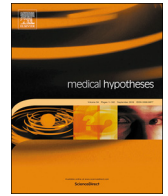




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## Kawasaki-like disease in children with COVID-19: A hypothesis



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### ABSTRACT

With rapid spread of severe acute respiratory syndrome- corona virus-2 (SARS-COV-2) globally, some new aspects of the disease have been reported. Recently, it has been reported the incidence of Kawasaki-like disease among children with COVID-19. Since, children had been known to be less severely affected by the virus in part due to the higher concentration of Angiotensin converting enzyme (ACE)-2 receptor, this presentation has emerged concerns regarding the infection of children with SARS-COV2. ACE2 has anti-inflammatory, anti-fibrotic and anti-proliferative characteristics through converting angiotensin (Ag)-II to Ang (1-7). ACE2 receptor is downregulated by the SARS-COV through the spike protein of SARS-CoV (SARS-S) via a process that is tightly coupled with Tumor necrosis factor (TNF)- $\alpha$  production. TNF- $\alpha$  plays a key role in aneurysmal formation of coronary arteries in Kawasaki disease (KD). Affected children by COVID-19 with genetically-susceptible to KD might have genetically under-expression of ACE2 receptor that might further decrease the expression of ACE2 due to the downregulation of the receptor by the virus in these patients. It appears that TNF- $\alpha$  might be the cause and the consequence of the ACE2 receptor downregulation which results in arterial walls aneurysm. Conclusion: Genetically under-expression of ACE2 receptor in children with genetically-susceptible to KD who are infected with SARS-CoV-2 possibly further downregulates the ACE2 expression by TNF- $\alpha$  and leads to surge of inflammation including TNF- $\alpha$  and progression to Kawasaki-like disease.

### What is known – what is new

#### What is known

- Kawasaki-like disease has been reported in children affected by COVID-19.
- ACE2 has anti-inflammatory effects and acts as functional receptor for SARS-CoV-2, having higher expression in children. Downregulation of ACE2 by SARS-CoV is carried out through a process linked with TNF- $\alpha$  which having a key role in the arterial aneurysm of coronary arteries in KD.

#### What is new

- Genetically under-expression of ACE2 receptor in genetically-susceptible children to KD could aggravate inflammation including TNF- $\alpha$  and leads to Kawasaki-like disease.
- Genetic study of affected children to find ACE2 gene polymorphism and the level of ACE2 expression might be helpful.

### Kawasaki-like disease in children with COVID-19: a hypothesis

Kawasaki disease (KD) is an acute systemic inflammatory disease of medium- and small-sized vessels that mostly involves children under 5 years old [1], with a worldwide pattern of distribution in children

with different ethnic origins [2]. However, its prevalence is higher in Asian countries like Japan, where the annual incidence rate of the disease had reached from 174.0 per 100,000 children under 5 years of age to 239.6 per 100,000 in 2010 and 342.2 per 100,000 in 2014 [3]. The higher risk of the disease is not restricted to the Japanese population, but among Korean and Taiwanese children as well [4,5]. The prevalence of the disease is significantly lower in non-Asian ethnicities like the UK [6], and Australia that has been reported to be 8.39 per 100,000 and 9.34 per 100,000 children under 5 years old respectively [7].

A seasonal pattern for the incidence of KD has been reported with the highest rate of the disease in January and June/July and the lowest rate in October [8].

Recently, several cases of Kawasaki-like disease have been reported in various locations that coincide with the SARS-CoV2 pandemic making concerns the association of COVID-19 with KD [9–11].

In a recent report by Verdoni, et al that has been published in The Lancet journal, a 30-fold increased incidence of Kawasaki-like disease over a month has been detected shortly after the spread of SARS-CoV-2 to Bergamo-Italy [12]. Children with the symptoms and signs of Kawasaki-like disease diagnosed after the SARS-CoV-2 pandemic and showing evidence of immune response to the virus were older, had a higher rate of cardiac involvement, and features of macrophage activation syndrome (MAS). Evidence of contact with the virus was endorsed by the presence of antibodies against SARS-CoV-2 in eight out of

*Abbreviations:* COVID-19, coronavirus disease-2019; SARS-CoV-2, severe acute respiratory syndrome- corona virus-2; MAS, macrophage activation syndrome; KD, Kawasaki disease; HCoV-NH, human corona virus-new haven; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; MMP, matrix metalloproteinase; ECM, extra cellular matrix; INF, interferon; IL, interleukin; TGF, tumor growth factor; CCL, chemokine ligand; CXCL, C-X-C motif chemokine ligand; ACE2, angiotensin converting enzyme2; RAS, renin angiotensin system; Ag II, angiotensin-II; AT1, angiotensin receptor type 1; Ang (1-7), angiotensin (1-7)

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ten in the group of patients presenting the symptoms of the disease after the onset of the local SARS-CoV2 epidemic [12].

