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Myocarditis in Multisystem Inflammatory Syndrome Associated with COVID-19

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Abstract

Viral infections commonly cause myocarditis, and it can be seen in pediatric patients with multisystem inflammatory syndrome as a complication of COVID-19. There are no long-term studies about this complication, but many studies have shown cardiac inflammation as a short-term outcome. The following systematic review focused on the association between myocarditis and COVID-19 in pediatric patients. A thorough search was done until March 2022 using the following databases: PubMed, Lancet, EBSCO, HCC library, UpToDate, AAP, and JAMA. After applying several inclusion and exclusion criteria, 65 clinical studies were chosen for our review. The outcome of these studies supported the relationship between myocarditis and multisystem inflammatory syndrome in COVID-19 pediatric patients. Even though there is a low overall risk of myocarditis associated with COVID-19, some studies indicate that the risk of developing myocarditis is undoubtedly higher among pediatric patients with COVID-19 when compared to non-COVID-19 patients. Also, myocarditis is an adverse effect in children after applying the COVID-19 vaccine.

Regarding the treatment of myocarditis, it is recommended the use of intravenous immune globulin (IVIG) and glucocorticoids, also provide cardiac support and anti-platelet therapy. Although patients have a favorable prognosis, some studies have shown that patients may present with residual cardiac lesions, so follow-up appointments and examinations are highly recommended. Recently, few studies have associated myocardial inflammation with COVID-19, and future studies are needed to have more available information.

Introduction

Epidemiology

The novel coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to more than 450.6 million confirmed cases and over 6 million global deaths as of March 9, 2022 [1].

Myocarditis is one of the most severe infectious diseases caused by multiple etiologies, most commonly viral infections, and can also result from severe acute respiratory syndrome (SARS-CoV-2 infection) [2]. Most reports have described the pediatric population as low risk for severe COVID-19. However, in April 2020, The National Health Service in England reported

cases of older children and adolescents presenting with fever, hypotension, severe abdominal pain, and cardiac dysfunction who tested positive for SARS-CoV-2 infection. This new syndrome was named multisystem inflammatory syndrome in children (MIS-C). Since then, there have been multiple similarly affected children in other parts of the world. Many pediatric patients with this syndrome have had similar manifestations to Kawasaki's disease, a rare childhood vasculitis characterized by conjunctival injection, polymorphous rash, cervical adenopathy, oral mucositis, peripheral edema, and fever [3].

The vulnerability to infection and clinical manifestations in affected individuals are related to age. In infected children and adolescents, symptoms are present in 20% to 30% compared with more than 60% of those older than 60 years of age. Studies evaluating COVID-19 in children in the United States report primarily respiratory symptoms and showed that severe infection was more likely in children with comorbidities, such as asthma, obesity, neurological impairment, and immunocompromised [4].

Most of the MIS-C cases present with a positive immunoglobulin G serology (75% to 90%) and negative polymerase chain reaction (PCR) tests for the virus (53% to 80%) [4]. This shows that MIS-C may be a post-infectious, immune-mediated complication rather than an acute infection. Acute myocardial dysfunction is the most common cardiac finding in patients with MIS-C. Studies from the United Kingdom and Italy have reported that patients had left ventricular (LV) systolic dysfunction and depressed LV ejection fraction of 50% to 60%. Elevated troponin (64% to 95%) and brain natriuretic peptide (73% to 95%) are also associated with the presentation of shock and LV dysfunction [4].

COVID-19 in children

Nowadays, it is well known that COVID-19 is an infectious disease caused by a Ribonucleic acid (RNA) virus called SARS-CoV-2 [5]. Coronaviruses are thought to be spread by respiratory droplets. Droplet transmission is usually limited to short distances, generally less than 6 ft. The incubation period is estimated to be 2 to 14 days (about 2 weeks). Diagnosis of COVID-19 is commonly made using polymerase chain reaction (PCR) testing via nasal swabs. However, clinical, laboratory, and imaging findings may also be used to make a presumptive diagnosis [6]. Although there is evidence that the infection is more common in adults than pediatric population, studies have shown that children are prone to get infected. Even if most cases are asymptomatic, they can also suffer from a naïve common cold to severe pneumonia, leading to hospitalization and severe complications. Within the complication of COVID-19, there is a pediatric multisystem inflammatory syndrome identified and named by The Royal College of Pediatrics and Child Health, the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) as a multisystem inflammatory syndrome in children (MIS-C). These three organizations have described it. Their definitions of this condition include the presence of fever, elevated inflammatory markers, multisystem organ involvement without alternative diagnoses, and evidence of COVID-19 infection or recent exposure to a COVID-19 case. The duration of fever, criteria for organ involvement, and need for documentation of SARS-CoV-2 infection vary between definitions [7].

