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Peer Reviewer of *World Journal of Cardiology*, Tolga Aksu, MD, Associate Professor, Department of Cardiology, University of Health Sciences, Kocaeli Derince Training and Research Hospital, Kocaeli 41000, Türkiye. aksutolga@gmail.com

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COVID-19 and cardiac complications: Myocarditis and multisystem inflammatory syndrome in children

Muhammed Güneş, Öner Özdemir

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Muhammed Güneş, Department of Pediatric Cardiology, Research and Training Hospital of Sakarya, Adapazarı 54100, Sakarya, Türkiye

Öner Özdemir, Department of Pediatric Allergy and Immunology, Research and Training Hospital of Sakarya, Sakarya University Medical Faculty, Adapazarı 54100, Sakarya, Türkiye

Corresponding author: Öner Özdemir, MD, Professor, Department of Pediatric Allergy and Immunology, Research and Training Hospital of Sakarya, Sakarya University Medical Faculty, Adnan Menderes cad, Adapazarı 54100, Sakarya, Türkiye. ozdemir_oner@hotmail.com

Abstract

Coronavirus is an important pathogen causing disease in humans and animals. At the end of 2019, an investigation into an increase in pneumonia cases in Wuhan, Hubei Province, China, found that the cause was a new coronavirus. This disease, which spread rapidly across China and caused an outbreak worldwide, resulted in a pandemic. Although this virus has previously been referred to as 2019-nCoV, which causes coronavirus disease 2019 (COVID-19), later it was named severe acute respiratory syndrome coronavirus 2. Children were usually asymptomatic and rarely severely affected. In April 2020, reports from the United Kingdom indicated that children may have Kawasaki disease or a clinical condition similar to toxic shock syndrome. This clinical picture was later defined as multisystem inflammatory syndrome in children. Since then, similarly affected children as well as cases with other cardiac complications have been reported in other parts of the world. In this review, we aimed to evaluate COVID-19 in terms of cardiac involvement by reviewing the literature.

Key Words: COVID-19; Cardiac complication; Myocarditis; Multisystem inflammatory syndrome in children; SARS-CoV-2

Core Tip: In April 2020, reports from the United Kingdom indicated that children may have Kawasaki disease or a clinical condition similar to toxic shock syndrome. This clinical picture was later defined as multisystem inflammatory syndrome in children. Since then, similarly affected children as well as cases with other cardiac complications have been reported in other parts of the world. In this review, we aimed to evaluate coronavirus disease 2019 in terms of cardiac involvement by reviewing the literature.

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INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) caused by coronavirus disease 2019 (COVID-19) in children can lead to death, if not diagnosed early. After it was first identified in the United Kingdom in April 2020, similar cases were reported in Europe and America[1-5]. Polymerase chain reaction (PCR) tests or antibodies were found to be positive in most of these children and were associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Various forms of cardiac involvement have been reported in the literature during MIS-C disease. These forms may affect the course of the disease. After the World Health Organization defined the picture as MIS-C in May 2020, guidelines on diagnosis and treatment have been continuously updated[6]. In this review, cardiac involvement that may occur during COVID-19 and MIS-C are discussed in light of the current literature.

PATHOGENESIS OF MYOCARDIAL DAMAGE AND HEART FAILURE IN COVID-19

The mechanisms of myocardial damage in COVID-19 are not clearly defined. Different variants of the virus may cause myocardial damage in children by various mechanisms. One theory suggests that entry of the virus into the host cell is facilitated by the binding of the spike protein to the angiotensin converting enzyme (ACE) 2 receptor. The virus causes a local inflammatory reaction with T-cell infiltration and B lymphocytes[7]. Permanent cell damage may lead to fibrosis formation and finally to the development of dilated cardiomyopathy[7,8]. Postmortem histological examination revealed local inflammation and the presence of a viral genome in the myocardial tissue. Accordingly, the negativity of markers indicating systemic inflammation in blood indicated the presence of direct damage caused by the virus itself[9].

In another study, researchers suggested that the cause of myocardial damage in adults was due to ischemia in the coronaries leading to a weakening of the blood supply to the heart muscle[10]. The main sign of myocardial damage in COVID-19 is thought to be endothelial inflammation leading to bleeding, thrombosis, and necrosis in intramural arteries. There is no correlation between markers of inflammation and myocarditis and no evidence that the virus directly triggers myocarditis. As a result, the theory that immune damage to the endothelium and microthrombosis formation play a role in the pathogenesis of myocarditis has been strengthened[11].

