A link between the COVID-19 pandemic and Kawasaki-like multi-system inflammatory syndrome in children

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

Manal Fouad Elshamaa. A link between the COVID-1 pandemic and Kawasaki-like multi-system inflammatory syndrome in children. J Pre-Clin Clin Res. 2020; 14(4): 151–155. doi: 10.26444/jpccr/130368

Abstract

Introduction. COVID-19 (coronavirus disease 2019) – the epidemic outbreak caused by coronavirus-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – is a global public health problem. Children are less affected and have a mild form of the illness. The association between SARS-CoV-2 disease, COVID-19 and late symptoms of vasculitis is often suspected, in particular in young asymptomatic patients, especially due to the post-viral immune response.

Objective. The aim of the review is to describe the characteristics of children and adolescents affected by the development of Kawasaki-like multi-system inflammatory syndrome (KD) (MIS-C), and assesses its possible temporal association with SARS-CoV-2 infection.

Brief description of the state of knowledge. A group of children who presented with KD-type MIS-C during the COVID-19 pandemic have been identified in the United Kingdom, the United States, and Italy. Some children were diagnosed with SARS-CoV-2 infection by real-time polymerase chain reaction and IgG antibodies. SARS-CoV-2 infection and hyperinflammation in COVID-19 can serve as an ‘initial trigger’ for KD. IVIG should be administered within seven days of onset of illness until KD symptoms disappear and COVID-19 test is negative. Large numbers of children in African countries with the SARS-CoV-2 epidemic are likely to be affected by KD, and in such cases, a shortage of IVIG supplies is expected.

Conclusions. This article suggests a correlation between COVID-19 and Kawasaki-like MIS-C, which is important for the care of sick children. However, the definitive relationship between childhood KD and COVID-19 needs to be confirmed by a large cohort study on a large numbers of infant and children patients worldwide.

Key words

COVID-19 pandemic, SARS-CoV-2, Kawasaki-like multi-system inflammatory syndrome, children

INTRODUCTION

The rapid spread of corona virus disease 2019 (COVID-19), due to the severe respiratory syndrome corona virus 2, has created a global epidemic with infected people of all ages living in almost every country in the world. COVID-19 is a global health emergency which first appeared in December 2019, caused by a new type of coronavirus-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By 5 May 5 2020, COVID-19 had been discovered in over 3.6 million people worldwide, although the medical burden of the pandemic was less in infected children. The paediatric population appears to be affected at a much lower rate than the adults population, with only 2% of cases reported in patients under 20 years of age [1, 2]. In children and adolescents, infection with SARS-CoV-2 is the leading cause of symptoms of mild respiratory deficiency, while the severe forms are reported in adults [3, 4]. The focus on children’s vulnerabilities are for two reasons: 1) the extent to which children can transmit COVID-19; this is the key to a country being able to re-establish its community after a shutdown; 2) new disease, such as severe Kawasaki disease (KD) or multiple systemic inflammatory syndrome in children (MIS-C) are of concern to North American and European countries.

OBJECTIVES

The aim of this review is to discuss the symptoms in children and adolescents suffering from an outbreak of a Kawasaki-like multi-system inflammatory syndrome, and to assess a possible correlation with the SARS-CoV-2 infection in order to provide an update on this relationship.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Pathogenesis of COVID-19 in children. SARS-CoV-2 has a significant genetic similarity (approximately 80%) to the causative agent of the severe acute respiratory syndrome (SARS) epidemic in 2002 – the severe acute respiratory syndrome corona virus (SARS-CoV) [5–7]. The surface of SARS-CoV-2 contains a spike protein that allows it to bind and target human cells. The SARS-CoV-2 receptor is an angiotensin converting enzyme 2 (ACE2) that is expressed mainly on the renal proximal tubular cells, epithelial cells, endothelial cells, and enterocytes. After attaching to ACE2, SARS-CoV-2 endocytoses inside the cell and attaches to a toll-like receptor (TLRs) in the endosome. This interacting form stimulates an interferon type 1 (IFN) response, and enhances the expression of other pro-inflammatory cytokines via the nuclear factor κB (NF-κB) [8–10].

