SciMedCentral

Annals of Pediatrics & Child Health

Research Article

Insights into Pediatric Multisystem Inflammatory Syndrome Associated With Kawasaki Disease and Covid-19

Khulud Y Qutub[1], Elaf M Aljafri[1], Elaf A AlHusaini[1], Fatimah M Bahathiq[1], and Ibrahim Al-Harbi[2]*

[1]University of Um AlQura, UAE

[2]Consultant Pediatric Hematology Oncology, King Fahad Armed Forces Hospital, UAE

*Corresponding author

Ibrahim Al-Harbi, Consultant Pediatric Hematology Oncology, King Fahad Armed Forces Hospital, Jeddah 23311, Saudi Arabia, UAE, Email: ialharbi@hotmail.com

Submitted: 11 January 2022

Accepted: 28 January 2022

Published: 31 January 2022

ISSN: 2373-9312

Keywords

- SARS-CoV-2; COVID-19; Coronavirus; Kawasaki disease; KD, Multisystem inflammatory syndrome; MIS-C; PIMS-TS; MIS-C; Pediatrics

Abstract

Our study aims to assess the differences between MIS-C and KD in the context of the COVID-19 pandemic. The authors' personalized assessment of the relationship between the two circumstances is presented in the present review. A critical examination of the published clinical results was done and the differences between MIS-C and KD in the context of the COVID-19 pandemic were analyzed and presented. There is a clear relationship between COVID-19 infection and the development of MIS-C. The number of children with KD and COVID-19 who have MIS-C is significantly higher, and it is linked to increased incidence of cardiac ailments as well as a higher rate of pediatric intensive care hospitalization. A lot of clinical and laboratory results pertain to cellular phenotypic data. Antibody data suggests that KD and MIS-C have slightly comparable but largely distinct markers.

INTRODUCTION

Today, COVID-19 pandemic has not only challenged the global public health but is also threatening the integrity of the international health care system. The first confirmed case of COVID-19 was reported in 2019 in Wuhan, Hubei Province, China [1]. SARS-CoV-2 infection can affect individuals of any age group, with higher incidence among the adults of middle age and older age, although a severe course of the disease has been observed in individuals of age more than 80 years, along with a high mortality rate (15%) [2]. On the other hand, 14% of the pediatric population is affected with a mild course of COVID-19 and a better prognosis. SARS-CoV-2 infection is associated with multisystem inflammatory syndrome in children (MIS-C), a novel ailment that affects young individuals and mimics other pediatrics inflammatory syndromes, such as Kawasaki Disease (KD). KD is a febrile, acute, systemic vasculitis, affecting the children with age 5 years or less. It is associated with polymorphic rash, fever, conjunctivitis, strawberry tongue, mucosal erythema, induration of feet and hands, etc [3].

On May 13, 2020, the Centers for Disease Control (CDC) published a case definition for MIS-C [4]. As of 15th May, 2021, the World Health Organization (WHO) has established a preliminary case definition in children [5]. Initially, the disease has a severe presentation with some patients requiring mechanical circulatory and respiratory assistance, although the rapid recovery with the use of immunoglobulin and steroids is currently observed. However, the long-term outcomes are still not known [6].

The onset of the MIS-C is the most confusing occurrence during COVID-19 pandemic [7]. A lot of these children affected by MIS-C required immediate intensive care therapy owing to multiorgan failure and circulatory shock, which was frequently caused by myocardial infarction. There were indications of macrophage activation syndrome (MAS) in some of them. Acute phase reactants were considerably elevated, as were the levels of D-dimer, ferritin, lymphopenia, hypoalbuminemia, and thrombocytopenia as evidenced from the lab findings.

According to epidemiologic statistics, MIS-C appeared 3–8 weeks following confirmed exposure or prior infection, indicating a post-SARS-CoV-2 infection inflammatory response, presumably via adaptive immune system [8]. Moreover, the majority of these children possess SARS-CoV-2 antibodies; however, a small proportion also test positive for RT-PCR analysis. Nonetheless, higher cycle criteria for RT-PCR detection of the virus in individuals with MIS-C indicated that these individuals were no longer contagious. Previous studies have significantly intensified the debate regarding whether KD and MIS-C refer to the same ailment or they are two different conditions with similar clinical characteristics. Most of the researchers believe that KD and MIS-C are two separate entities [8,9], however, some researchers believe that the two disorders are part of a continuous spectrum, where the phenotypic disparities observed between these two ailments are attributed to the kinetics or amplitude of the immune response [10].