The Royal College of Pediatrics and Child Health's definition entails a child presenting with persistent fever (>38.5 °C), inflammation (neutrophilia, elevated C reactive protein (CRP), and lymphopenia), and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional clinical features, including children fulfilling full or partial criteria for Kawasaki disease.

Meanwhile, the CDC defines a case as an individual of less than 21 years old presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (≥ 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); and no plausible alternative diagnoses; and positive for current or recent SARS-CoV-2 infection by PCR, serology, or antigen test, or COVID-19 exposure within 4 weeks prior to the onset of symptoms.

Lastly, the WHO's definition includes individuals of less than 19 years of age with fever ≥ 3 days; and two of the following: Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet), hypotension or shock, features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echo findings or elevated troponin/NT-proBNP), evidence of coagulopathy (by PT, PTT, elevated d-dimers), acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) and elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin, and no other apparent microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, and evidence of COVID-19 (PCR, antigen test, or serology positive) or likely contact with patients with COVID-19. Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome [7].

Pathophysiology

Since there is insufficient data regarding SARS-CoV-2, the exact mechanism causing damage to myocardial cells in MIS-C is poorly understood. In most cases of MIS-C, children had a negative SARS-CoV-2 antigen [8]. However, they tested positive for anti-SARS-CoV2 antibodies suggesting that MIS-C is associated with post-infectious immune dysregulation [8-10].

A study points out that SARS-CoV-2 might, directly and indirectly, affect myocardial tissue [8]. While the direct cardiac effect involves the angiotensin-converting enzyme 2 (ACE2) receptors, the indirect cardiac effect can be caused by a cytokine storm (cytokine-mediated injury) induced by SARS-CoV-2 [8,10].

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SARS-CoV-2, a single-stranded RNA virus, has a spike protein that binds to the ACE2 receptor, whose expression is higher in the lungs, heart, and endothelial cells. This might explain why SARS-CoV-2 has a specific attraction to these organs. The interaction between the spike protein and the ACE2 receptor eases the viral entry and infection of the target cells. As a result, there is a decrease in ACE2, causing an increase in angiotensin II activity, which damages the lung, heart, and endothelial cells, and indirectly causes a cytokine storm [8,10].

Some studies mention cases of MIS-C where children with severe myocarditis were correlated with higher levels of inflammatory cytokines (Interferon (IFN)-α2, IFN-γ, IL-17A, IL-8, IL-6 TNF-α, and IL-10) [8,9]. This might explain the indirect cardiac effects induced by SARS-CoV-2. Even after recovering from COVID-19 infection and regardless of the children's condition (e.g., asymptomatic or symptomatic), SARS-CoV-2 causes dysregulation in the immune system (overactivation of macrophages), leading to cytokine storm. This cytokine-mediated injury has been associated with direct damage to cardiac cells, dysfunction of the endothelial cells, and thrombogenesis. It is also believed that autoantibodies created by molecular mimicry are associated with direct cardiomyocyte injury and apoptosis [8,10]. However, due to limited studies, it is unknown why some patients are affected while others are not, and this requires further investigation.

Multisystem inflammatory syndrome in children

Multisystem inflammatory syndrome in children (MIS-C) is a newly described hyperinflammatory syndrome associated with antecedent COVID-19 exposure. Therefore, there is no long-term data about complications, but many studies have shown cardiovascular involvement and short-term outcomes. For example, a study from the Children's Hospital of Philadelphia and St. Peter's University Hospital evaluated the cardiac outcomes during a 3-month follow-up period to determine the short-term impact of acute myocardial injury caused by MIS-C, which found that myocardial injury did not have short-term echocardiographic outcomes. This suggests that functional recovery and coronary outcomes are favorable in MIS-C. These findings can help us with outpatient management strategies and recommendations for returning to competitive sports [11].

A review of cardiac involvement in MIS-C in children reported that laboratory testing typically shows neutrophilia and lymphopenia, elevated inflammatory markers including C-reactive protein, fibrinogen, ferritin, and elevated D-dimer. In addition, 5,34 BNP (B-type natriuretic peptide) levels may be markedly elevated and associated with modest elevations in troponin [4]. Many studies support short-term complications, but there is still a need for data supporting long-term complications. Since MIS-C and its association with COVID-19 is newly described, we need to consider it while treating children with COVID-19.

