REVIEW ARTICLE

IDENTIFYING MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN AFTER COVID-19 INFECTION

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Introduction: Since its discovery, the novel coronavirus disease 2019 (COVID-19) has evolved into a global pandemic that has affected millions. The pediatric population was once thought to be mostly spared from the SARS-CoV-2 virus. However, a severe hyperinflammatory sequela of the virus known as multisystem inflammatory syndrome in children (MIS-C) has since been identified and poses a great risk to pediatric morbidity and mortality. The goal of this manuscript is to clarify and characterize MIS-C as a diagnosis, including current management and future considerations.

Methods: A thorough literature search was performed using Google Scholar and PubMed databases for articles published January 2020 through August 2021.

Results: A two-tiered diagnostic approach was created for any pediatric patient presenting with fever and an epidemiologic link to SARS-CoV-2. The mean age at time of diagnosis was 9.3 years old, with 56.8% of patients identifying as male and the majority identifying as either Hispanic (36.5%) or Black (35.1%). Common signs and symptoms included fever, cough, tachycardia and tachypnea. Current treatment recommendations included IVIG, glucocorticoids, and aspirin, with the more severe cases needing hospitalization and immune modulator therapy. Discussion: MIS-C is a serious and potentially fatal sequelae after COVID-19 infection in the pediatric population. Much is still unknown regarding the long-term effects of MIS-C. Further emphasis should be placed on identifying definitive treatment and preventative strategies. Osteopathic family physicians are the primary providers for many of the patients who may present with signs and symptoms of MIS-C, and familiarity with the workup and treatment can help improve care.

INTRODUCTION

On December 31, 2019, the World Health Organization (WHO) was first notified by a group of scientists in China of a group of unexplained cases occurring in Wuhan, China and presenting as a pneumonia-like illness. Over the next 18 months, this unknown illness would become known around the world as the novel coronavirus disease 2019 (COVID-19), which has developed into a global pandemic with almost 200 million confirmed cases and over 4 million reported deaths as of the start of August 2021.[1]

During this time, much surrounding COVID-19, including its diagnosis, management and prevention, has continued to evolve. The causative agent—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—continues to spread across the globe despite continued efforts to contain the virus.[2,3,4] The development of a vaccine has helped to decrease transmission rates, hospital admissions and overall mortality.[4] However, new COVID-19 variants, skepticism and misinformation surrounding the vaccine, and social and political biases, have made controlling the spread of SARS-CoV-2 difficult.[5,6]

While in adults the presentation and severity of COVID-19 can vary greatly, it was initially thought that children were mostly spared from showing signs and symptoms of the virus, and therefore assumed to have lower rates of infectivity.[7,8] In an early study of 171 children with confirmed COVID-19 diagnoses, it was found that only 3 cases needed intensive care unit admission and only 1 case resulted in death.[9] These results suggested that children were less likely to be infected by SARS-CoV-2, and those who were infected had a milder clinical course when compared to adults. However, most of the children in these studies were symptomatic when diagnosed, and therefore only followed until symptom

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resolution. Because many children infected with COVID-19 are asymptomatic, this made determining an exact rate of infectivity difficult for this patient population, as well as challenging when trying to identify any possible negative effects the virus could have in both symptomatic patients and asymptomatic carriers.

In April 2020, a United Kingdom report highlighted a group of 8 previously healthy children presenting with a hyperinflammatory state and signs of multiple-organ damage.[10] While never tested directly, all of these cases were linked to recent COVID-19 exposure. This newly identified hyperinflammatory syndrome associated with COVID-19 was eventually named by the U.S. Centers for Disease Control and Prevention (CDC) as multisystem inflammatory syndrome in children (MIS-C) and has become a serious complication of the virus with morbidity and mortality rates in children much higher than previously suspected.[11,12]

With the discovery of new variants, rates of COVID-19 and MIS-C diagnosis in children have only continued to increase. Since there is currently no diagnostic testing for MIS-C, it presents a major public health concern for the pediatric population. The authors wish to clarify and further characterize the epidemiology, pathogenesis, clinical identification, symptomatology, diagnostic criteria, management and long-term outcomes of MIS-C, including new advancements and understanding of this novel syndrome since its discovery.

METHODS

A thorough search of available literature in the English language was performed using Google Scholar and PubMed databases for articles published from January 2020 through August 2021. Due to the rapidly changing and continued evolving understanding of COVID-19 and MIS-C, multiple various search criteria were used, including "coronavirus disease 2019;" "severe acute respiratory syndrome coronavirus 2;" "multisystem inflammatory syndrome in children;" "hyperinflammatory syndrome;" "Kawasaki disease;" "toxic shock syndrome;" "shock;" "children;" "pediatrics;" "pandemic;" and "vaccine."

