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COVID-19 ASSOCIATED MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN AND ADULTS- A MINI REVIEW

Microbiology

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ABSTRACT

Children infected with Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) generally experience mild and non-fatal symptoms but recently there has been increasing recognition of a typical paediatric inflammatory multisystem disorder temporally associated with SARS-CoV-2 known as Multisystem Inflammatory Syndrome in children (MIS-C)which can lead to severe illness and long-term side-effects.Clinical and laboratory features of MIS-C are very similar to those of Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome, but the disease has some distinctive features with a clear pathophysiological and clinical definition. A similar condition has also been reported in case of some adult individuals associated with COVID-19, named as Multisystem Inflammatory Syndrome in adults (MIS-A). Most of these patients experiencea type of mixed cardiogenic and vasoplegic shock along with severe hyper-inflammation. This review briefly presents the highlights of the different reported cases of MIS-C and MIS-A presented till recently.

KEYWORDS

COVID, Multisystem Inflammatory Syndrome, Kawasaki Disease, Inflammation

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is spreading globally at a very alarming rate. This virus has already presented a multitude of clinical disorders of which most are extremely lethal. In the last few months a new paediatric disease associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has made its way into the limelight.

It is known as Multisystem inflammatory syndrome (MIS) and is potentially lethal among infants (1). Prior to May, 2020 independent reports across the world suggested that children infected with coronavirus disease 2019 (COVID-19) are highly resilient and present with a mild upper respiratory illness (2). But the whole concept changed from the month of May, 2020 when some investigators from UK published a report describing eight severely ill pediatric patients presenting hyperinflammatory shock with multiorgan involvement (3). Specifically, the clinical manifestation of these children included high fever, edema, rash, conjunctivitis, and gastrointestinal symptoms. The Royal College of Paediatrics and Child Health (RCPCH) immediately took notice of this case and referred to this acute condition as pediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) (4). As more cases were confirmed globally, the illness was labelled as multisystem inflammatory syndrome in children (MIS-C) by the Centre for Disease Control and Prevention (CDC) and the World Health Organization (WHO) (5).One of the initial challenges faced by the clinicians was differentiating patients with MIS-C versus Kawasaki disease (KD) or toxic shock syndrome (TSS) since the clinical symptoms and physiological interpretations are quite similar (6). KD is caused due to vasculitis and typically presents with high fever and acute mucocutaneous inflammation in children <5 years of age where as TSS is depicted by fever, rash, shock, vomiting and diarrhea (7). Since June 2020, several case reports have described a similar syndrome in adults. Most of these patients presented cardiovascular, gastrointestinal, dermatologic, and neurologic symptoms without severe respiratory illness and concurrently tested positive for SARS-CoV-2, by polymerase chain reaction (PCR) or antibody assays indicating recent infection (8).

A systematic search was performed using the following databases: PubMed, Scopus, and Science Direct. Additionally, references of included articles and any reviews focusing on MIS were also taken into consideration. Our search terms included “multisystem inflammatory syndrome in children”, “pediatric multisystem inflammatory syndrome” and “multisystem inflammatory syndrome in adults”. Only published peer-reviewed articles reporting cases of MISwere considered for this review.

Multisystem Inflammatory Syndrome In Children

Many cases has been reported in the last few months demonstrating a type of inflammatory syndrome in children severely affected with SARS-COV-2 and meet the current diagnostic criteria of MIS, but they most likely represent a very small proportion of the actual MIS-C cases worldwide (9). The limited number of reports available till date, a broader definition of MIS-C has been proposed which describes this illness as a spectrum ranging from persistent fever and inflammation, to characteristic features of Kawasaki disease in children, and to children who are severely ill with shock and multiple organ failure (10).Despite overlap in clinical presentation, the initially speculated relationship between MIS-C and toxic shock syndrome seems implausible because no evidence of staphylococcal or streptococcal toxins have been found to be involved in the cause of MIS-C. Overlap has also been observed between the diagnostic criteria of Kawasaki disease, Kawasaki disease shock syndrome, and the newly emerged MIS-C (11). According to criteria developed by the American Heart Association, the diagnosis of Kawasaki disease includes the presence of a high fever for 5 days or more and at least four of the five principle clinical features (12). Kawasaki disease shock syndrome is another severe form of Kawasaki disease, defined as complete or incomplete Kawasaki disease complicated by haemodynamic instability, resulting in the patient requiring intensive care, without evidence of another bacterial infection such as group A streptococcus or staphylococcus (13). The cause and factors contributing to the development of Kawasaki disease shock syndrome still remains mostly unclear, but a contributory role for underlying inflammation and more intense vasculitis has been suggested on the basis of laboratory results, progression, and the disease outcome (14). A large number of MIS-C cases present with Kawasaki-like clinical symptoms, and cardiac impairment and shock similar to Kawasaki disease shock syndrome (15).