KD is an inflammatory vascular disease with an unknown etiology. Several potential theories have been hypothesized. Among those theories, an infectious etiology based on the genetic predisposition has been attracted. The genetic factor has been considered as a significant facet because there is a high rate of difference in the prevalence of disease between different ethnicities [13]. Interestingly, in Hawaii, the annual incidence of KD among Japanese-American children less than 5 yrs of age is similar to the incidence of Japanese living in Japan [14,15]. Another supporting statement regarding the genetic basis of KD is based on some case series in which the simultaneous occurrence of KD has been reported in monozygotic twins [16,17]. According to the finding of Makino, et al, 1.9% and 1% of patients with KD had a sibling or a parent with a history of KD respectively [3]. Such a potential association between parents and children, as well as between siblings, has been reported by other studies [18,19], supporting the genetic cause.

On the other hand, the infection-based hypothesis comes from the fact that the disease has an acute onset pattern that is compatible with the appearance of infectious diseases, and its incidence is higher in some special months and special places [2]. For instance, in Japan, the different pattern of KD in 2009 and 2010 in comparison with previous years supports the infection-based hypothesis [20]. According to Nakamura, et al, the pattern of KD had been affected in 2009 after the epidemic of influenza A/H1N1 in Japan [21].

In this respect, some studies reported the isolation of various microorganisms from patients with KD including adenovirus type2 [22], measles [23], Epstein–Barr, human immunodeficiency virus (HIV) [24], parvovirus and retroviruses [25]. Benseler, et al reported a documented source of infection, both bacterial and viral in a third of patients with typical KD [25]. Furthermore, Rowley, et al established the cytoplasmic inclusion bodies that are compatible with the viral protein aggregations and nucleic acid in ciliated bronchial epithelium of acute KD patients [26].

Considering the infectious cause for KD, a case-control study by Esper, et al suggested an association between human coronavirus- new haven (HCoV-NH) infection and KD [27]. Nonetheless, their finding was not confirmed by other studies [28]. Also, HCoV-NL63 was detected in only 2% of swab respiratory samples of the patients with acute KD gathered in Netherland and United states in two episodes prospectively during winter and spring when is the peak of the virus in Europe and North America in an equal number using RT-PCR assays [29]. Despite these considerations, there was not found any association between KD and HCoV-NL63. The lack of this association has also been demonstrated by Ebihara, et al [30].

Both innate and adaptive immunity are involved in the pathogenesis of KD. It is known that endothelial cell damage and inflammation are the two essential processes resulting in coronary endothelial dysfunction in KD. Endothelial cell Pyroptosis is considered to play a key role in the pathophysiology of KD- related endothelial cell damage [35].

During acute KD, cytokines are released particularly from monocyte/macrophages that leads to vascular endothelial damage [31,32]. Coronary arteries are especially involved with the utmost degree of inflammation in KD resulting in coronary arteritis. It begins with cell infiltration of lymphocytes and macrophages of the tunica intima and tunica adventitia within 6–8 days after KD onset that will progress to all arterial vessel wall on almost 10th day of the disease [33]. As well as macrophages, lymphocytes and neutrophils have been shown to be involved in the process of arterial inflammation particularly in the initial stage of inflammation [34].

Among cytokines, Tumor necrosis factor (TNF)- $\alpha$  which is a critical pleiotropic cytokine in the regulation of immune cells is prominently elevated in children during the acute phase of KD. TNF- $\alpha$  has been demonstrated to play a critical role in many autoimmune processes, as well as in the acute inflammatory response to infections [36]. There is

now progressing evidence that TNF- $\alpha$  is critical in the pathogenesis of KD, overtly at the level of the coronary artery [37]. TNF- $\alpha$  upregulates the expression and activity of many members of the matrix metallo-proteinase (MMP) family of enzymes. MMPs are a family of zinc-dependent extracellular matrix(ECM)-degrading proteases that have the common capability to abolish molecules of the ECM predominantly elastin which is an important compartment of ECM of arterial walls. As a result, the breakdown of elastin which is essential for the structural integrity of vessel walls leads to vessel wall inflating [38].