However, the etiology of heart failure due to COVID-19 is multifactorial. (1) Virus-induced infiltration of the myocardium by inflammatory cells that can impair cardiac function; (2) necrosis of the myocardium due to pro-inflammatory cytokines (monocyte chemoattractant protein-1, interleukin-1β; interleukin-6, tumor necrosis factor-α); (3) damage to the endocardium by endothelial damage due to microthrombosis; and (4) heart failure caused by acute respiratory distress syndrome and severe hypoxia due to respiratory failure[7].

ACUTE MYOCARDITIS IN COVID-19 PATIENTS

COVID-19 usually proceeds with mild respiratory symptoms in children[12]. As with other viral agents, COVID-19 has the potential to cause myocarditis. The prevalence of myocarditis due to COVID-19 is not yet known. The approach in COVID-19 patients presenting with acute myocarditis is not different to other classical viral myocarditis. All types of rhythm disturbances can be seen in acute myocarditis cases. In a case presented by Kohli *et al*[9], atrial fibrillation developed, and cardioversion was required[13].

Unlike adults, cases of acute fulminant myocarditis due to SARS-CoV-2 infection with left ventricular dysfunction are rarely seen[14]. Recently, rare cases of acute fulminant myocarditis have been reported and these patients required treatment in intensive care units. In these patients, acute myocarditis develops before respiratory symptoms develop[9, 13]. Extracorporeal membrane oxygenation (ECMO) was applied in an infant with fulminant myocarditis with a fatal course reported by Kesici *et al*[14], but the patient died[9]. In the cases of acute fulminant myocarditis presented in the literature, adolescents presenting with chest pain, fever, palpitations, weakness, and pallor, as well as infants presenting with fever, vomiting, pallor, rapid breathing, and decreased sucking can be seen. ECMO was applied in a patient with sustained ventricular tachycardia presented by Tseng *et al*[15]. The presented cases had a fulminant course and this is not

a condition frequently encountered in other forms of viral myocarditis. The reason for this is still unclear. Histological cardiac evaluations are needed for this. Therefore, acute myocarditis due to COVID-19 should be kept in mind in patients who develop malignant arrhythmia in the absence of fever and respiratory symptoms (Figure 1).

Symptomatic treatment is usually applied according to the severity of myocarditis. In all of these cases, severe left ventricular failure developed and they received various inotropic treatments as well as intravenous immunoglobulin (IVIG) and steroid treatments.

COVID-19 AND MIS-C DEVELOPMENT

In April 2020, reports from the United Kingdom indicated that children may have Kawasaki disease or a clinical condition similar to the described shock syndrome. Since then, similarly affected children have been reported in other parts of the world. This clinical definition is called MIS-C[16]. In both Kawasaki disease (KD) and MIS-C, symptoms and organ dysfunction result from a cytokine storm[17].

It was observed that the inflammatory storm was more prominent in MIS-C[18]. According to Rodriguez-Smith *et al* [19], the measured levels of S-100 and interleukin (IL)-18 are similar in MIS-C and KD. Therefore, interferon-γ-stimulated chemokine ligand 9 is an indicator that may be important in differentiating MIS-C from KD. The main mediator of coronary artery inflammation in KD is IL-1. However, the main mediators of MIS-C are IL-6 and IL-8 and the inflammatory response seems to be triggered by these factors[17].

A mucosal biopsy from a COVID-19 patient with gastrointestinal system involvement and symptoms showed the presence of SARS-CoV-2 in endothelial cells. Recent studies have reported autoantibodies targeting antigens in mucosal and cardiac tissues in MIS-C patients[20]. At the beginning of the pandemic, pediatric patients were not considered to be at high risk for severe COVID-19 symptoms such as severe acute respiratory syndrome due to the lower presence of ACE 2 receptors in epithelial cells[21]. Later in the pandemic, more serious COVID-19-related complications such as thrombotic events, myocardial dysfunction, and coronary artery disease or aneurysms have been observed in pediatric patients with MIS-C[22]. In a study published in the United States, it was shown that the most common finding in children with MIS-C was cardiac dysfunction with a rate of 40.6%[23]. Serological evidence for SARS-CoV-2 or a history of contact with a COVID-19 patient was found in all patients[24,25]. It has been shown that vaccinated children are less frequently diagnosed with MIS-C[26].

