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Mini Review**Syndrome resembling Kawasaki disease in COVID-19 asymptomatic children**

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Abstract:

The current knowledge about the COVID-19 (Coronavirus Disease-2019) pandemic is still limited and is unravelling with the passing days, especially clinical data, and research in pediatric age group. Recently, there is a new and crucial development reported recently among the COVID-19 asymptomatic children, a novel syndrome affecting asymptomatic COVID-19 children, presenting as a hyperinflammatory syndrome which is like Kawasaki disease shock syndrome. The purpose of this correspondence is to discuss some important findings of the syndrome for the better understanding of the disease.

Keywords: COVID-19; children; multisystem inflammatory syndrome; Kawasaki disease.

Main Text:

Until now, children are considered as the population that is minimally affected by COVID-19 [1]. However, after the start of covid-19 pandemic, clinicians in many parts of the world have recognized a new syndrome resembling Kawasaki disease (vasculitis) in pediatric patients [2]. The syndrome has been named as pediatric multisystem inflammatory syndrome (MIS-C) and is characterized by high fever rash hypotension, gastrointestinal symptoms, and organ dysfunction. All patients finally developed warm vasoplegic shock unresponsive to volume resuscitation. Other features besides fever and rash included small pleural pericardial and ascitic effusions, suggestive of a widespread inflammatory process [3]. Surprisingly, respiratory symptoms do not seem to be common. Although this syndrome resembles Kawasaki disease in many aspects, but the classical symptoms of Kawasaki disease, like bilateral conjunctival injection, strawberry tongue and rash, are not always present [4]. According to study published in Lancet, among the eight kids between the age of 4 and 14 years, three needed mechanical ventilation, and one died. The investigation showed either positive RTPCR (reverse transcriptase polymerase chain reaction) or positive antibodies to SARS-COV-2(Severe Acute Respiratory Syndrome Coronavirus), which suggests that this syndrome occurs in the convalescent phase of the disease. The highest risk of this syndrome has been found to be between the ages 5 and 14 years. However, the risk for this syndrome remains very small [3].

Laboratory investigation revealed that MIC-S has far more elevated CRP (C –reactive protein), D dimer ferritin, elevated cardiac enzymes, and low lymphocyte count in CBC (complete blood count), compared to Kawasaki syndrome. The complications of this syndrome include multi organ failure, thrombosis, ischemic events, and coronary aneurysms. ECG (electrocardiogram)

were found to be nonspecific and echocardiograph showed eco bright coronary arteries which progressed to coronary aneurysm in one patient [5]. Regarding the treatment all patients were treated with intravenous immunoglobulins and aspirin, however aspirin should be withheld as it can lead to bleeding episodes. All the children were discharged from ICU (intensive care unit) after 4 to 6 days. All children have been given follow up with cardiologist to rule out coronary abnormalities caused by the virus.

In one of the case studies done in United Kingdom, 8 patients presented with fever, conjunctivitis, extremity pain, edema, and diarrhea and all the patients had fluid refractory shock requiring vasopressors. Surprisingly, there were minimal respiratory symptoms, 50% of these patients had a family exposure to SARS-COV-2, but RT-PCR was found to be negative. Majority of patients had some cardiac dysfunction and increased inflammatory markers and troponin [6]. In Bergamo, Italy, a comparative study was done between 19 patients who presented with Kawasaki like illness before the pandemic, to ten patients who presented with Kawasaki like illness after the start of pandemic. Those patients who presented after the start of pandemic had an average age of 7.5 years, while for the other group, the average age was 3 years and 50 % of the patients had incomplete features of Kawasaki disease. Non-Kawasaki signs and symptoms included diarrhea, meningeal signs, and symptoms of hypoperfusion. Most of the patients had neutrophilia hyponatremia, hypertriglyceridemia, high ESR (erythrocyte sedimentation rate), CRP, ferritin, and pro-BNP (brain natriuretic peptide). Only two patients had positive swab for SARS-COV-2. These two patients and six other patients have positive serologies, whereas, 50% of 10 patients had positive x-ray (radiograph) and 60% had abnormal echocardiography [7].

