# Kawa-COVID-19

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To the Editor,

COVID-19 appears to be less common in children, with a typically moderate and non-fatal course. On the other hand, children could be seriously impacted in rare situations, and clinical signs may differ from those seen in adults. Children with COVID-19 demonstrated signs of an immunological response to the virus, were older, had a greater likelihood of cardiac involvement, and exhibited Kawasaki disease-like symptoms (KD). Kawa-COVID-19 is a novel systemic inflammatory illness in children that is temporally linked to SARS-CoV-2 infection. To corroborate these findings and further understand the pathogenesis of Kawa-COVID-19, more prospective worldwide investigations are needed.

Children and younger people appear to be less affected by COVID-19 than adults; pediatric cases make up only 2.1-7.8% of confirmed cases in Europe, North America, and Asia. Respiratory involvement also appears to have a more benign outcome, with almost no fatalities.

Only a few cases with severe and fatal results have been described in the pediatric series. Nonetheless, it appears that the respiratory tract is not the only organ susceptible to SARS-CoV-2 infection (1).

According to accumulating evidence, COVID-19 tissue damage is mostly mediated by the host's innate immunity. Reports from the United Kingdom in April 2020 described a clinical presentation in youngsters that resembled Kawasaki disease (KD) or toxic shock syndrome. Since then, there has been an upsurge in the number of children from other regions world-wide that have been afflicted in the same way. However, it's still unclear if these symptoms belong to the same disease spectrum or a collection of separate post-infectious disorders. Kawasaki disease (KD) is a self-limiting and acute vasculitis of medium and small vessels with uncertain causes. KD affects children as young as two years old, with 75% of those affected under the age of five; boys are 1.5 times more likely than girls to have the condition. Fever, abdominal ache, red eyes, vomiting or diarrhea, and a rash on the trunk are the first symptoms. Some youngsters get a large red lip and tongue, while others develop swollen neck glands. Because of its potential

*Keywords: Covid19, Kawasaki, SARS-CoV-2, children, systemic inflammatory syndrome.*

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0393-974X (2022)

ocular involvement, the KD is of great interest to ophthalmologists. Iridocyclitis, punctate keratitis, vitreous opacities, papilledema, subconjunctival hemorrhage, and conjunctival injection are the most common ocular symptoms. In most cases, the latter is bilateral, painless, nonexudative, and limbic sparing. Patients with KD may experience haemodynamic instability during the acute phase of the disease, a condition known as KD shock syndrome (KDSS).

*Kawa-Covid-19*

Kawa-COVID-19 represents a new systemic inflammatory syndrome mimicking KD associated with SARS-CoV-2 in children. In 44% of the cases of Kawa-COVID-19, severe illness necessitated intensive care. Although all patients had complete or incomplete KD, pretty apparent deviations from usual KD have been described that should call attention to this disease and suggest that it is a distinct entity consistent with the series of Verdoni et al. (2, 3).

First, the median age at presentation is higher than in classical KD, with higher age (>5 years) indicating the need for ICU care. Second, myocarditis is distinct from conventional KD in incidence and severity. Third, stomach pain and/or diarrhoea were observed more frequently (81%) than in traditional KD (approximately one out of three patients). Finally, the cytokine storm was more common in the illness we describe, as evidenced by heart failure, pneumonia, gastrointestinal, neurological, and renal symptoms, all of which were related to higher CRP levels, ferritin, and cytokines (particularly IL-1, TNF, and IL-6). Apart from heart failure, these symptoms are also common in people with severe COVID-19 (4). However, in contrast to severe adult COVID-19, our patients rarely showed respiratory symptoms, implying that children had a different underlying host immunological response.

In the context of the SARS-CoV-2 pandemic, doctors should suspect Kawa-COVID-19 in any kid presenting with unexplained high fever and a rise in CRP, especially if mild signs of COVID-19 or proven exposure to SARS-CoV-2 were reported in the previous four weeks. In such circumstances, the classic clinical indicators of KD and digestive problems and respiratory characteristics should be thoroughly examined. In order to diagnose life-threatening problems, some investigations should be conducted regularly. These include tests for myocarditis (troponin, NT-proBNP, ECG), MAS (white blood cells, fibrinogen, ferritin, albuminaemia), and renal impairment (white blood cells, fibrinogen, ferritin, albuminaemia) (creatinine, urea, proteinuria). Because of the potential of rapidly progressing Kawa-COVID-19 and heart failure, clinicians should be especially cautious with patients over the age of 5 who have increased ferritin levels (over 1400 g/L).