RESULTS

Several meta-analyses and systematic reviews[13–18] have been conducted since the discovery of MIS-C, encompassing over 500 published articles to date. A summary of findings is detailed below, including diagnostic criteria, demographics, clinical characteristics, laboratory and imaging findings, treatment and management, and clinical outcomes and complications of patients with MIS-C.

Diagnostic criteria

The CDC and WHO have similar case definitions for diagnosing MIS-C, both of which are outlined in Table 1.[19,20] While these criteria were initially used to make a formal diagnosis, as MIS-C became more widespread, a tiered diagnostic approach was adopted for any patient presenting to the emergency department with unremitting fever and an epidemiologic link to SARS-CoV-2.[16,21]

TABLE 1:
CDC and WHO case definitions of multisystem inflammatory syndrome in children.

CRITERIA	CDC CASE DEFINITION	WHO CASE DEFINITION
Age	<21 years old	<19 years old
Fever	Fever >38.0°C (100.4°F) for ≥24 hours **or** subjective fever lasting ≥24 hours	Fever for ≥3 days
Clinical Presentation	**2 or more** organ system involvement: o Cardiac o Renal o Respiratory o Hematologic o Gastrointestinal o Dermatologic o Neurological	**2 or more** of the following: o Rash or non-purulent conjunctivitis or muco-cutaneous inflammation o Hypotension or shock o Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities o Evidence of coagulopathy o Acute gastrointestinal problems
Inflammatory Laboratory Evidence	Including **any** of the following: Elevated CRP, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, LDH, IL-6, neutrophilia, lymphocytopenia or hypoalbuminemia	**1 or more** of the following: Elevated markers of inflammation such as ESR, CRP **or** procalcitonin
Diagnosis of Exclusion	No alternative plausible diagnoses	No other obvious microbial cause of inflammation (including sepsis, or bacterial shock syndromes)
Link to SARS-CoV-2	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test **or** COVID-19 exposure within the 4 weeks prior to onset of symptoms	Evidence of COVID-19 (RT-PCR, antigen test, or serology positive) **or** likely contact with patients with COVID-19

This includes performing an initial evaluation screen (tier 1) through measuring a complete blood count (CBC), complete metabolic panel (CMP), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and SARS-CoV-2 PCR laboratory values. If these results are consistent with MIS-C diagnosis, a complete diagnostic evaluation (tier 2) should be performed. Tier 2 evaluation consists of more complex testing, including measuring brain natriuretic peptide (BNP), troponin-T, procalcitonin, ferritin, prothrombin time (PT), partial thromboplastin time (PTT), D-dimer, fibrinogen, lactic dehydrogenase (LDH) and triglyceride levels, as well as a cytokine panel, SARS-CoV-2 serology, blood smear, electrocardiogram (ECG) and echocardiogram.[21] Blood cultures are also indicated for patients presenting with severe symptoms, such as fever and 2 or more organ systems involvement.

The tier approach is a good evaluation design, as it permits effective and cost-efficient screening for patients who may have MIS-C. Since MIS-C is still a rare complication of SARS-CoV-2 infection with a current estimated incidence rate of 2 out of 200,000 individuals,[22] it is not necessary to perform a full work-up on each patient. However, in patients who exhibit signs and symptoms of MIS-C, a second, more thorough evaluation should be completed due to the severe cardiovascular and respiratory complications that MIS-C can cause.

Demographics

The mean age of patients at time of diagnosis of MIS-C was 9.3 years old, with 56.8% of patients identifying as male.[17] Patient race/ethnicity varied, with 36.5% identifying as Hispanic, 35.1% Black, 25.2% white, 16.2% Asian, and 14% other.[18] Of all patients diagnosed with MIS-C, 31% reported a previous comorbid condition, the most common being a past medical history of obesity or asthma.[1]

Clinical characteristics

All patient presentations met the criteria for MIS-C diagnosis. The most common symptoms present at time of diagnosis were fever, diarrhea, cough and abdominal pain. Common clinical signs were mainly cardiovascular dysfunction (tachycardia, hypotension) followed by respiratory dysfunction (tachypnea, low oxygen saturation).[14]

Laboratory and imaging findings

The most common laboratory findings were elevated inflammatory markers. Of these, the most elevated were ESR and CRP, albeit these are considered non-specific markers of inflammation for a variety of disease processes.[17] While imaging was rarely necessary at time of diagnosis, the most commonly performed was echocardiography, and it frequently demonstrated decreased cardiac ventricular function.