PATHOGENESIS OF MIS-C DEVELOPMENT IN COVID-19

Many hypotheses related to the pathogenesis of MIS-C have been presented, but none of them have been fully proven. Some researchers think that there is a delayed immune response that occurs 2 to 6 wk after infection[27,28]. In childhood, the early and pulmonary stages of COVID-19 are mild or asymptomatic. In the early stage, macrophages are activated and T helper cells begin to release cytokines. Subsequently, plasma and B cells produce antibodies and cause the immune response to intensify. This response results in the hyperinflammatory condition called MIS-C[28]. The fact that most children with MIS-C have positive serology and negative PCR tests supports this view. In addition, it has been reported that autoantibody responses against intestinal and endothelial cells are produced in children with MIS-C[29,30]. The fact that MIS-C is more common, especially in Africans shows the importance of genetic factors[31]. Another hypothesis suggests that neutrophil extracellular traps (NETs) play a role in the pathophysiology of MIS-C. The function of NETs is to trap the virus inside the cell. NETs stimulated by viruses cause hyperimmune and hyperinflammatory responses. These are thought to be increased in patients with respiratory failure and severe disease manifestations[32]. More studies are needed to elucidate the exact mechanism of myocardial damage seen in MIS-C.

MIS-C DIAGNOSTIC CRITERIA

According to the American Centers for Disease Control and Prevention, in a person younger than 21 years of age, MIS-C criteria (Figure 2) without an alternative diagnosis are as follows:

Clinical criteria

Minimum 24-h history of subjective or objective fever ≥ 38.0°C; severe illness requiring hospitalization; two or more organ systems affected (*i.e.* cardiac, renal, respiratory, hematological, gastrointestinal, dermatological, neurological).

Laboratory confirmation of inflammation

One or more of the following: elevated C-reactive protein (CRP), erythrocyte sedimentation rate, fibrinogen, procalcitonin, D-dimer, ferritin, lactate dehydrogenase or interleukin 6; elevated neutrophil or decreased lymphocyte counts; low albumin level.

Laboratory or epidemiological evidence of SARS-CoV-2 infection

PCR, positive SARS-CoV-2 test by serology, or symptoms development after a history of COVID-19 contact 4 wk before the onset of COVID-19[15,23,33].

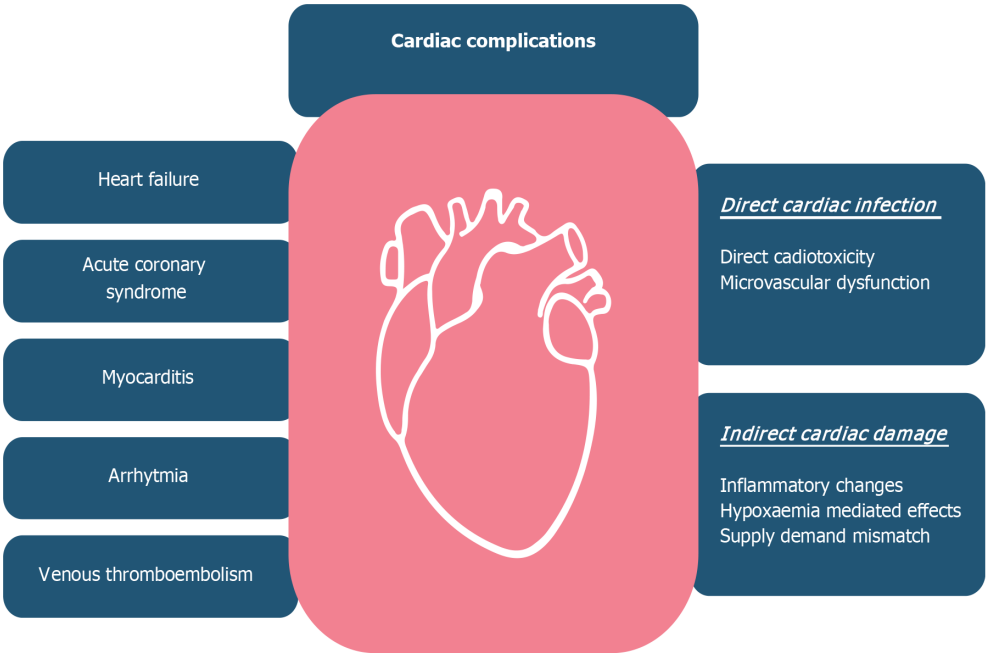

Figure 1 Cardiac complications of coronavirus disease 2019.