As it is still argued that whether KD and MIS-C are separate disorders or part of the same disease, in this review, an

attempt was made to analyze the evidence pertaining to the said condition. The authors' personalized assessment of the relationship between the two circumstances is presented in the present review.

KAWASAKI DISEASE (KD)

In the 1960s, KD was discovered in Japan by Dr. Tomisaku Kawasaki [11]. KD can be diagnosed using the criteria established by the American Heart Association in 2017 (Table 1) [11].The initial treatment recommended for KD patients is a high-dose intravenous IVIG injection (2 g/kg) within 10 days post diagnosis or onset of illness. Furthermore, a moderate to high dose (80–100 mg/kg/d) ASA should be administered reasonably until the fever disappears. Complications of the disease can arise if delayed or no treatment has been administered. Major complications include coronary dilation and aneurysms (26% to 40%), along with pericarditis (18%) and myocarditis (3%) (Table 2) [12].

Several therapeutic approaches for refractory instances of KD have been proposed, including further IVIG, corticosteroids, cyclosporine A, and cytokine blocking techniques. It is noteworthy

Table 1: Criteria of Kawasaki disease by 2017 Criteria of the American Heart Association.

Classic KD is diagnosed when having fever for at least 5 days (the day of fever onset is considered as the first day of fever) along with at least 4 of the 5 following principal clinical features. In the presence of ≥4 principal clinical features, particularly when redness and swelling of the hands and feet are present, the diagnosis of KD can be made with 4 days of fever, although experienced clinicians may establish the diagnosis with 3 days of fever in rare cases:
1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like
4. Erythema and edema of the hands and feet in the acute phase and/or periungual desquamation in the subacute phase
5. Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral
A thorough history may reveal the presence of ≥1 principal clinical features during the illness, but these features may be resolved by the time of presentation.
Patients lacking full clinical features of classic KD are often examined for incomplete KD (fever for ≥5 days plus two or three of the clinical criteria). The presence of coronary artery abnormalities confirms the diagnosis of KD in most cases.
Laboratory tests typically show normal or elevated white blood cell count with predominance of neutrophils and elevated levels of acute phase reactants such as C-reactive protein and erythrocyte sedimentation rate during the acute phase. It may also reveal the presence of low serum sodium and albumin levels, sterile pyuria, and elevated serum liver enzymes. Thrombocytosis is commonly observed in the second week after fever onset.
Other clinical findings may include the following:
Cardiovascular
• Myocarditis, pericarditis, valvular regurgitation, shock • Coronary artery abnormalities • Aneurysms of medium-sized noncoronary arteries • Peripheral gangrene • Aortic root enlargement
Respiratory
• Peribronchial and interstitial infiltrates on CXR • Pulmonary nodules
Musculoskeletal
• Arthritis, arthralgia (pleocytosis of synovial fluid)
Gastrointestinal
• Diarrhea, vomiting, abdominal pain • Hepatitis, jaundice • Gallbladder hydrops • Pancreatitis
Nervous system
• Extreme irritability • Aseptic meningitis (pleocytosis of cerebrospinal fluid) • Facial nerve palsy • Sensorineural hearing loss
Genitourinary
• Urethritis/mastitis, hydrocele
Others
• Desquamating rash in the groin • Retropharyngeal phlegmon • Anterior uveitis by slit-lamp examination • Erythema and induration at BCG inoculation site

Table 2: Complications of Kawasaki Disease.