Clinical and Cardiac manifestations

SARS-CoV-2 infections in children usually present asymptomatically (15%). However, when symptoms occur, patients usually present mild and moderate signs (40%). In most patients (80-85%), the symptoms can be confused with the flu or common cold. Also, it is not uncommon to see children and adolescents with anosmia and ageusia. Nevertheless, a substantial percentage of those infected (15-20%) present severe or critical symptoms, such as pneumonia and severe acute respiratory distress, which can worsen quickly [7,12,13]. In laboratory tests may have leukocytosis and an increase in acute phase reagents and liver enzymes. The most common finding in computed tomography imaging of the chest is bilateral lung involvement with ground-glass opacity. In addition, an electrocardiogram (ECG) can reveal sinus tachycardia secondary to fever [12,13].

A wide variety of signs and symptoms can accompany MIS-C, including gastrointestinal, cardiovascular, hematological, respiratory, dermatological, or mucocutaneous involvement; generally, very few debuts with symptoms of SARS-CoV-2 infection, and symptoms of MIS-C do not occur until approximately 25 days (about three and a half weeks) after infection. Fever, vomiting, rash, abdominal pain, diarrhea, bilateral bulbar conjunctival injections, shock, lip, and oral cavity changes, limb changes, and cervical lymphadenopathy are common symptoms. In addition, inflammation of the central nervous system results in headaches, altered mental status, irritability, and neck stiffness, among other symptoms [7].

The presentation of myocarditis due to COVID-19 in the pediatric population is usually infrequent. Symptoms such as tachycardia, tachypnea, and an abnormal respiratory exam are commonly found. Chest pain, syncope, palpitations, and isolated gastrointestinal symptoms (e.g., abdominal pain and vomiting) may also occur. This pathology presents a heterogeneous clinical course that ranges from asymptomatic congestive heart failure (CHF) with gradual onset to fulminant myocarditis complicated with cardiogenic shock and sudden death [14], so knowing how to detect it and being able to carry out adequate management is of vital importance.

Results

Throughout the COVID-19 pandemic, significant medical advancements have been achieved regarding complications related to this airborne disease in children. Myocarditis caused by multisystem inflammatory syndrome (MIS-C) is a clear example of this, in which breakthroughs have been made concerning its pathophysiology, most common clinical manifestations, diagnosis, treatment, and follow-up over time. However, several gaps in knowledge remain to be clarified for a better understanding of this clinical condition [15-17].

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First of all, even though risk factors such as asthma, obesity, and immune disorders have been linked to a more severe COVID-19 disease in children, there is not enough scientific evidence to demonstrate a direct association with MIS-C-related myocarditis [15]. Some studies have shown higher disease prevalence in Black and Hispanic children, but the relationship with other risk factors has yet to be determined [18]. Regarding clinical manifestations, it is well known that patients with MIS-C often experience fever, gastrointestinal symptoms, and shock. Additionally, patients may exhibit symptoms commonly seen in Kawasaki diseases, such as conjunctivitis, mucosal changes, peripheral edema, and rash. Cardiac involvement frequently includes pericarditis, acute myocarditis, and sepsis-related cardiomyopathy [16]. Cardiovascular manifestations in the early stages of the disease can include left ventricular dysfunction, coronary artery dilation, aneurysm, and a broad spectrum of arrhythmias, which might range from innocent premature atrial or ventricular beats to sustained arrhythmias causing hemodynamic collapse [19]. Despite the wealth of information regarding early cardiac manifestations, the medium and long-term consequences of cardiac involvement in COVID-19/MIS-C are unknown [7,20]. Considering the unclear prognosis and the possibility of cardiac progression, long-term monitoring of these patients is essential [7].

Finally, there are currently no approved therapies for myocarditis in MIS-C patients with COVID-19, and the management has been mainly based on expert consensus and known similar conditions [17]. Treatment protocols for other types of myocarditis and Kawasaki disease have been used as a management guide, resulting in positive outcomes for some individuals [16,20]. These therapy options include immunomodulatory agents, cardiac support, and anticoagulation. Because of the limited knowledge and the small number of cases reported so far, more information is needed to create better recommendations for managing these patients [20].