In another study among households in Shenzhen, China, children below the age of 10 years were found positive for COVID-19, as adults, however, they were found to have less severe symptoms [8]. Likewise, other reports from various countries including South Korea, Italy, and Iceland, have reported less rates of infection among children than the adults on the basis of mass testing [9]. Some preliminary data of almost 300 infected children suggested that lower concentration of cytokines is being produced by children compared to the affected adults. These cytokines are the proteins secreted by the body's immune system and is constant with Kawasaki disease as a disease related with the dysfunction of acquired immune system. Cytokines slows down the function of heart *via* activation of direct immune stimulation associated with myocytolysis [10].

There is enough data that suggests the resemblance of the symptoms of this infection and Kawasaki disease. However, differences are also seen, like age appears to be higher than the classical Kawasaki disease which is usually 3. Additionally, it has been found African children are more to MIS-C while Kawasaki is more common in children of Asian ancestry, indicating a racial predisposition. Another striking point is the gastrointestinal symptoms, SARS-COV-2 have the potential to infect enterocytes *via* ACE2 (angiotensin converting enzyme 2) receptors being expressed in gastric epithelia which can lead to diarrhea in approximately 1/3 infected adults. On the contrary, occurrence of diarrhea in a post COVID-19 disease is likely not associated directly with infection. In typical Kawasaki disease, emesis is less common than in COVID-19 linked syndrome (Riphagen S, et al, 2020) [12]. The syndrome associated with covid-19 seems to present more gastrointestinal symptoms like vomiting, diarrhea and abdominal pain, compared to classical Kawasaki diseases. Also, in various studies it has been found that MIS-C presents with low platelet count while Kawasaki presents with increased platelet count.

It cannot be excluded that the MIS-C present different unrelated Kawasaki disease, atypical Kawasaki disease, toxic shock syndrome and myocarditis, which are different entities with different mechanisms [13]. For instance, a study on 9 patients suggested inverse correlation with Kawasaki disease as per the age. Another study from New York have reported the immune response is linked to the gene abnormalities (Reuters.2020).

Interestingly, it seems that this syndrome might not be specific to this virus, it may be that other viruses can also activate this hyperinflammation in children. There may be factors like genetic predisposition which may make some children susceptible to this syndrome [15]. Centers for Disease Control and Prevention (CDC), Royal college of Physicians for child health (RCPCH) and World Health Organization (WHO) have published few case definitions for this syndrome, which are as follows: A) patient aged < 21 years having fever 1: laboratory finding of inflammation, 2: symptoms of clinically severe illness which require hospital admission, with involvement of multiorgan system (≥ 2) (respiratory, renal, hematologic, cardiac, gastrointestinal, neurological and dermatologic) ; B) No alternative credible diagnoses; C) currently or recently tested positive by RT-PCR for SARS-CoV-2 infection, or by serology, or antigen test; or exposure to COVID-19 within one month, before the appearance of symptoms, 1. Pyrexia $> 38.0^{\circ}\text{C}$ for more than 24 hours, or record of subjective fever which lasts for more than 24 hours, 2. Others includes, but not limited to the following criteria: an elevated acute phase reactants (CRP, ESR, procalcitonin, ferritin), fibrinogen, lactic acid dehydrogenase (LDH), D-dimer or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin. Additionally, some patients may have complete criteria for Kawasaki disease others may not, but needs to be notified if they fulfil the case definition for MIS-C. Also, report the MIS-C in any pediatric mortality with positive SARS-CoV-2 infection [16] [17] [15].

Conclusion:

Therefore, our conclusion is that this may be a novel syndrome affecting asymptomatic COVID-19 children, presenting as a hyperinflammatory syndrome which is like Kawasaki disease shock syndrome. The relation between SARS-COV-2 and MIS-C in children will continue to be elucidated by further research.

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