Complication	Frequency	Comments
Shock	Approximately 7%	• Associated features: o Consumptive coagulopathy, cardiac abnormalities, such as CAAs, impaired left ventricular systolic function, higher C-reactive protein levels, and mitral regurgitation. Low responsiveness to IVIG therapy and requires additional treatment
Macrophage activation syndrome	Rare	• Reported rarely in children with persistent fever after IVIG treatment. Heralded by fall in ESR due to consumptive coagulopathy; also marked by ferritin levels >5000 ng/mL. Treatment with intravenous methylprednisolone, biologic response modifiers, or cyclosporine may be needed.
Cardiac complications		
Ventricular dysfunction	Occurs during the acute phase in one-quarter to one-half of patients with KD	7- In most cases, the ventricular function is only mildly or moderately depressed; severe ventricular dysfunction is rare. Most commonly manifested by tachycardia and an S3 gallop; uncommonly may progress to heart failure. It may be caused by direct myocardial inflammation (i.e., myocarditis) or from indirect negative inotropic effects of the systemic inflammatory response; ischemic cardiomyopathy may occur in patients after myocardial infarction. Ventricular function usually improves rapidly after treatment with IVIG.
Pericardial effusion	Occurs in <5% of patients	Very rarely causes tamponade.
CAAs (including dilation and/or aneurysm)	CAAs occur in approximately 25% KD patients in the IVIG era.	**1.** Cardiomyopathy may occur in patients after myocardial infarction. **2.** Ventricular function usually improves rapidly after treatment with IVIG. **3.** Risk factors associated with CAAs include: a. Late diagnosis and delayed treatment with IVIG - Age less than 1 year or more than 9 years b. Male sex - Fever for more than 14 days Serum sodium < 135 mEq/L, WBC count > 12,000/mm^3, hematocrit < 35%
Myocardial infarction	Rare	▪ The principal cause of mortality in KD. ▪ Occurs only in patients with CAAs, most frequently in patients with giant CAAs. The highest risk period is in the first 6 to 12 months, but risk continues into adulthood.
Arrhythmia	Rare	▪ Rarely occurs during the acute phase as a consequence of acute myocarditis. Beyond the acute phase, it primarily occurs due to myocardial infarction or ischemia. Ventricular arrhythmias are likely indicators of underlying myocardial damage and related to higher risk of sudden death.
Accelerated atherosclerosis	Rare in patients without CAAs	Patients who have CAAs in the acute phase that persists in follow-up are considered to have a higher risk of early atherosclerotic disease. Patients who have acute CAAs that eventually regress to normal are considered to have a moderate risk for early atherosclerotic disease. Patients who never had CAAs do not exhibit a risk for cardiovascular disease compared with the general pediatric population.
Noncoronary vascular involvement	Peripheral (rare) Visceral (very rare)	Peripheral aneurysms may present as pulsatile masses in axillae or inguinal area ▪ Peripheral arterial obstruction can lead to gangrene and ischemia. Most commonly occurs in children with severe KD, including those with large or giant CAAs.

that with KD, delaying anti-inflammatory medication and, as a result, prolonged systemic inflammation raises the risk of the associated problems [13]. As a result, early identification and adequate therapy are critical steps in avoiding treatment-refractory clinical outcomes.

COVID-19

Global public health has been facing challenges of various newly emerging and reemerging pathogens. New RNA enveloped viruses known as coronaviruses (COVID-19), that rapidly infect humans, other mammals, and birds lead to respiratory and other systemic involvement. Six species of coronaviruses were previously identified to infect humans, including SARS-COV-2, which is zoonotic in origin. In 2002 and 2003 too, coronavirus outbreaks occurred in Guangdong Province, China [14]. However, in December 2019 and January 2020, a novel CoV (2019-nCoV) was first recognized in Wuhan, China. The identification of the viruses was done through testing whole-genome sequencing, direct PCR, and culture of broncho-alveolar lavage fluid specimens [14].

By March 10, 2020, more than 110,000 infections and 4000 deaths had occurred worldwide owing to the COVID-19 infection. Furthermore, the Chinese Center for Disease Control and Prevention documented 72,314 infected cases with less

than 1% as children <10 years old [2]. As of 28th May 2020, UK reported a high incidence of confirmed cases (269,127) and up to 37,837 deaths [15]. Coronavirus primarily transmits from person to person via aerosols and respiratory droplets. Direct contact transmissions can also play a critical role in disease transmission, especially a hand to face contact.

Although COVID-19 virus can be transmitted from asymptomatic individuals, the most contagious individuals are those who are symptomatic [16,17]. Available data suggests that 33% of people with SARS-CoV-2 develop an asymptomatic infection that never develops into a symptomatic ailment [18]. Though they may give an imaging abnormality [19].