It seems that systemic inflammation is the most striking finding in both KD and COVID-19 [39,40]. SARS-CoV2 is a viral disease with inflammation and infection of endothelial cells. The presence of viral elements and inflammatory cells within endothelial cells and the evidence of endothelial cell death suggesting that SARS-CoV-2 infection facilitates endotheliitis through direct viral involvement and inflammatory response [41]. Covid-19 induced endotheliitis could be the explanation for systemic microcirculatory dysfunction in different vascular beds [41]. Moreover, it has been suggested that the induction of apoptosis and pyroptosis might have an important role in endothelial cell damage in patients with COVID-19 [41].

Acute respiratory distress syndrome (ARDS) is known to be the main cause of death in patients with COVID-19 [42]. One of the principal mechanism of ARDS is cytokine storm which is the lethal uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines (IFN- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-6, IL-12, IL-18, IL-33, TNF- $\alpha$ , TGF $\beta$ , etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc) by immune effector cells in SARS-CoV infection [42,43].

While most children have shown the less severe form of COVID-19 and are less susceptible to the severe form of the disease compared with adults; some children show the Kawasaki-like syndrome which has been characterized by a cytokine storm.

Angiotensin converting enzyme (ACE)2 has been demonstrated to be the functional receptor for the entrance of the SARS-COV-2 into the cytoplasm [45]. The classical axis of the renin-angiotensin-aldosterone system (RAS) consists of ACE, angiotensin II (Ang II), and angiotensin receptor type 1 (AT1). This system could induce tissue injury, inflammation, and fibrosis. In contrast, ACE2 employs the opposite effects on tissue fibrosis and inflammation by converting Ang II to angiotensin-(1-7) which has anti-inflammatory, anti-proliferative, and anti-fibrotic properties [44].

In a study by Xie et al, ACE2 was recognized to vividly decrease with aging in rat models [46]. This finding as well as the increased concentration of ACE2 receptors in lung pneumocytes of children might be an explanation for this evidence that young people seem to be less susceptible to SARS-CoV2 detrimental effects, suggesting a negative correlation between ACE2 expression and SARS-CoV-2 severe outcomes [47,48].

So, it appears that children have shown a less severe form of COVID-19 likely due to the high ACE2 receptor concentrations, as well as a more qualified immunity, and a constitutional high lymphocyte rather adults [48].

On the other hand, the ACE2 gene maps to chromosome Xp22, exhibits a high degree of genetic polymorphism [50].

Concerning the appearance of Kawasaki-like disease in children with COVID-19, a hypothesis might be proposed based on the influence of the immunomodulatory function of ACE2 and Ang-(1-7). If we hypothesize that children infected by SARS-COV-2 and showing Kawasaki-like disease are genetically having a lower expression of ACE2 receptors in comparison with their counterparts, we can partly explain the surge of inflammation in this group of patients.

It has been identified that SARS-CoV down-regulates ACE2 receptors that are associated with severe clinical outcomes. The down-regulation of the ACE2 receptor is carried out through the spike protein of the virus (SARS- $\alpha$ ) via a process that is tightly coupled with TNF- $\alpha$  production [49].

The progression of some children presenting with Kawasaki-like disease to the coronary artery aneurysm might be explained by the fact that downregulation of ACE2 receptor by SARS-CoV-2 in children with already genetically underexpression of this receptor might lead to further decrease of ACE2 expression and consequently lower concentration of Ang-(1-7) resulting in a rush of inflammation. Production of TNF- $\alpha$  which has been demonstrated to play a key role in inducing coronary artery aneurysm in KD, could be the cause and consequence of ACE2 downregulation.

However, to date, there is no clear answer to the enquiries concerning Kawasaki-like disease in children with COVID-19. It must take into consideration that both KD and COVID-19 have many unknown facets making this issue more difficult to be understood.

Genetic study of children resembling the Kawasaki-like disease to identify the probable ACE2 gene polymorphism, ACE2 expression, and their immunologic response could clear some ambiguities not only in Kawasaki-like disease but also in KD.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110117>.

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