Patients should have SARS-CoV-2 RT-PCR testing, at least in nasopharyngeal secretions and stool, as well as SARS-CoV-2 serology, as RT-PCR may be negative due to the late development of this condition after initial COVID-19 signs of exposure and other viral investigations to rule out alternative diagnoses (4).

Because of the rapid progression of the disease, patients should be closely monitored and treated as soon as possible. Myocarditis and dilated coronary arteries were seen in 44% and 19% of patients, respectively. As in classic KD, treatment with IVIg 2 g/kg should be given quickly and appeared to be efficacious in most cases (5). Associated anti-inflammatory medication, such as steroids or biologics, was required in 31% of patients and should be explored if a severe course is noted or factors that predict a severe outcome, such as age over 5 years and increased ferritin levels (>1400 g/L). Several more therapeutic options may be investigated based on KD literature data.

Although it has been more than half a century since T. Kawasaki initially reported his 50 cases in Japan12, the origin of Kawasaki disease is still unknown (6).

Patients with Kawasaki illness diagnosed during the COVID-19 pandemic had clinical and biochemical traits different from our previous cohort of patients; thus, we classified them as Kawasaki-like diseases. They were elderly, with respiratory and gastrointestinal involvement, meningeal symptoms, and symptoms of cardiovascular involvement from a clinical standpoint. According to biochemical results, they developed leucopenia with significant lymphopenia, thrombocytopenia, and elevated ferritin, as well as indications of myocarditis. Patients with COVID-19 have similar clinical characteristics. Furthermore, these patients exhibited a more severe

disease course, requiring supplementary steroids with resistance to intravenous immunoglobulin and biochemical evidence of MAS and clinical symptoms consistent with KDSS. SARS-CoV-2 has been shown to have a pro-inflammatory effect in individuals with the most severe respiratory complications of COVID-19.

In line with MAS, many of these patients develop a constellation of symptoms known as a cytokine storm, including fever, lymphopenia, increased transaminases, lactate dehydrogenase, D-dimer, and ferritin. Similarly, MAS is a cytokine storm that may affect Kawasaki illness patients (7-10).

## CONCLUSION

The present literature's review suggests that SARS-CoV-2 infection is connected to an auto-inflammatory disease similar to KD (Kawa-COVID-19). This disease, however, varies from classical KD in that it develops at an older age and has a higher incidence of severe myocarditis and/or pericarditis. Age higher than 5 years and high ferritin (>1400 g/L) are both indicators of a severe course. Furthermore, only 5 out of 16 patients (31%) had remission of inflammatory symptoms with a single IVIg, while 10 patients (62%) required a second line of treatment. To properly comprehend this novel disease entity, more prospective international collections of Kawa-COVID-19 are needed and the investigation of immunological and host genetic variables.

When contemplating social reintegration programs for the pediatric population, the link between SARS-CoV-2 and Kawasaki-like disease should be considered. However, the Kawasaki-like disease described here is uncommon, affecting only around one out of every 1000 infants infected with SARS-CoV-2. This estimate is based on the limited information available from case studies in this area. Interestingly, both genetic and immunomediated emerged recently as potential contributors of Kawacovid (11, 12). In this context, we may speculate that intricated immunoregulatory pathways and genetic components of disease interact and make some children prone to different cardiovascular and other complications following Kawasaki disease and Covid19 infection. This model of complex disease pathophysiology is observed in different pediatric conditions in which both genetic and non-genetic factors interact closely, highlighting how molecular etiological mechanisms underlying a wide group of paediatric conditions are important to be identified to dissect both contributory and causative factors (13-21).

In the last decade, genome (or exome) sequencing and omic-related technologies have been relevant and important to understanding many rare and neglected pediatric diseases (22-31). The advances from these genes or biomarker discovery studies gave us a deeper knowledge of the subtle molecular huts that cause rare conditions or rare complications in pediatric age. In addition, they led us to better understand the intricate interplay between genetic and non-genetic (e.g., immunomediated, endocrinological, metabolic) factors (32-40).

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