Because the clinical presentation and laboratory findings of MIS-C can closely mimic other pediatric inflammatory diagnoses, most especially Kawasaki disease, careful consideration must be given in order to make the correct diagnosis. Kawasaki disease is an acute inflammatory illness of unknown origin that was originally founded in Japan in 1967 and primarily affects children 5 years of age and younger.[12] Common initial signs and symptoms include fever, a classic "strawberry" red tongue, rash, irritability and fatigue,[12] many of which are also seen in patients with MIS-C.

TABLE 2:
Comparison of MIS-C and Kawasaki Disease.

	MIS-C	KAWASAKI DISEASE
Age	Older children and adolescents with median ages of 8–11 years	Infant and younger children, 76% of affected children <5 years
Race and Ethnicity	Black and Hispanic descent	Asian descent
Clinical Presentation:		
GI Symptoms	GI symptoms very common (53%–92%)	GI symptoms less common (20%)
Myocardial Dysfunction and Shock	Myocardial dysfunction common, elevated BNP (73%), troponin (50%), 48% receive vasoactive support	Myocardial dysfunction much less common, normal troponin, 5% receive vasoactive support
Organ Dysfunction	Multiorgan dysfunction common	Multiorgan dysfunction uncommon
Inflammatory Markers	Highly elevated CRP, ferritin, procalcitonin and D-dimer, lymphopenia and thrombocytopenia	Elevated CRP and D-dimer, normal ferritin, thrombocytosis
Treatment	IVIG, corticosteroids, IL-1 blocker, IL-6 inhibitors	IVIG, corticosteroids, IL-1 blocker
Average Outcomes	Fatality rate: 1.4%–1.7%	Fatality rate: 0.01%

Table 2 below compares the most common presentations and objective data for both MIS-C and Kawasaki disease.[23,24] Utilizing similar guidelines and algorithms as seen in Table 2 can greatly impact patients' medical decision making by allowing for accurate diagnosis and subsequent management.

Symptomatic treatment, clinical management and complications

The overall goal of MIS-C treatment is to stabilize the patient and prevent life-threatening long-term complications, especially any cardiac manifestations such as myocardial fibrosis/scarring and coronary artery aneurysms. To prevent these complications, most patients with confirmed MIS-C diagnosis were initially stabilized with intravenous immune globulin (IVIG) as well as adjunctive high-dose glucocorticoids for more severe cases.[15–17] Daily therapeutic aspirin was also given to patients who had an increased risk for coagulation and thrombosis, seen with elevated D-dimer and fibrinogen.[25]

According to several recent studies, IVIG and steroids are considered mainstay therapy for all patients diagnosed with MIS-C.[15–17] IVIG therapy has been shown to reduce inflammatory markers in MIS-C patients post-infusion, as well as result in overall decreased rates of myocarditis compared to those who did not receive IVIG.[16,26] In a study that compared the use of combination IVIG and steroid therapy versus IVIG monotherapy on the development of cardiac dysfunction, it was found that there was a 44% risk reduction in those patients receiving combination therapy.[2]

In more severe treatment-resistant cases of MIS-C, additional treatment modalities should be initiated. For those patients presenting with severe multisystemic shock, empiric broad-spectrum antibiotic therapy should be started following a blood culture draw.[16,17,27] In the pediatric setting, an appropriate antibiotic regimen of ceftriaxone plus vancomycin is usually sufficient.[27] If blood culture results are negative infection, antibiotic therapy should be discontinued. Furthermore, in patients who continued to worsen with decreased responses to IVIG, steroids and/or aspirin alone, it is recommended that immune modulators be initiated. These include anakinra (IL-1 receptor blocker), tocilizumab (IL-6 inhibitor) and infliximab (anti-TNF-α), which can be added to the treatment regimen and has been shown to have improved outcomes in some patients.[27] The efficacy of these medications in the treatment of MIS-C, as well as other immune modulators, are currently still being tested.