As we begin adventuring back to a normal pre-covid era with vaccines, we still see a rise in COVID cases. Even though cases tend to be mild in those patients with a complete vaccination scheme. There has also been a worldwide disinformation campaign about the vaccine causing concern and hesitancy among some people [21]. The primary purpose of this systematic review is to gather additional information about COVID complications, specifically from the pediatric population [21,22]. Our Systematic Review emphasizes myocarditis in multisystem inflammatory syndrome associated with covid-19 exposure. We believe that the unification of the few studies available will help inform and provide earlier detection, management, and adequate treatment [22]. For this study, 64 articles were gathered according to specific criteria. A thorough search was done until March 2022 using the following databases: PubMed, Lancet, EBSCO, HCC library, UpToDate, AAP, and JAMA. Articles are directly related to the pediatric population and are no older than four years from publication. Excluded articles were those written in another language other than Spanish and English, those that included subjects with a previous history of cardiac pathology before covid, and subjects with previous immunologic diseases.

Discussion

Myocarditis post covid infection

Considering the current evidence on myocarditis secondary to COVID-19 infection in the pediatric population, one of the main aims of this systematic review was to collect current information regarding this condition. In addition, to provide a better understanding of its pathophysiology, symptomatology, diagnosis, treatment, follow-up, and prognosis. Despite the low overall risk of myocarditis associated with COVID-19, some studies indicate that the risk of developing myocarditis is approximately 30 times higher among pediatric patients with COVID-19 when compared to non-COVID-19 patients [23,24]. Myocarditis is defined as acute inflammation of the myocardium, which can be due to different causes, with viral infection being the most prevalent among them [23]. As COVID-19 has been shown to prefer ACE-2 receptors in the lungs and heart, it may explain why the incidence of myocardial injury is higher with COVID-19 infection than with other viral infections [24,25]. It remains unclear how COVID-19 causes cardiac injury, but several mechanisms could be involved. According to the literature, the most accepted hypotheses include systemic inflammation and cytokine storm due to the infection, direct viral damage to the heart, extrapulmonary migration of infected alveolar macrophages, cell-mediated cytotoxicity, demand ischemia, vasospasm, and an induced state of hypercoagulation [26, 27].

Regardless of whether myocarditis is present, patients with COVID-19 commonly present with fever, chest pain, fatigue, and dyspnea, which are similar to symptoms of non-COVID-19 myocarditis. Diagnostic challenges may be incurred when the most prevalent symptoms of both conditions overlap [23]. Therefore, diagnostic tools such as serum biomarkers, CRP, EKG, echocardiography, and cardiac MRI are critical to achieving a more accurate diagnosis [23,27]. Most patients with acute viral myocarditis have elevated cardiac biomarkers, and COVID-19 myocarditis is no exception. Although every cardiac biomarker may be elevated, troponin is the most common [28]. However, patients with COVID-19 might also have slightly elevated troponin levels due to systemic inflammation. Hence, the absence of an increase in cardiac troponins does not exclude myocarditis [28,29]. A similar phenomenon occurs with CRP, which is often elevated in patients with COVID-19, regardless of whether or not there is myocardial injury [29]. Most patients with myocarditis manifest nonspecific electrocardiographic changes, including sinus tachycardia, ST-segment changes, T-wave abnormalities, and occasional atrioventricular blocks [26,29]. On echocardiography, the most common findings are left ventricular systolic dysfunction, pericardial effusions, diffuse hypokinesia, and cardiomegaly or

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increased wall thickness [26-28]. The purpose of this imaging study should not be to diagnose myocarditis but to help determine if there are other causes of cardiac injury and evaluate the structural and functional changes resulting from myocarditis. The gold standard non-invasive test for myocarditis is cardiac magnetic resonance imaging, which often shows myocardial edema and damage [26]. As the laboratory tests are not entirely reliable in identifying COVID-19-induced myocarditis, it is necessary to consider the entire clinical context of the patient to identify this condition correctly.

Myocarditis post-vaccination

Due the COVID-19 pandemic, parents have been forced to make some tough decisions about how best to keep their kids safe and well. The most challenging decision for most parents is to vaccinate or no vaccinate [30]. We should be aware that all vaccines have side effects, and the COVID-19 vaccine is not an exception. One of the most critical side effects is myocarditis. Even though most patients with suspected vaccine-associated myocarditis have a normal ventricular systolic function on echocardiogram, many have abnormal findings suggestive of myocarditis on cardiac MRI in elevated troponin and electrocardiographic changes [31]. Therefore, we should indicate laboratory works and imaging studies for any pediatric patient with suspected myocarditis after receiving the COVID-19 vaccine.