COVID-19 incubation period is generally 14 days after exposure, with most cases exhibiting symptoms 4-5 days post-exposure. The most common reported symptoms among symptomatic COVID-19 patients include cough (in 50% cases), fever (43% cases), myalgia (36% cases), headache (34% cases), dyspnea (29% cases), sore throat (20% cases), diarrhea (19% cases), nausea/vomiting (12% cases), loss of taste or smell (less than 10% cases), and abdominal pain [2]. The severity of symptoms ranges from mild to critical, as a patient can present with mild pneumonia only, or with respiratory failure, shock, or multiorgan dysfunction [20].

SARS-CoV-2 is diagnosed using various techniques with varying characteristics, such as the time of results, cost, availability and requirement of a trained person, sensitivity, and specificity. Some of these tests include nucleic acid amplification tests (NAATs) and antigen tests [21]. Children affected with SARS-CoV-2 infection generally develop a mild or asymptomatic condition and does not warrant a specific therapy. Most children with mild or moderate diseases can be managed as an outpatient using over-the-counter antipyretics, analgesics, and hydration with isolation measures [22]. Hospitalized children who require supplemental oxygen may be administered with dexamethasone or remdesivir [22]. The most common COVID-19 complication includes acute respiratory failure and multiple organ complications involving the heart [23].

Main treatment modalities employed for COVID-9-infected children include supportive therapy, such as respiratory support, antipyretics, hydration, etc [24]. Since children are typically excluded from early-stage clinical trials for the evaluation of new drugs, determining their efficacy and safety among pediatric cases is difficult.

Anti-inflammatory and antiviral medications should be investigated in severely affected pediatric cases, preferably in the context of a clinical study. Hyperinflammation and cytokine storm are frequently connected with severe illness, which can result in acute respiratory distress syndrome [25]. As a result, along with antivirals, immune-system-targeted medicines are also recommended. Numerous drugs have been recommended for children in hospitals, but not in the setting of a clinical study, rendering it challenging to estimate their effectiveness [26].

Remdesivir, an adenine nucleoside analogue, is an antiviral drug that has been indicated as the preferred treatment agent for pediatric COVID-19 cases [24]. It is also indicated for use in children with Ebola, but no pediatric safety information has been presented for this agent [27]. It appears to have some effectiveness in adults, and planned clinical trials with children are currently underway [28]. Remdesivir is currently recommended by the National Institutes of Health (NIH) for people with severe illness. Dexamethasone is recommended in pediatric patients who require mechanical breathing, according to the NIH criteria, which also suggest treatment based on individual factors in milder cases. Convalescent plasma is yet another prospective COVID-19 supplementary therapy; however, very few studies have assessed its efficacy [29].The usage of convalescent plasma in pediatric cases was first described by Shekerdemian et al. [26], although the outcomes were not explored. Several clinical studies pertaining to the use of convalescent plasma in pediatric COVID-19 cases are now underway.

The antiviral drug combination lopinavir/ritonavir is indicated to treat HIV infection in people of all ages, including infants. Given a lack of established efficacy and reservations about their pharmacodynamics, the NIH advises avoiding using this pair beyond the planned clinical trials on COVID-19 cases [21]. Another therapy option that has been posited is hydroxychloroquine. It has been reported to prevent the cellular entry of SARS-CoV-2 and impede with ACE-2 receptor glycosylation, thereby limiting the viral dissemination [30].The medication is easily accessible and has been approved by FDA for use in children population. A combinatorial therapy involving hydroxychloroquine and azithromycin is not recommended owing to a significant incidence of QT prolongation. Shekerdemian et al., documented its use in a children cohort in North American intensive care units, although no particular outcome of the said treatment regimen was reported [26]. Other than in clinical trials, the NIH advises against using this combinatorial regimen [NIH]. Tocilizumab has been administered in adults with episodes of hyperinflammation and cytokine storm caused by SARS-CoV-2 infection, with varying outcomes and in a limited number of pediatric cases who were presented at the ICU; however, its efficacy has not been ascertained [26,31].

MULTISYSTEM INFLAMMATORY SYNDROME (MIS)

A UK clinician identified increase in the reports of healthy children with symptoms of both MIS and KD. These children were tested positive for COVID-19 confirmed through serological assay or RT-PCR.