Two major immune responses have been reported against SARS-CoV-2: an initial innate IFN immune response which...
has been described previously, and a secondary immune response that causes a cytokine storm. The first IFN response is targeted to effectively include and eliminate the virus, and the initial IFN peak appears to be important for the efficient control of the virus [11]. The constancy of IFN activity produced during an innate immune reaction is necessary for the recovery of the patient [12]. When macrophages are activated by IFN-α/β receptors after the initial IFN response, they release pro-inflammatory cytokines and chemo-attractants [13].

The other response to SARS-CoV-2 is that the antigen-presenting cells transform the spike protein antigens into T lymphocytes, leading to B lymphocytes activation and anti-spike immunoglobulins production. The coated SARS-CoV-2 enters the macrophages via Fc receptors when these immunoglobulins bind to the spike proteins [14] A cytokine storm occurs in the adaptive phase when these macrophages release pro-inflammatory cytokines [14, 15].

COVID-19 cell/tissue damage can occur in two ways: 1) direct damage of SARS-CoV-2 by viral replication; 2) the cytokine storm which causes deleterious effects of excessive immune response [16]. Studies in mice and non-human primates have shown that an immune response that is a disproportionate immune response to the virus greater than the virus titer was associated with death in SARS-CoV infection [17, 18]. Most people with infectious disease are mildly infected, although virus can lead to a serious illness primarily diagnosed as a respiratory distress syndrome (ARDS) with increased cytokines that lead to death [19]. Cytokine storm caused by unrestricted immune response leads to multi-organ disease due to hyperinflammation [20]. Although the entire world is more likely to be infected with SARS-CoV-2, this virus, however, infects certain groups of people with more serious illness. The elderly, smokers, and those with chronic illnesses, such as diabetes and high blood pressure, are the main risk groups [21–23].

At present, the exact cause a mild illness in children infected with SARS-CoV-2 remains obscure. Many agents could share in this mild response in children; however, the specific effects of these agents have not yet been studied: 1) children travel less than adults which could be a protective factor [24]; 2) in childhood, smoking is not a problem and children’s airways have a lower risk of air pollution than adults [24]; 3) common chronic illness of adulthood, such as hypertension or type 2 diabetes mellitus, are not common in children [10]; 4) the large number of microorganisms that colonize the upper respiratory tract of children can compete with SARS-CoV-2 [25–27]; 5) the innate immune reaction is more powerful in children, although the adaptive immune system is less developed and less mature than in adults [10, 28]. This can lead to a significant removal of the virus and the reduction of an exaggerated adaptive reaction; 6) the patterns of ACE2 expression in children may differ from those in adults [29].

A link between kawasaki-like MIS-C in children and the COVID-19 pandemic. In Italy, the United Kingdom and United States over the last few months, there has been an obvious group of children symptomized by with a KD-like illness, (https://time.com/5832461/ Kawasaki-disease-COVID-19/). Blood parameters overlap in the reported cases while showing symptoms compatible with in COVID-19 in children. SARS-CoV-2 infection has also been confirmed in some paediatric patients by using real-time polymerase chain reaction (RT-PCR) and IgG antibodies

Although the relationship of KD to COVID-19 has not yet been elucidated, the inflammatory syndrome linked with SARS-CoV-2 infection is of growing concern due to coronavirus infection, and the possible link with KD affecting young children. According to this hypothesis, the case of a 6-month-old infant presented with classic KD and tested positive in COVID-19 has been described in a recent study. The infant was treated with the recommended regimen of intravenous immunoglobulins (IVIG) and aspirin, which relieved the clinical symptoms [30]. An cohort study of COVID-19 in the Italian province of Bergamo also reported severe KD [31]. These studies have strengthened the possible association between COVID-19 and KD and broadened our conception of the two diseases in pediatrics.