A retrospective study from 26 pediatric medical centers across the United States and Canada before July 4, 2021, shows that most patients with suspected myocarditis received mRNA vaccine, with 131 (94.2%) after the Pfizer-BioNTech and 5 (3.6%) after the Moderna vaccines. One case (0.7%) occurred after the Johnson & Johnson vaccine. Only a few patients reported symptoms after the first dose (12 patients, 8.6%), and most patients had symptoms after the second dose (128 patients, 91.4%). It is essential to mention that none of these patients died or required extracorporeal life support (ECLS). Some demographic variables, such as age, gender, and race, can also play a key role. For example, it is unknown why myocarditis associated with the COVID-19 vaccine is more common in adolescents and young adults, male and white race [31], and therefore, we highly recommend further studies.

The most common symptoms of myocarditis associated with the COVID-19 vaccine are chest pain, fever, and shortness of breath. While most patients can have elevated troponin I or T and ECG abnormalities, not all patients will present with echocardiography and cardiac MRI abnormalities. Therefore, most patients can have a pseudo-infarct presentation with chest pain, shortness of breath, ST elevation on ECG, and increased troponin, though normal left ventricular systolic function. Most patients can be treated with NSAIDs only, and few patients might need the use of a glucocorticoid, intravenous immunoglobulin (IVIG), or colchicine [31].

Although there is an association between the COVID-19 vaccine and myocarditis, the clinical course is benign and has a rapid resolution of symptoms [30,31]. Therefore, the CDC recommends that everyone six months and older should be vaccinated for COVID-19. However, the long-term effects of these vaccines related to myocarditis are still unknown, and thus, we recommend further studies and surveillance in these patients.

Treatment and Prognosis

Since reported cases are minor and knowledge is still scarce it is important to note that there are still ongoing updates on a definite treatment plan. However, elevated inflammatory markers and exceptionally high IL-6 are some of the main characteristics presented in most cases, and therefore innovative proposed management has revolved around immunomodulatory treatment. Most cases reported using 2g/kg of IVIG, opting to treat the similarities between Kawasaki and MIS-C. The clinical approach by a multidisciplinary team provided to patients included cardiac support and antiplatelet therapy as an addition to either IVIG or with Steroids [7].

Management is focused on supportive care to maintain hemodynamic stability and ensure adequate systemic perfusion. In patients with suspicion or evidence of ventricular dysfunction, smaller fluid boluses (10 mg/kg) should be administered with careful monitoring for signs of fluid overload between each bolus. It is suggested intravenous immune globulin (IVIG) and glucocorticoids for all patients with cardiac involvement [7]. Most patients are treated with IVIG 2 g/kg in a single infusion over 8 to 12 hours [32]. Obese patients dose should be based upon ideal body weight, and some centers limit the maximum dose to 100 grams given IVIG shortages as well as expense. For patients with significant LV dysfunction, if there is concern that the patient will not tolerate the volume load of the full dose in a single infusion, it can be given in divided doses over two days.

When IVIG is not available, treatment with glucocorticoids alone is a reasonable option. It is supported by evidence in case series where 70 to 95 percent of patients were treated with IVIG, with or without additional medications. The vast majority of patients in these series improved and recovered cardiac function. There is indirect evidence supporting IVIG use from studies involving patients with similar conditions, such as KD, toxic shock syndrome, and myocarditis [33].

Glucocorticoid therapy is suggested in addition to IVIG in patients with moderate or severe manifestation, such as shock requiring vasopressor, LV systolic dysfunction, elevated troponin or brain natriuretic peptide, arrhythmia, CA aneurysm (Z-score ≥2.5), or other manifestations requiring pediatric intensive care unit care, persistent fevers, rising inflammatory markers, evidence of intravascular coagulopathy, in spite of treatment with IVIG. These findings may suggest cytokine storm, which may not respond to IVIG therapy [33].

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Glucocorticoid therapy is typically given concomitantly with IVIG. Glucocorticoids may be given as a second-line treatment in patients with less severe manifestation if there is an inadequate response to IVIG. Methylprednisolone is the glucocorticoid of choice at a dose of 2 mg/kg/day in two divided doses [33]. Once the patient has defervesced and is improved clinically, this can be transitioned to an equivalent oral dose of prednisolone or prednisone by the time of discharge and then tapered off over two to four weeks. In life-threatening circumstances or refractory cases, pulse doses of methylprednisolone 30 mg/kg/dose, with a maximum of 1gr have been used, even though there are few supporting data [34].