MIS-C is usually characterized by abdominal pain, persistent fever, vomiting, skin rash, diarrhea, and mucocutaneous lesions. Several severe cases also exhibit shock and hypotension. Most MIS-C patients show upregulated levels of markers of inflammation and heart damage [4]. Some cases also develop cardiac dysfunction, acute kidney injury, and myocarditis. However, none of the cases exhibit any trend of common symptoms and exhibit varying symptoms. Usually, the symptoms of MIS-C emerge weeks after SARS-CoV-2 infection [4].

The treatment of MIS-C requires the use of intravenous immunoglobulin and/or corticosteroid as the first-line therapy [22]. Clinical data on MIS-C gathered from several case series across the United States and Europe revealed that the general MIS-C presentation appeared to overlay KD with notable

variances. Rashes, lymphadenopathy, conjunctivitis, extremities edema, and fissured lips have been found in a large proportion of patients. Reduced LV function was noted in a number of patients. In many of these patients, cardiac magnetic resonance imaging revealed elevated signal intensity on T1 and T2-weighted imaging, commensurating with diffused myocardial edema and no augmentation on late gadolinium imaging, indicating notable fibrosis [32].

DISCUSSION

KD primarily affects children with age < 5 years. Children who develop KD are at risk for coronary arteries aneurysm. The incidence of KD varies from one region to the other. In US, KD incidence is about 25/100,000 children. On the other hand, in countries like Japan, the incidence is about 10 times higher than that [33].

Since KD tends to affect coronary arteries, it often leads to coronary artery aneurysms (CAAs). The risk of CAAs is approximately 25% in the untreated cases. This risk drops to 3% in treated cases. There is also a potential risk for sudden death especially in those children who did not get treated [34].

MIS-C is an acute illness that primarily affects children and has been found to have a temporal association with COVID-19. Since early 2020, many clinicians and researchers have found an association between COVID-19 and MIS-C [35].This suggests that both illnesses share a fundamental trigger in genetically vulnerable children. Contrary to this, some researchers present with an argument that MIS-C patients belong to an older age group, and it entails a more severe form of inflammation than KD, more gastrointestinal manifestations with a variety of clinical features, including thrombocytopenia, lymphopenia, elevated NT-proBNP, elevated troponin, elevated ferritin, and elevated D-Dimer, along with a greater potential for shock and LV dysfunction than KD patients [36]. Its clinical symptoms resemble those of toxic shock syndrome, which is caused by a surge in cytokine release, which causes capillary leak as well as hypotension [37].

The enormous stimulation of pro-inflammatory cytokines shown in MIS-C patients is similar to that observed in KD and adult COVID-19 patients [38].While toxic shock syndrome is associated with cytokine storm, SARS-CoV-2 infection leads to an upregulation of proinflammatory cytokines and macrophage activation [39]. Raised blood ferritin and IL-6 have been found to be substantial determinants of mortality among adult COVID-19 patients [40]. Macrophage activation syndrome (MAS), is associated with the cytokine storm in MIS-C, similar to KD and autoimmune disorders [41].

Coronavirus has been hypothesized as a possible cause for KD earlier, with inconsistent results. In limited case reports that could not be replicated in other places, specific coronavirus strains have also been linked to KD [42]. Because coronavirus is an RNA virus with a genome sensitive to mutation and genetic drift, identifying any drivers of the development of KD is hence difficult. Despite this, the lack of prior symptoms, a latency period of 3-6 weeks, and the increased prevalence of positive antibody responses show that SARS-CoV-2 is a trigger factor for the outlined condition [43,44].

Our study aims to assess the disparities between pediatric multi-system inflammatory syndrome and KD in the context of the COVID-19 pandemic. Several studies have focused on the relationship between MIS-C, COVID-19 and KD in children. Riphagen et al. [7], reviewed the files of 186 children with MIS-C. He found an incidence of COVID-19 in 70% of the cases (131 children out of 186). Another prospective observational study on children with SARS-CoV-2 infection and KD, with features that meet the criteria of KD, showed that these children presented symptoms that deviated from the symptoms of classic KD and resembled more to the symptoms of KD shock syndrome, which is a rare complication of KD. However, the procalcitonin levels in their cohort were 10 times higher compared to those recently reported in children with KD shock syndrome [45].