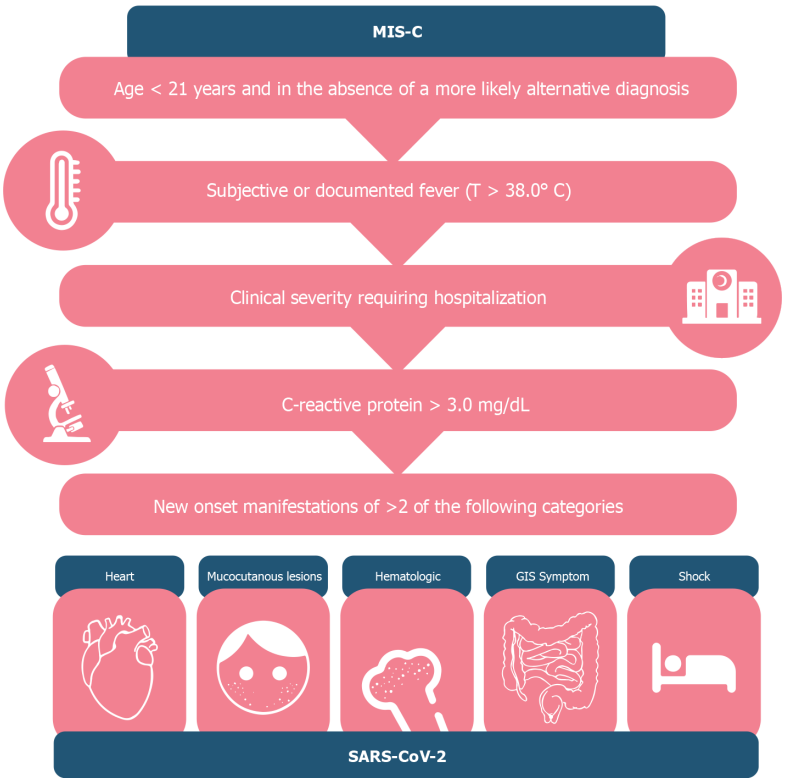

Figure 2 The relation between severe acute respiratory syndrome coronavirus 2 infection and multisystem inflammatory syndrome in children. MIS-C: Multisystem inflammatory syndrome in children; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

MANAGEMENT OF MIS-C

Children with a diagnosis of MIS-C should be hospitalized and followed up by an experienced team. Children who are clinically well enough not to require hospitalization should not be considered to have MIS-C. In these children, close follow-up should be continued as infection markers may increase later. Supportive care is determined according to the severity of the symptoms. Patients presenting with a shock condition should be hospitalized in the intensive care unit as they may need inotropic support and mechanical ventilation[33]. Vasodilatory shock may be seen in some children, and vasopressor drugs should be used in this situation. However, milrinone could be used with caution due to its va-

sodilatory effect[34]. A broad-spectrum antibiotic should be administered until blood culture results are available.

Immunomodulator therapy

Although the exact pathogenesis of MIS-C is not understood, immune dysregulation is suggested to play an important role[35]. Autoantibody production resulting in activation of Fc-y receptors on neutrophils and macrophages and causing secretion of pro-inflammatory cytokines is one of these mechanisms[20,36-38]. Accordingly, immunomodulation is an important step in treatment. IVIG, glucocorticoids, and biological agents constitute the main treatment approaches (Figure 3)[39,40]. Treatment aims to correct cardiac dysfunction and damage in other organs by suppressing inflammation[27,41].

Steroids are used at low doses in patients with moderate to severe disease or at high doses in patients with refractory disease. Biological agents such as anakinra, tocilizumab, or infliximab are preferred in cases resistant to first-line therapies according to new guidelines[42]. In a series of 52 cases (30 MIS-C and 22 severe diseases) reported from Türkiye, it was emphasized that patients presented with different clinical pictures especially conjunctival hyperemia, high CRP values, and a low leukocyte count could be independent parameters used in diagnosis of the disease[43]. IVIG was administered to 30, a steroid to 27 (high dose steroid in 1 patient), anakinra to 26, plasmapheresis to 14, and various vasoactive agents to 13 patients with severe myocardial involvement. No deaths due to MIS-C were reported in this series. The common opinion of authors in the literature related to MIS-C is that mortality in children is very low with correct treatment in those diagnosed early. In the case of cardiac involvement, the importance of treatment under intensive care conditions has been emphasized.

Anti-platelet therapy

Patients with MIS-C are at high risk of thrombotic complications for many reasons including hypercoagulopathy, possible endothelial damage, stasis due to immobilization, ventricular dysfunction, and coronary artery aneurysm. Low-dose aspirin (3-5 mg/kg/d, max. 81 mg) should be started and can be discontinued at 4 wk if there is no coronary artery aneurysm. Treatment with aspirin should be avoided in patients with active bleeding, significant bleeding risk, and/or a platelet count of 80000/μL. Therapeutic anticoagulation with enoxaparin or warfarin is recommended in patients with a coronary artery diameter Z-score > 10[44,45].