Infliximab, a tumor necrosis factor (TNF) inhibitor, has been used as second-line therapy in patients with MIS-C who have persistent inflammation or myocardial dysfunction [35,36] and also has been used in conjunction with intravenous immune globulin (IVIG) for initial therapy. Adjunctive therapies with interleukin (IL) 1 inhibitor like anakinra, canakinumab, and IL-6 inhibitors like tocilizumab are uncertain [33]. Anakinra, canakinumab, and tocilizumab are alternative options for the treatment of MAS (Macrophage Activation Syndrome) or CRS (cytokine release syndrome) in patients who cannot receive glucocorticoids and those who are refractory to glucocorticoids. IL-1 and IL-6 inhibitors were used in approximately 10 to 20 percent of patients in available case series [33].

Anti-platelet and, or anticoagulation treatment is recommended based on the risk of thrombotic complications from multiple causes including hypercoagulable state, possible endothelial injury, stasis from immobilization, ventricular dysfunction, and coronary artery aneurysm [7].

A low-dose aspirin of 3 to 5 mg/kg daily is indicated in all patients based on indirect evidence from patients with KD. Specific indications include patients with current or prior VTE should receive therapeutic anticoagulation typically with low-molecular-weight heparin. Patients with large or giant CA aneurysms should receive therapeutic anticoagulation in addition to aspirin [33].

The decision to administer an anticoagulant in addition to low-dose aspirin for VTE prophylaxis is individualized, weighing the risk of thrombosis and risk of bleeding. These decisions are made on a case-by-case basis [33].

The use in antiviral therapy is still uncertain and not well studied. The use of antiviral therapy is reserved in case of overlapping clinical features due to COVID-19 and in children with an ongoing COVID-19 infection and positive PCR testing. Therefore, antiviral therapy may have a positive effect on the disease process in some, but not all, patients. We advise consultation with an infectious disease specialist to guide decision-making [7].

Patients periodically receive cardiac monitoring to monitor for sequels and exercise restriction recommendations, two weeks in patients without cardiac involvement and up to six months in patients with ventricular dysfunction. Echocardiograms and ECGs are also routinely monitored for a year. Patients who suffer from thrombotic events are on anticoagulation for around three more months. The prognosis has been favorable. Most patients have had complete recovery before discharge. Only a handful have been reported needing ECMO (extracorporeal membrane oxygenation), continuing with ventricular dysfunction and relatively low mortality [7].

Follow Up

Although early diagnosis and management with classical therapies lead to a favorable outcome and most children make a complete recovery, some patients have shown residual cardiac lesions, so follow-up appointments and examinations should be made to confirm the full resolution of the disease [32]. In addition, it should be considered that the information available on post-COVID-19 infection myocarditis and the long-term cardiac sequelae of MIS-C are limited, so we recommend following the guidelines of Kawasaki disease and viral myocarditis pathology [15].

It is essential to carry out a medium and long-term follow-up, where laboratory tests should be obtained to document the normalization of inflammatory markers and resolution of hematologic abnormalities. These can also guide weaning from corticosteroids if used in the acute phase. Echocardiographic images should be performed at regular intervals to assess ventricular function and coronary artery dimensions, ECG if there are reports of arrhythmias, including atrioventricular block, which may progress after initial diagnosis, Holter monitor if abnormalities are identified on the ECG, cardiac magnetic resonance imaging used to assess ventricular function, edema, diffuse fibrosis, and scarring. Also, evaluation of suspension or continuation of antiplatelet therapy and immunomodulation are evaluated in children with inflammatory cardiomyopathy. This could reduce the further need for transplantation in children with chronic dilated cardiomyopathy and is often used to treat infective myocarditis [37].

Furthermore, it is recommended two weeks restriction of physical exercise if there is no evidence of cardiac involvement or 3-6 months if there's evidence of cardiac involvement. However, due to the high prevalence of myocardial involvement, restriction of physical exercise for at least six months following diagnosis is recommended [7]. Follow-up should be done at least one year after the initial diagnosis. The suggested outpatient follow-up is 7-10 days: Lab work such as CBC, electrolytes, renal function, liver enzymes, CRP, ESR, PCT, coagulation, viscoelastic test, D-dimer, ferritin, LDH; echocardiogram; ECG; Holter monitor if 1st-degree AVB or arrhythmia; and pharmacological decisions. 4-6 weeks: Echocardiogram, ECG, Holter monitor if 1st-degree AVB or arrhythmia; if normal echocardiogram, consider stopping