Hypoalbuminemia, hyponatremia, gastrointestinal complications and intravenous immunoglobulin resistance are also common in Kawasaki disease shock syndrome as well as MIS-C (16). Although features of MIS-C overlap with those of Kawasaki disease, a recent study found a wider spectrum of MIS-C symptoms. Despite differences in the disease severity, cases of coronary aneurysms have occurred in many patients, including those with shock, fever or inflammation and may or may not meet the criteria for Kawasaki disease (17). In addition to a wider clinical spectrum, there are several other distinct features of MIS-C compared with Kawasaki disease, including the age and ethnic groups affected. Kawasaki disease typically affects children under 5 years of years age whereas patients with MIS-C are typically older, mostly above 7 years and show greater elevation of inflammatory markers (18). The main event of MIS-C that differentiates it from

Kawasaki disease is a more rapid and serious advancement of symptoms, especially fever and multisystem organ problems like cardiac and respiratory problems, most likely within a few days. Over 80% of patients with MIS-C also present with an unusual cardiac injury shown by high concentrations of troponin and brain natriuretic peptide, whereas others develop arrhythmia, left ventricle dysfunction, and unusual coronary dilatation or aneurysms (19). There are various risk factors for developing severe disease among children infected with SARS-CoV-2; the most common include age, viral load, and chronic comorbidities (20).

Multisystem Inflammatory Syndrome In Adults

Till date only three published case series were identified describing adult patients with manifestations consistent with MIS. The first study describeda total of seven young adult men aged 20–42 years without any previous medical history, who suddenly experienced mixed cardiogenic, vasoplegic shock and hyperinflammation along with high SARS-CoV-2 immunoglobulin G antibody titers indicating active or previous infection (21). All of the patients had markedly elevated inflammatory markers and required inotropes or vasopressors for treatment. All of them were treated with corticosteroids and anticoagulants. All seven patients recovered and were discharged home after 7 to 18 days of hospitalization with improved cardiovascular function (22). The second case series described multiple patientswith large-vessel strokes and associated with positive SARS-CoV-2 RNA in their body. These patients had elevated inflammatory markers and minimal respiratory symptoms, consistent with MIS-A (22). The authors of this study proposed endothelial dysfunction and coagulopathy related to SARS-CoV-2 infection as potential etiologies (23). Incidence of large-vessel stroke among young adults during this same time the previous year was statistically much lower (23). The third study described the pathologic findings of endothelialitis and complement deposition in the vessels of two patients with illness resembling MIS-A (cardiac dysfunction, abdominal signs and symptoms, and rash) associated with positive SARS-CoV-2 test results (24). One of these two patients had no underlying medical conditions and recovered; the other had multiple underlying conditions and was at higher risk for severe COVID-19. He died hours after seeking care. Pathologic findings were similar in case of both of these patients (25).

DISCUSSION

In the event of the current COVID-19 pandemic, there have been increasing observations of an acute inflammatory illness occurring mostly in children; 4–6 weeks after the peak of COVID-19 infections. The disease has a strong resemblance with Kawasaki disease and toxic shock syndrome but has been characterized separately by investigators (26). A similar inflammatory condition has also been observed in adults and found to involve multiple organ systems. The exact pathophysiology of this MIS in both children and adults is currently unknown. In some patients, persistent infection outside the upper respiratory tract have been observed with SARS-CoV-2 RNA identified inmultiple organs including the heart, liver, brain, kidneys, and gastrointestinal tract (27). Scientists have proposed different mechanisms for extrapulmonary dysfunction in COVID-19 including endothelial damage and thromboinflammation, dysregulated immune responses, and dysregulation of the renin-angiotensin-aldosterone system (28). The interval between infection and development of MIS in adults is still unclear, adding more to the uncertainty regarding whether MIS-A represents a manifestation of acute infection or an entirely post-acute phenomenon. In adult patients with COVID-19, dyspnea is experienced typically after about 5–8 days and critical illness about 10–12 days after onset of initial symptoms (29). In patients who reported typical COVID-19 symptoms before MIS onset, MIS-A was experienced approximately 2–5 weeks later. However, many MIS-A patients reported no preceding respiratory symptoms, making it difficult to estimate when initial infection occurred (30).The majority of patients with MIS-A survived, similar to those with MIS-C, associated with receiving care in acute, often intensive, health care settings (30). Thus from the various case reports and case series we have observed that many potential therapies might benefit these type of patients and hence clinicians should consider MIS within a broader differential diagnosis when caring forthe COVID-19 patients.

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