte, x10^3/μL	*223 (190-393)	217.8 ± 94.1
Ferritin, μg/L	215.6 ± 212.1	854.7 ± 296.2
D-Dimer, μg/L	563 ± 230	*1700 (400-7640)
Fibrinogen, mg/dL	479 ± 190	582 ± 98
CRP, mg/L	*15.2 (8-35)	102.3 ± 58.5
Procalcitonin, μg/L	*0.04 (0.01-0.2)	*0.215 (0.16-3)
Urea, mg/dL	34.5 ± 13.4	*47.5 (19-94)
Creatinine, mg/dL	0.74 ± 0.16	0.715 ± 0.343
Alanine aminotransferase, U/L	28.3 ± 9.2	*36 (25-463)
Aspartate aminotransferase, U/L	27.2 ± 12	*50 (27-534)
Creatinine kinase, U/L	215.2 ± 110.5	369 ± 175
Lactate dehydrogenase, U/L	351.7 ± 73.3	*418 (252-1796)
Troponin I, ng/L	6 (2-20)	*1559 (10-3808)

PMNL: Polymorphonuclear leukocyte, CRP: C-reactive protein
*Data not normally distributed were given as median (minimum-maximum).
Others provided normal distribution and were presented as mean ± standard deviation.

through COVID-19 (Table 2). The peak serum leukocyte count of the cases was 15550/μL (range 11500-34000, reference range 3600-10200) while ferritin level was 854.7 ± 296.2 μg/L (reference range 11-307), CRP level was 102.3 ± 58.5 mg/L (reference range 0-5) and procalcitonin was 0.215 μg/L (range 0.16-3, reference range 0-0.065). Significant elevation was also detected in coagulation and cardiac markers [D-Dimer 1700 μg/L (range 400-7640, reference range 170-550), fibrinogen 582 ± 98 mg/dL (reference range 170-550), troponin I 1559 ng/L (range 10-3808, reference range 0-16)].

It was discovered that all of the patients received high dose methylprednisolone, five (83.3%) enoxaparin sodium, four (66.7%) colchicum dispert, and three (50.0%) antiplatelet treatment during their hospitalization. Also, three (50.0%) of the patients recovered without sequelae. Two (33.3%) of the patients developed hemiplegia, and one (16.7%) patient had cardiac failure. None of the patients were mortal.

DISCUSSION

MIS-A is a rare post-COVID syndrome that occurs in the post-acute period. Likewise, we observed that MIS-A is not among the primarily considered ones in adult patients due to its clinically different presentations. Also, we noted that cases presented in this study were not evaluated as MIS-A at the time of hospitalization. However, despite many cases and clinical studies related to MIS-C in the literature[6,7,9], studies of these types are limited to adult patients, while also most of these are case reports[10-14]. In the literature, there are studies reported from Türkiye[15-17]. In one of these studies, a 24-year-old female patient with shock, cardiac dysfunction, abdominal pain, an elevated inflammatory marker, and SARS-COV-2 IgG positivity was presented. The patient was treated with ibuprofen, colchicine, and steroid, and all laboratory values returned to normal on the 50th day[15]. In another case report, a 40-year-old male patient who had COVID-19 23 days ago and an 18-year-old female patient who

had COVID-19 two months ago were presented, both patients were treated with pulse steroid and IVIG, and a cure was provided[16].

In parallel with our findings, MIS-A case series studies have also presented that clinical features of MIS-A are similar to those of MIS-C, and fever, gastrointestinal system, and cardiovascular system pathologies are predominant. In addition, the hemodynamic instability associated with myocardial dysfunction revealed as a result of cardiac imaging was reported both in our study and in other studies cited in the literature[18-21]. In one of our cases, extreme findings such as multiple cranial nerve paralysis, blindness, and encephalopathy were observed. However, different from the other studies, the mean age of our patients was slightly higher. We hypothesize that the lower number of applications for diagnostic testing due to the retrospective screening of SARS-CoV-2 RT-PCR positive patients in terms of MIS-A criteria, asymptomatic COVID-19 at the young age group, or its course with mild symptoms was a critical factor for the observed higher mean age. Due to the low rate of PCR testing in the young patient group who had asymptomatic-mild COVID-19, our mean age was found to be higher than in other studies. Additionally, we believe that the increase in the average age of the cases was due to the diagnosis of MIS-A was not among the primary concerns in the clinics where the cases were first applied, and no diagnostic test was performed for COVID-19.

Patients who developed MIS-A after the COVID-19 vaccine have also been reported[19,22-24]. In Türkiye, vaccination against COVID-19 started with the inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac) on January 13, 2021, and Pfizer-BioNTech was put into use on April 12, 2021. None of our patients had COVID-19 vaccine history before the clinical presentation of MIS-A developed. Consequently, our patients' clinics were related to the hyperimmune response developed due to the infection.

As a laboratory finding, specific pathologies of the system and organ with the involvement are also observable along with high inflammation markers and coagulation parameters. However, in adult patients, this situation is often considered as heart failure, cardiac arrhythmia, myocarditis, cerebrovascular accident, etc., rather than MIS-A, which results in the disregarding MIS-A diagnosis and only providing treatments for the affected system. However, with the emergence of the pandemic, a more careful evaluation of laboratory and clinical findings, and the initiation of specific treatments such as interleukin antagonists, intravenous immunoglobulin (IVIG), steroid treatments, and anticoagulants should be considered, especially in patients who meet the criteria for the commonly ignored multisystem inflammatory syndrome.

Analysis of the treatments provided to the patients in the study revealed that they were given anticoagulant and steroid treatments. All patients received parenteral glucocorticoid therapy, and more than half received low molecular weight heparin. However, we observed that IVIG or IL-1 and IL-6 inhibitors were not used. The pathogenesis underlying MIS-A is unclear but may involve abnormal immune responses to SARS-CoV-2, including macrophage hyperactivation, antigen-antibody complex deposition, and formation of autoantibodies[25]. IL-1 or IL-6 antagonists were not used in our patients and hyperinflammation was suppressed in all patients with high-dose corticosteroid therapy. Although none of our cases resulted in death, the complicated course is seen as an important clinical problem. Since suppression of hyperinflammation in the early period will prevent the development of comorbidity and sequelae, it is crucial to consider MIS-A in the differential diagnosis.

Moreover, since other branches do not consider MIS-A in the differential diagnosis during hospitalization, no patients underwent antibody testing; therefore, only SARS-CoV-2 RT-PCR positive patients were included in our study. Despite without any history of previous symptomatic COVID-19, PCR/antibody/antigen tests for SARS-CoV-2 should be requested for patients meeting clinical and laboratory criteria, and MIS-A should be ruled out. It is necessary to increase physicians' awareness from the specific branches and emergency service physicians

that primarily follow up patients. Establishing a warning and surveillance system for patients who meet the laboratory criteria in terms of MIS-A over the hospital automation system may be a proper solution to increase the diagnosis rate.

ETHICS COMMITTEE APPROVAL

The study protocol was accepted by the Ethical Committee of Adana City Training and Research Hospital Noninterventional Clinical Research Ethics Committee (Protocol serial number: 1479, date: 01/07/2021).

CONFLICT of INTEREST

The authors declared no potential conflicts of interest with respect to the research.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: TT, TAG, AA, BMS

Analysis/Interpretation: TT, EO, AA

Data Collection or Processing: MOT, ABU, TAG

Writing: TAG, MOT, BMS, ABU

Review and Correction: TT, EO, AA, TAG

Final Approval: All of authors

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