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aspirin. 4-6 months: echocardiogram, ECG, Holter monitor if 1st-degree AVB or arrhythmia. Exercise stress test for patients with a history of ventricular dysfunction, elevated BNP, or elevated troponin. Consider cardiac MRI in patients with a history of ventricular dysfunction, elevated BNP, or elevated troponin. If the echocardiogram is expected, consider stopping aspirin. Other pharmacological decisions. 9-12 months: Echocardiogram, ECG, Holter monitor if 1st-degree AVB or arrhythmia; If normal echocardiogram, consider stopping aspirin. More frequent follow-up may be necessary if there is ventricular dysfunction or coronary artery dilation [7,15].

These are the suggested measures for follow-up in patients with myocarditis in MIS-C. However, it is necessary to clarify the impact on the clinical prognosis in this population [38] and thus determine more specific behaviors.

Conclusion

The pediatric population is at low risk for COVID-19 complications. However, there have been cases of myocarditis in MIS-C post-COVID-19 infection that have required further studies. Most studies agree that MIS-C is related to a post-infectious immune-mediated complication. In contrast, acute myocardial dysfunction is an infrequent finding among patients, and the risk is still 30 times higher in COVID-19 patients. Short-term complications have been reported, but long-term complications are still under study. Management has been based on treatments of similar diseases. The prognosis has been favorable as most patients have had complete recovery before discharge. Moreover, it is necessary to clarify the impact on the clinical prognosis in this population and thus determine more specific interventions. Follow-up should be done for up to one year from diagnosis to confirm complete resolution.

References

1. (2022) Covid-19 dashboard by the center for systems science and engineering (CSSE) at Johns Hopkins University (JHU).
2. Park H, Yun KW, Kim KR, Song SH, Ahn B, et al. (2021) Epidemiology and clinical features of myocarditis/pericarditis before the introduction of mRNA COVID-19 vaccine in Korean children: Multicenter study. J Korean Med Sci 36(32): e232.
3. Rowley A (2020) Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. Nat Rev Immunol 20(8): 453-454.
4. Alsaied T, Tremoulet AH, Burns JC, Saidi A, Dionne A, et al. (2021) Review of cardiac involvement in multisystem inflammatory syndrome in children. Circulation 143(1): 78-88.
5. Gorbalenya AE, Baker SC, Baric RS (2020) The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 5(4): 536–544.
6. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC (2020) Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. JAMA 324(8): 782-793.
7. Sperotto F, Friedman KG, Son MBF, Vanderpluym CJ, Newburger AW, et al. (2021) Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr 180 (2): 307-322.
8. Das BB, Sexon SK, Deshpande S, Shekerdemian LS (2021) A review of the cardiac and cardiovascular effects of covid-19 in adults and children. Tex Heart Inst J 48(3): e207395.
9. Cevins C, Luka M, Smith N, Meynier S, Magérus A, et al. (2021) A monocyte/dendritic cell molecular signature of SARS-CoV-2-related multisystem inflammatory syndrome in children with severe myocarditis. Med NY 2(9): 1072-1092.e7.
10. McMurray JC, May JW, Cunningham MW, Jones OY (2020) Multisystem inflammatory syndrome in children (MIS-C), a post-viral myocarditis and systemic vasculitis-a critical review of its pathogenesis and treatment. Front Pediatr 8: 626182.
11. Matsubara D, Chang J, Kauffman HL, Wang Y, Nadaraj S, et al. (2022) Longitudinal Assessment of cardiac outcomes of multisystem inflammatory syndrome in children associated with COVID-19 infections. JAHA 11(3): e023251.
12. Ferrero P, Piazza I, Bonino C, Ciuffreda M (2020) Patterns of myocardial involvement in children during COVID-19 pandemic: early experience from northern Italy. Ann Pediatr Cardiol 13(3): 230-233.
13. Sanna G, Serrau G, Bassareo PP, Neroni P, Fanos V, et al. (2020) Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review. Eur J Pediatr 179(7): 1079-1087.
14. Shah HP, Frye R, Chang S, Faherty E, Steele J, et al. (2021) Challenges of diagnosing viral myocarditis in adolescents in the era of COVID-19 and MIS-C. Case Rep Pediatr 2021: 4797498.
15. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, et al. (2020) Multisystem Inflammatory Syndrome in US. Children and Adolescents. N Engl J Med 383(4): 334-346.
16. Dobson CP (2021) Cardiac sequelae of COVID-19 in children and young adults. Pediatr Ann 50(3): e128-e135.
17. Wolfler A, Mannarino S, Giacomet V, Camporesi A and Zuccotti G (2020) Acute myocardial injury: a novel clinical pattern in children with COVID-19. Lancet Child Adolesc Health 4(8): e26-e27.
18. Tissières P, Teboul JL (2020) SARS-CoV-2 post-infective myocarditis: the tip of COVID-19 immune complications? Ann Intensive Care 10(1): 98.
19. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, et al. (2020) Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 324(3): 259-269.
20. Vukomanovic VA, Krasic S, Prijic S, Ninic S, Minic P, et al. (2021) Differences between pediatric acute myocarditis related and unrelated to SARS-CoV-2. Pediatr Infect Dis J 40(5): e173-e178.
21. Stierman B, Abrams JY, Godfred-Cato SE, Oster ME, Meng L, et al. (2021) Racial and ethnic disparities in multisystem inflammatory syndrome in children. AAP 40(11): e400-e406.
22. Capone CA, Misra N, Ganigara M, Epstein S, Rajan S, et al. (2021) Six-month follow-up of patients with multisystem inflammatory syndrome in children. AAP 148(4): e2021050973.
23. Jaiswal V, Sarfraz Z, Sarfraz A, Mukherjee D, Batra N, et al. (2021) COVID-19 Infection and Myocarditis: A State-of-the-Art Systematic Review. J Prim Care Community Health 12: 21501327211056800.
24. Boehmer TK, Kompaniyets L, Lavery AM, Hsu J, Ko JY, et al. (2021) Association between COVID-19 myocarditis using hospital-based administrative data--United States, March 2020-January 2021. MMWR Morb Mortal Wkly Rep 70(35): 1228-1232.