FOLLOW-UP OF MIS-C PATIENTS

Echocardiography

For hospitalized MIS-C patients with ventricular dysfunction or coronary artery dilatation, echocardiography (ECHO) should be repeated before discharge or on days 5-7. If the first echocardiogram is normal, it should be repeated on days 7-10. Repeat ECHO is recommended on days 7-10, 4-6 wk, 4-6 mo, and 9-12 mo after discharge[46,47].

Electrocardiography

In MIS-C patients, electrocardiography (ECG) should be performed at 48-h intervals. If grade 1 atrioventricular (AV) block is present, continuous telemetry monitoring is recommended. Holter ECG is recommended on the 7th-10th day after discharge if there is a grade 1 AV block or arrhythmia. Repeat ECG after 4-6 wk and 4-6 months, if there is arrhythmia or 1st-degree AV block, Holter ECG is recommended. After 4-6 months, if arrhythmia persists or ventricular dysfunction and increased troponin, brain-type natriuretic peptide values are present in the initial diagnosis, an exercise stress test is recommended[46,47].

Exercise restriction

Exercise restriction is recommended for 2 wk in the absence of cardiac involvement and 3-6 mo in the presence of cardiac involvement[47,48].

CONCLUSION

Unlike adult patients, COVID-19 has a milder course in children. However, although MIS-C cases due to COVID-19 are rare, they cause deaths in children when not recognized early. Optimal results are obtained with intensive care unit treatments in cases diagnosed early. Early recognition of the disease and consideration of the latest guidelines are very important for the diagnosis and treatment of MIS-C. To clarify the pathogenesis of MIS-C, rational management strategies, and possible preventive measures are important for planning. MIS-C patients need to be registered to keep track of risk factors, and prognosis, and this is possibly the most appropriate way to identify sequelae. Genetic research will be vital to understanding why some children develop MIS-C after SARS-CoV-2 infection.

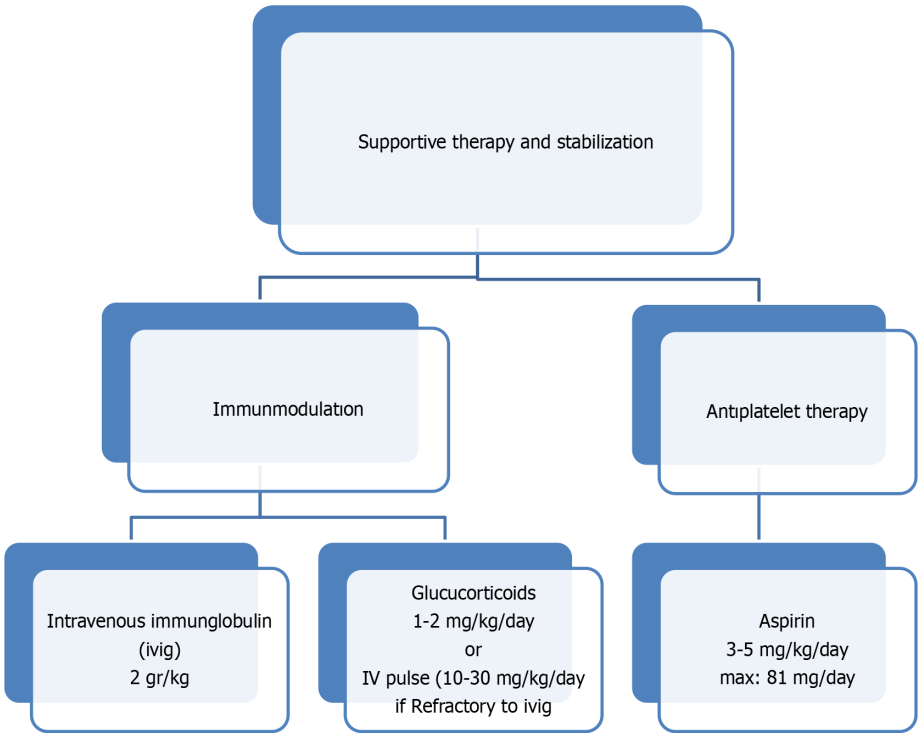

Figure 3 The management algorithm of multisystem inflammatory syndrome in children.

FOOTNOTES

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ORCID number: Öner Özdemir 0000-0002-5338-9561.

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