Finally, serial laboratory testing of systemic inflammatory markers (ESR and CRP) and cardiac monitoring (troponin-T and BNP) were performed to track the progress of the patient. Additionally, other systemic complications, such as respiratory distress, signs of hypercoagulability and development of systemic shock were frequently monitored and evaluated.[15–17]

Prevention

There is still much to elucidate surrounding the pathogenesis and possible transmission of MIS-C. Because studies have shown that MIS-C symptoms only present in relation to either active COVID-19 infection or recent exposure, SARS-CoV-2 may act as a trigger for immunomodulator in the development of MIS-C.[28] There is still confusion regarding why some children develop MIS-C, while others do not. Some researchers suggest that pre-existing conditions, race and severity of inflammatory response to COVID-19 may play a role in its development.[29] However, no definitive cause or explanation has yet been proven. Therefore, it is important to focus on preventative public health policies that decrease transmission of SARS-CoV-2 to decrease the incidence of MIS-C. These include strategies such as wearing masks, socially distancing, proper hand hygiene and encouraging COVID-19 vaccination.

Comparison to adults

As knowledge surrounding MIS-C continues to evolve and expand across the globe, there have been a few, rare, documented cases of a similar hyperinflammatory response in connection with recent COVID-19 exposure/diagnosis in adults.[30] So called "MIS-A" because they are occurring in adults at least 21 years of age, these cases are being considered the same as MIS-C, with similar treatment and management strategies. While MIS-C has been recognized as a true syndrome in the pediatric population, MIS-A is not as well defined.[31]

DISCUSSION

Since the first diagnosed cases in 2020, COVID-19 has rapidly developed into a very serious global health concern. In part due to its high infectivity rate, the SARS-CoV-2 virus has spread to nearly every country in the world, resulting in hundreds of millions of positive cases, and almost 4 million deaths worldwide. As a relatively new pandemic, new discoveries about the virus and a better understanding of its potential impact are continuing to evolve. What was once thought of as a disease that mainly impacted adult patients and the immunocompromised, it is now known that COVID-19 also greatly impacts the pediatric population, with hundreds of new cases occurring in the United States alone. Even as variants spread, they are affecting many children, resulting in increased pediatric morbidity and mortality rates.[32]

MIS-C, a very serious sequelae of SARS-CoV-2 infection, is quickly becoming a public health concern. Due to the severity of symptoms, as well as a current lack of understanding surrounding future complications from the disease, much has been discussed as to the best diagnostic, management and preventative measures for children against MIS-C.

A two-tier diagnostic approach to MIS-C is the current recommendation to minimize costs, time, and resources.[16,21] Any pediatric patient who presents with fever, multi-organ

symptoms, and recent association with COVID-19 should be tested for SARS-CoV-2 infection and referred to a pediatric infectious disease specialist/hospital unit. Symptomatic treatment with IVIG, glucocorticoids, and/or aspirin, as well as close monitoring for specific organ system findings is recommended while serial inflammatory marker labs are performed to aid in monitoring disease progression.[17,26]

Because MIS-C is a relatively new diagnosis, future emphasis needs to be placed on monitoring the evolution of MIS-C diagnosis, including more definitive testing and treatment options. Additionally, future research should focus on determining any sequalae for children who are diagnosed with MIS-C, including possible organ system complications, weakened immune systems, or risk for future infections. As current vaccines are being authorized for children aged 12–18 years (as well as possible authorization for younger ages in the future), it is important to determine the efficacy of these vaccines in preventing not only SARS-CoV-2 infection, but also in preventing MIS-C diagnosis. As more is discovered surrounding the pathogenesis and clinical outcomes of MIS-C, it is important to consider new treatment and management strategies, including immune modulators such as anakinra, tocilizumab, infliximab and others, which are currently undergoing clinical trials.[33]

CONCLUSION

Since its discovery in late 2019, COVID-19 infection from the SARS-CoV-2 virus continues to pose a serious epidemiologic threat to most of the world. The pediatric population faces a unique and unexpected sequela of being infected by the virus after the discovery of MIS-C hyperinflammatory syndrome, which has affected more than 6000 pediatric individuals in the United States alone. Due to the severity of symptoms, as well as a current lack of understanding surrounding future complications from the disease, much has been discussed as to the best diagnostic, management, and preventative measures for children against MIS-C. Following a two-tiered approach to diagnosis MIS-C is critical for accurate identification of the syndrome. Current evidence suggests symptomatic patients should be treated with IVIG and glucocorticoids, as well as monitoring for worsening organ dysfunction. As new discoveries and understandings of MIS-C continue to evolve, it is important to continue following the latest CDC and WHO guidelines for appropriate treatment and management. The osteopathic family physician plays a key role in primary care in the United States, and prompt identification and treatment of this disorder is critical.

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