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25. Priyadarshni S, Westra J, Kuo Y, Baillargeon JG, Khalife W, et al. (2021) COVID-19 Infection and Incidence of Myocarditis: A Multi-Site Population-Based Propensity Score-Matched Analysis. Cureus 14(2): e21879.

26. Carretta DM, Silva AM, D'Agostino D, Topi S, Lovero R, et al. (2021) Cardiac Involvement in COVID-19 Patients: A Contemporary Review. Infect Dis Rep 13(2): 494-517.

27. Ho JS, Sia CH, Chan MY, Lin W, Wong RC (2020) Coronavirus-induced myocarditis: A meta-summary of cases. Heart Lung 49(6): 681-685.

28. Rathore SS, Rojas GA, Sondhi M, Pothuru S, Pydi R, et al. (2021) Myocarditis associated with Covid-19 disease: A systematic review of published case reports and case series. Int J Clin Pract 75(11): e14470.

29. Kariyanna PT, Sutarjono B, Grewal E, Singh KP, Aurora L, et al. (2020) A Systematic Review of COVID-19 and Myocarditis. Am J Med Case Rep 8(9): 299-305.

30. Can the COVID-19 Vaccine Cause Myocarditis? (2022). Accessed: April 22, 2022.

31. Truong DT, Dionne A, Muniz JC, McHugh KE, Portman MA, et al. (2022) Clinically Suspected Myocarditis Temporally Related to COVID-19 Vaccination in Adolescents and Young Adults: Suspected Myocarditis After COVID-19 Vaccination. Circulation 145(5): 345-356.

32. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, et al. (2020) Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. Circulation 142(5): 429-436.

33. F Son MB, Friedman K (2022) COVID-19: Multisystem inflammatory syndrome in children (MIS-C) management and outcome. Accessed: July 5, 2022.

34. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, et al. (2021) American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 1. Arthritis Rheumatol 73(4): e13-e29.

35. Abdel-Haq N, Asmar BI, Deza Leon MP, McGrath EJ, Arora HS, et al. (2021) SARS-CoV-2-associated multisystem inflammatory syndrome in children: clinical manifestations and the role of infliximab treatment. Eur J Pediatr 180(5): 1581-1591.

36. Radia T, Williams N, Agrawal P, Harman K, Weale J, et al. (2021) Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation. Paediatr Respir Rev 38: 51-57.

37. Canter CE, Simpson KE (2014) Diagnosis and treatment of myocarditis in children in the current era. Circulation 129(1): 115-128.

38. Rodriguez-Gonzalez M, Castellano-Martinez A, Cascales-Poyatos HM, Perez-Reviriego AA (2020) Cardiovascular impact of COVID-19 with a focus on children: A systematic review. World J Clin Cases 8(21): 5250-5283.

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