KD, an early childhood acute fever, is a systemic vasculitis which affects mainly the medium and small-sized arteries [32] with a special predilection for the coronary arteries. It was first introduced in the 1960s by the Japanese paediatrician, Dr Tomisaku Kawasaki. The highest incidence of KD is in Japan where more than 300/100,000 children ≤ 4 years old are affected annually by the disease, compared to 25/100,000 children ≤ 5 years in North America [33, 34]. Sporadic cases of atypical Kawasaki disease had been reported in Egypt [35, 36].

Although the cause of KD remains uncertain, unknown infectious agents (referred to as ‘X’ pathogens) might be the primary cause. The role of a viral trigger has been suggested in some children with a genetic predisposition, as several studies have linked multiple viral agents to KD [37–39], including seasonal coronaviruses [40, 41], but not all studies concur [42, 43]. A classic diagnosis of KD requires at least five days of fever and the occurrence of four of the following (if the fever is found with < 4 of the following, the presence of an Echo-proven coronary artery disease could confirm the diagnosis of the disease, together with the exclusion of other similar diseases [44]: 1) changes in the extremities, e.g. oedema, erythema, and desquamation. This limits motion and prevents the children from lifting weights; 2) desquamation of the fingers and toes is usually seen 1–2 weeks after the onset of fever, begins primarily in the periungual region, then can affect the palms and soles; 3) bilateral non-exudative conjunctivitis; 4) non-vesicular polymorphous rash; 5) unilateral cervical lymphadenopathy, >1.5 cm, the least common clinical feature, found in about 40% of patients; 6) oral cavity changes, e.g. fissured or swollen lips, pharyngeal erythema, dry strawberry tongue.

There is an increase in endothelial inflammation and injury/dysfunction, probably after SARS-CoV-2 infection through the endothelial ACE2, as suggested by recent observations of an increased accumulation of inflammatory cells in the endothelium. An exacerbation of the inflammatory response within the coronary lesions can be caused by a systemic inflammatory response to pneumonia, leading to endothelial dysfunction [45] and an acceleration in the development of...
Children and adolescents with Kawasaki disease (KD) are at risk of a SARS-CoV-2 infection and hyper-inflammation as a consequence of this infection may act as the main ‘triggers’ leading to KD (Fig. 1).

The World Health Organization (WHO) has developed an early case report form and a case definition for multi-system inflammatory diseases in children and adolescents. The definition of the initial case reflects the clinical and laboratory characteristics found in the previously reported cases, and is used to identify suspected or confirmed cases for both treatment and preliminary reporting and follow-up.

**Preliminary definition of cases.** Children and adolescents aged 0–19 years with fever > 3 days, and two of the following: 1) presence of a polymorphic rash or signs of mucocutaneous inflammation (mouth, hands, feet) or possibly non-suppurative bilateral conjunctivitis; 2) pericarditis, valvitis, myocardial dysfunction or abnormalities of coronary artery (echo findings or increased levels of troponin/N-terminal (NT), pro-hormone B-type Natriuretic Peptide (NT-proBNP); 3) signs of shock or hypotension; 4) acute gastrointestinal disorders (diarrhea, vomiting, or abdominal pain). Additionally, increased erythrocyte sedimentation rate (ESR), C-reactive protein, procalcitonin, and other inflammatory markers; 5) coagulopathy parameters: prothrombin time (PT), partial thromboplastin time (PTT), increased D-dimer levels.

Additionally, there are no other clear microbial causes of inflammation, such as bacterial sepsis, staphylococcal or streptococcal shock syndrome. COVID-19 also evidences (antigen test, seropositive result or real-time PCR (RT-PCR) or probable communication with COVID-19 patients [46].

The presence of a positive SARS-CoV-2 test in KD patients elucidates the significance of COVID-19 testing in patients with KD. This is a valuable point, because most parents are reluctant to visit a hospital because of the executive order: ‘stay-at-home’ and the risk of catching an infection in the hospital [47]. Thus, KD may remain undiagnosed or incorrectly managed. Complete recovery usually occurs in most patients with KD after a few weeks. However, early management is needed to avoid the probable complications. Approximately 25% of children with untreated KD develop coronary artery abnormalities, which are the main cause of short- and long-term morbidity and mortality. Myocardial infarction is the leading cause of mortality in KD. It can happen in the acute phase, but usually occurs during the first year from the first attack, but occurs later in patients with giant aneurysms [48].