Anderson et al. [46], discovered that MIS-C patients exhibited higher IgG antibody levels that neutralize SARS-CoV-2 more efficiently compared to severe COVID-19 cases, implying that MIS-C patients have a better adaptive immune response. Regrettably, there are still significant disparities in the manifestation of MIS-C and SARS-CoV-2 infections, which may be linked to hereditary factors, such as HLA alleles.

Another group of researchers attempted to distinguish between COVID-19 and MIS-C infections. They reported that within 5.3 weeks since the pandemic began, epidemiological trend of MIS-C cases paralleled with the incidences of COVID-19 infection [3]. As a result, MIS-C did not commence with acutely infected patients at the outset of the outbreak. When matching symptoms such as fever were present in both the studied groups, cough and rhinorrhea were noted to be the most common in COVID-19 patients, but diarrhea, vomiting, and skin rash are more typical in MIS-C patients. Many additional researchers in other cohorts around the world have corroborated the distinctions between clinical presentations of COVID-19 and MIS-C [47].

A group of researchers recruited and monitored three groups of individuals: those with mild COVID-19 infection, severe COVID-19 infection, and no COVID-19 infection [48]. The clinical findings revealed severe innate immune dysfunction in all three groups of studied patients, as evidenced by raised cytokines levels, incidences of lymphopenia, and upregulation of endothelial dysfunction markers. All patients had aberrant erythrocyte phenotype with a higher proportion of severe COVID-19 infection and the maximum abnormalities in MIS-C patients. COVID-19 and MIS-C cases, on the other hand, exhibited considerable disparities. Severe COVID-19 infection was associated with aberrations comparable to those reported in MAS, including increased levels of ferritin, lactate, prothrombin, and transaminase, as well as significant thrombocytopenia. RT-PCR revealed low cycle threshold (Ct) counts, indicating a high viral load, along with markedly elevated levels of serum interferon-gamma levels in active cases. Furthermore, laboratory evidence revealed significant cardiac dysfunction and vascular injury in MIS-C cases, along with higher Ct. Elevated Ct values may indicate a lower viral load or residual RNA from a previously treated viral infection. In episodes of MIS-C, the patients were substantially younger. These findings indicate that MIS-C essentially activates the immune system and these patients, when exposed to SARS-CoV-2, do not experience an active coronavirus infection; however, they would still harbor viral RNA.

Another study published in August 2020 investigated the association of KD with a new ailment described as Kawa-COVID-19. They reported that Kawa-COVID-19 cohort differed from the classical KD in many aspects. Children with Kawa-COVID-19 are older at onset, higher incidence of myocarditis, and lower platelet count. The authors concluded, in children, CoV-2 infection is associated with Kawa-COVID-19 [9].

When contrasted to KDSS, MIS-C shock individuals demonstrated considerably more aberrant laboratory findings. CRP and ferritin levels were elevated in both patient groups who suffered shock, while ferritin and CRP levels were lower in KDSS patients. In addition, contrary to the COVID-19 patients, patients with KDSS exhibited negligible lymphopenia and only minor thrombocytopenia that resolved within a time period of 10-14 days and transitioned into thrombocytosis that lasted for several weeks. Platelet counts resumed to normal levels following the acute phase of COVID-19 in patients who experienced shock. The most distinguishing clinical hallmark of the MIS-C is myocardial involvement, which results in severe cardiac dysfunction and elevated levels of BNP and troponin in the laboratory findings. The most critically ill patients have the highest coronary artery damage and subsequent cardiac dysfunction. BNP and troponin levels were noted to be somewhat higher in many cases [49,50]. In another study, Consiglio et al.[51], reported that MIS-C had some similarities with both adult hyperimmune and Kawasaki syndrome post COVID-19 infections, although the majority of cytokine patterns were unique in each of these outlined categories. The cytokine levels of MIS-C cases and SARS-CoV-2-infected pediatric cases were more comparable to those of KD patients, yet they diverged many a times. The levels of CXCL-10, IL-6, ADA, IL-17, and stem cell factors were noted to be significantly different. Compared to MIS-C and SARS-CoV-2-positive patients, KD patients exhibited higher homogenous expression of CXCL10, IL-6, and IL-17. However, the levels were more varied between SARS-CoV-2-positive and MIS-C patients, with far less notable differences between the studied groups, implying a continuum rather than two distinct disorders.