Most KD patients respond well to IVIG treatment; however, an additional anti-inflammatory treatment (aspirin and corticosteroids) is required in 10–20% of patients [34]. These response variations raise the question of whether this group is a KD with SARS-CoV-2 which is the causative agent, or whether it demonstrates a new Kawasaki-like disease characterized by a multi-system inflammatory syndrome. Therefore, KD patients should be monitored carefully for possible COVID-19 infections, and after IVIG infusion KD should be quarantined, or discharged if SARS K0V-2 test is positive. IVIG should be given within seven days of onset until symptoms of KD disappear and the COVID-19 test is negative.

Cardiac biopsy and scintigraphy have shown that mild myocarditis is common in the early stages of KD [49, 27] and usually improves rapidly when the inflammation resolves [49–51]. However, in the case of KD shock syndrome, more severe myocarditis with decreased left ventricular contractility may occur. KD shock syndrome is more common in Western countries than in Asia; however, it is a rare complication affecting 1.5% – 7.0% of patients with KD [52]. Myocardial dysfunction and decreased peripheral vascular resistance are the main causes of this syndrome, and is often treated in the intensive care unit by intravenous fluid resuscitation, vasoactive agent infusion and inotropic drugs [53, 54].

KD shock syndrome may mimic toxic shock syndrome [53], justifying the routine use of antibiotics in this setting. The pathophysiology of KD shock syndrome is still unknown. The presence of elevated levels of circulating pro-inflammatory cytokines may contribute to the distributive factor in the development of shock. KD shock syndrome has been shown to be accompanied with elevated levels of C-reactive protein, procalcitonin, and IL-6 [52]. This major inflammatory condition associated with multiple organ failure, recently named Paediatric Multisystem Inflammatory Syndrome (PIMS) [55], reflects a specifically potent post-viral immune response to SARS-CoV-2 in contrast to other viral agents [56]. In fact, in COVID-19 in adults, cytokine storm syndrome with increased IL6 levels as an inflammatory marker has been reported [57] and is accompanied with increased mortality [58]. Of note, KD shock syndrome was associated with old age, elevated levels of D-dimer, decreased levels of hemoglobin and albumin, and severe hyponatraemia [52].

In sub-Saharan Africa, KD is rarely reported, but may be more common than previously reported [59]. In the United Kingdom and the United States the incidence in children of Asian descent was 2.5 times higher than in children of European descent, with the average risk for children of African descent being 1.5 times higher [60, 61]. In addition, Afro-Americans might show increased susceptibility to severe SARS-CoV-2 infection as they have been disproportionately affected by the COVID-19 epidemic [62, 63]. Thus, large numbers of children with KD may be exposed in African countries with generalized SARS-CoV-2 epidemics, and in such cases, a decrease in IVIG can be expected. In Asian countries, there are no reports of Kawasaki like-multi-system inflammatory syndrome associated with SARS-CoV-2 infections.
Co-2 infection. [1] Racial differences have been reported in previous cases of KD shock syndrome, with the incidence lower in Asian countries than in Western countries [49]. Therefore, more confirmatory studies are needed from a global perspective regarding the clinical properties of COVID-19 and the possible association between COVID-19 and KD. While this article proposes a potential inflammatory syndrome linked with COVID-19, it is imperative for parents and healthcare providers to know that children are generally at minimal risk of SARS-CoV-2 infection. Recognizing this inflammatory syndrome in children can provide important data about the immune reaction to SARS-CoV-2 and the potential correlation of immune defences that may be relevant for both children and adults. The reason for some children becoming seriously ill with COVID-19, while the majority do not show signs of the disease or are asymptomatic, may be explained by an antibody-mediated bias; vaccines studies might also be implicated.

CONCLUSION

The link between Covid-19 and PIMS is therefore critical worldwide. The link between Covid-19 and childhood KD still needs to be explained by an antibody-mediated bias; vaccines studies might also be implicated.

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