Another epidemiological study reported that myocarditis and Kawasaki-Like Disease (KLD) are the most prevalent clinical features of CoV-PIMS cases with a frequency of 61% to 70% of the cases. Also, MAS was reported in 23% of the cohort. The study concluded that in pediatric cases, SARS-CoV-2 infection is associated with MIS emergence [52].

A recent study from New York reported a strong association between exposure to SARS-CoV-2 infection and MIS-C emergence in KD-affected children. In this study, among 17 patients who developed MIS-C post-COVID-19 infection, only 14 had KD, while those KD exhibited a higher incidence of cardiac complications [53].

CONCLUSION

We found that there is a definite link between pediatric COVID-19 infection and MIS-C. Among those with children with COVID-19 and KD, the proportion of MIS-C cases is even higher and is associated more with cardiac complications as well as increasing incidence of PICU admission. Unique features of COVID-19-associated MIS-C are higher CRP levels and neutrophil-lymphocyte ratio and lower platelets count. Such pediatric cases warrant early diagnosis and intervention because of the high risk of critical deterioration and pediatric intensive care admission among these children.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382: 727-733.
2. Wu Z, McGoogan J. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA, 2020; 323: 1239-1242.
3. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem inflammatory syndrome in children: A systematic review. EClinical Medicine. 2020; 26: 100527.
4. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C) [Internet]. Centers for Disease Control and Prevention. 2021.
5. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 [Internet]. World Health Organization. 2021.
6. Panupattanapong S, Brooks E. New spectrum of COVID-19 manifestations in children: Kawasaki-like syndrome and hyperinflammatory response. Cleve Clin J Med. 2020.
7. Riphagen S, Gomez X, Gonzalez- Martinez C, Wilkinson N, Theohari P. Hyper inflammatory shock in children during COVID-19 pandemic. Lancet. 2020; 395: 1607-1608.
8. Levin M. Childhood multisystem inflammatory syndrome - a new challenge in the pandemic. N Engl J Med. 2020; 383: 393-395.
9. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis. 2020; 79: 999-1006.
10. Yeung RS, Ferguson PJ. Is multisystem inflammatory syndrome in children on the Kawasaki syndrome spectrum? J Clin Invest. 2020; 130: 5681-5684.
11. McCrindle B, Rowley A, Newburger J, Burns J, Bolger A, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki Disease: A scientific statement for health professionals from the American Heart Association. Circulation 2017; 135: e927-e999.
12. Sundel R. Kawasaki disease: complications: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2019.
13. Gruber CN, Patel RS, Trachman R, Lepow L, Amanat F, Krammer F, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell. 2020; 183: 982-95.e14.
14. Ramcharan T, Nolan O, Lai C, Prabhu N, Krishnamurthy R, Richter AG, et al. Paediatric inflammatory multisystem syndrome: temporally associated with sars-cov-2 (pims-ts): cardiac features, management and short-term outcomes at a UK tertiary paediatric hospital. Pediatr Cardiol. 2020; 41: 1391-1401.
15. Bourouiba L. Turbulent gas clouds and respiratory pathogen emissions. JAMA. 2020; 323: 1837-1838.
16. Van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med. 2020; 382: 1564-1567.

17. Oran DP, Topol EJ. The proportion of SARS-CoV-2 infections that are asymptomatic: a systematic review. Ann Intern Med. 2021; 174: 655-662.

18. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020; 63: 706-711.

19. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, Felix SEB, et al. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69: 759-765.

20. Covid-19 testing: what you need to know [Internet]. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases. Testing for COVID-19. 2021.

21. 21. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [Internet]. National Institutes of Health. 2021.

22. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med. 2020; 383: 334-346.

23. Emergency preparedness and response: a multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). 2019. [Internet]. Centers for Disease Control and Prevention. 2021.

24. Chiotos K, Hayes M, Kimberlin DW, Jones SB, James SH, Pinninti SG, et al. Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2. J Pediatric Infect Dis Soc. 2020; 9: 701-715.

25. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol. 2020; 2: e474-e484.

26. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr. 2020; 174: 868-873.

27. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020; 395: 1569-1578.

28. Mulangu S, Dodd LE, Davey RT, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019; 381: 2293-2303.

29. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA. 2020; 323: 1824-1836.

30. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 6. 2020; 16.

31. Alzghari SK, Acuña VS. Supportive treatment with tocilizumab for COVID-19: a systematic review. J Clin Virol. 2020; 127: 104380.

32. Blondiaux E, Parisot P, Redheuil A, Tzaroukian L, Levy Y, Sileo C, et al. Cardiac MRI of children with multisystem inflammatory syndrome (MIS-C) associated with COVID-19: case series. Radiology. 2020; 202288.

33. Sadeghi P, Izadi A, Mojtahedi SY, Khedmat L, Jafari M, Afshin A, et al. A 10-year cross-sectional retrospective study on Kawasaki disease in Iranian children: incidence, clinical manifestations, complications, and treatment patterns. BMC Infect Dis. 2021; 368.

34. Son MBF, Newburger JW. Kawasaki Disease. Pediatr Rev. 2018; 39: 78-90.

35. Bautista-Rodriguez C, Sanchez-de-Toledo J, Clark BC, Herberg J, Bajolle F, Randanne PC, et al. Multisystem Inflammatory Syndrome in Children: An International Survey. Pediatrics. 2021; 147: e2020024554.

36. Loke YH, Berul CI, Harahsheh AS. Multisystem inflammatory syndrome in children: Is there a linkage to Kawasaki disease?. Trends Cardiovasc Med. 2020; 30: 389-396.

37. Low DE. Toxic shock syndrome. Crit Care Clin. 2013; 29: 651-675.

38. Chang F-Y, Chen H-C, Chen P-J, Ho M-S, Hsieh S-L, Lin J-C, et al. Immunologic aspects of characteristics, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). J Biomed Sci. 2020; 27: 72.

39. Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A. Aricò M, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League against rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Oganisation collaborative initiative. Arthritis Rheumatol. 2016; 68: 566-576.

40. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395: 1054-1062.

41. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020; 395: 1771-1778.

42. Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis. 2005; 191: 499-502.

43. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020; 10: 102-108.

44. Koyama T, Weeraratne D, Snowdon JL, Parida L. Emergence of drift variants that may affect COVID-19 vaccine development and antibody treatment. Pathogens. 2020; 9: 324.

45. Li Y, Zheng Q, Zou L, Wu J, Guo L, Teng L, et al. Kawasaki disease shock syndrome: clinical characteristics and possible use of IL-6, IL-10 and IFN-γ as biomarkers for early recognition. Pediatr Rheumatol Online J. 2019; 17: 1.

46. Anderson EM, Diorio C, Goodwin EC, McNerney KO, Weirick ME, Gouma S, et al. SARS-CoV-2 antibody responses in children with MIS-C and mild and severe COVID-19. medRxiv. 2020.

47. Aronoff SC, Hall A, Del Vecchio MT. The natural history of SARS-Cov-2 related multisystem inflammatory syndrome in children (MIS-C): a systematic review. J Pediatric Infect Dis Soc. 2020; 9: 746-751.

48. Diorio C, Henrickson SE, Vella LA, McNerney KO, Chase J, Burudpakdee C, et al. Multisystem inflammatory syndrome in children and COVID-19 are distinct presentations of SARS-CoV-2. J Clin Invest. 2020; 130: 5967-5975.

49. Cao L, Zhang S, Luo X, Wang E, Bai Y, Li Z, et al. Myocardium injury biomarkers predict prognosis of critically ill coronavirus disease 2019 (COVID-19) patients. Ann Palliat Med. 2020; 9: 4156-4165.

50. Grimaud M, Starck J, Levy M, Marais C, Chareyre J, Khraiche D, et al. Acute myocarditis and multisystem inflammatory emerging disease following SARS-CoV-2 infection in critically ill children. Ann Intensive Care. 2020; 10: 69.

51. Consiglio CR, Cotugno N, Sardh F, Pou C, Amodio D, Rodriguez L, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell. 2020; 183: 968-981. e7.

52. Belot A, Antona D, Renolleau S, Javouhey E, Hentgen V, Angoulvant F, et al. SARS-CoV-2-related paediatric inflammatory multisystem

syndrome, an epidemiological study, France, 1 March to 17 May 2020. Euro Surveill. 2020; 25: 2001010

53. Cheung EW, Zachariah P, Gorelik M, Boneparth A, Kernie SG, Orange JS, et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. JAMA. 2020; 324: 294-296.