Coronavirus Pandemic

Kawasaki like illness due to COVID-19: a review of the literature

Yulin Fang1, Veeraraghavan Meyyur Aravamudan2, Gurusaravanan Kutti Sridharan3, Keyur Kamlesh Mehta4, Ramkumar Sekhar5, Nagendra Boopathy Senguttuvan6, Indumathi Venkatachalam7, Muhammad Bilal Abid8

1 Ministry of Health Holdings, Singapore
2 Department of Medicine, Woodlands Health Campus, Singapore
3 Banner University Medical Centre, University of Arizona, Tucson, AZ, United States
4 Children’s Heart Institute, The Heart Program at Inova Children’s Hospital, VA, United States
5 Department of Cardiology, Khoo Teck Puat Hospital, Singapore
6 Sri Ramachandra Medical College and Research Institute, Chennai, India
7 Department of Infectious Disease, Singapore General Hospital, Singapore
8 Divisions of Infectious Diseases and Hematology/Oncology, Medical College of Wisconsin, Milwaukee, WI, United States

Abstract

Introduction: Viral infections have been described as triggers for Kawasaki Disease (KD), a medium vessel vasculitis that affects young children. Akin to the H1N1 pandemic in 2009, there is a similar rise in the incidence of KD in children affected with Coronavirus disease 2019 (COVID-19). Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been reported to induce an exaggerated systemic inflammatory response resulting in multi-organ involvement, particularly initiated with pulmonary parenchymal damage. This review article will discuss KD-like manifestations in COVID-19 patients in the pediatric cohort.

Methodology: Search terms “Kawasaki” “COVID-19” “SARS-COV-2” “PIM-TS” and “MIS-C” were used to look for relevant articles in PubMed and Google Scholar published in the last 5 years.

Results: There is some evidence to suggest that SARS-CoV-2 stimulates dysfunctional and hyperactive immune reactions mimicking KD in young patients.

Conclusions: Therapeutic options, both investigational and repurposed, include intravenous immunoglobulins, steroids and anticoagulation. More studies are required to evaluate the effectiveness of these treatment options.

Key words: Kawasaki-like disease; COVID-19; SARS-CoV-2.


(Received 18 October 2020 – Accepted 02 March 2021)

Copyright © 2021 Fang et al. This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

The Coronavirus 2019 (COVID-19) pandemic has stressed healthcare systems globally. The heterogeneity in presentations of COVID-19, coupled with varying severity and outcomes across different age groups, are constant challenges both for clinicians and researchers. The novel coronavirus responsible for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is known to induce a systemic inflammatory response affecting multiple organs, with lungs being most common and severely affected. Some of the extrapulmonary manifestations include involvement of the systemic vasculature, similar to Kawasaki disease (KD). Several case reports have shown that SARS-CoV-2 stimulates an immune reaction mimicking KD. This review article will discuss KD-like manifestations in COVID-19 patients in the pediatric cohort.

Kawasaki disease

Diagnosis and epidemiology

Kawasaki disease (KD) is an acute idiopathic vasculitis affecting medium-sized blood vessels. Children younger than five years of age are most commonly affected. Tomisaku Kawasaki first reported this condition in 1967 [1]. Diagnosis is clinical and is based on a combination of fever for at least five days and generalized inflammation involving lymph nodes, skin and mucous membranes. The diagnostic criteria of KD – mainly fever, rash, mucus membrane, and vessel involvement - are provided in Table 1.
It is the most common cause of coronary artery disease in children [2], with development of coronary artery ectasia in up to 25% of untreated patients [3]. In addition to coronary arteries, KD is also known to affect other vessels, including cerebral [4], femoral and iliac arteries [5], though not as widely reported as its cardiovascular complications. Kawasaki disease is more common in children of Asian descent, with most of the initial cases reported in Japan. As many as 1 in 65 Japanese children develop KD by five years of age, with the highest incidence in children 9-11 months old [6]. This indicates a potential role of genetics in the development of Kawasaki disease-related symptoms with certain ethnicities at higher risk compared with others [7] (Table 2).

Pathogenesis and complications
Most cases of KD are self-limiting and have an uncomplicated course. Although the etiology of KD remains unknown, a double hit hypothesis involving an infectious trigger in a genetically predisposed individual is proposed [8]. Many viruses have been isolated from patients with KD, including adenovirus, Epstein-Barr virus (EBV), human immunodeficiency virus (HIV) and parvoviruses [9]. Viruses are known to trigger a cascade of immune pathways in patients, such as the activation of cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS) pathway. cGAMP is one of the deoxyribonucleic acid (DNA) sensors in the body that helps to identify foreign viral DNA material within cells. Once foreign DNA is detected, cGAS produces cGAMP which triggers the activation of simulator of interferon genes (STING) within the endoplasmic reticulum, resulting in the release of cytokines and inflammatory molecules such as type 1 interferons (IFN) as part of the immune response towards the foreign infective agent [10]. STING also acts on the retinoic acid inducible gene-1 (RIG-1), a ribonucleic acid (RNA) sensor and mitochondrial antiviral signaling protein (MAVS) to detect viral RNA and trigger an immune response, indicating a role of the STING pathway in protecting against RNA viruses as well [10]. The STING pathway has been found to be activated in KD with increased IFNs, neutrophils and cytotoxic T cells seen on histology of coronary artery tissue taken from KD patients [11]. Inflammatory markers such as interleukin (IL) -6 and vascular endothelial growth factors (VEGFs) are released by cells of the innate immune system such as monocytes, macrophages, and dendritic cells leading to inflammation of vessels. It has been suggested that an autoantigen located in the walls of coronary arteries may serve as a target for these inflammatory factors, explaining the development of coronary artery aneurysms in KD but this has yet to be proven [12]. Apart from inducing inflammation, neutrophils, macrophages and dendritic cells have also been found to invade into the artery walls, causing damage with their cytotoxic activities. There also appears to be an excessive activation of cytotoxic CD-8 T cells, further supporting the possibility of an infectious agent as a trigger for the immune activation seen in KD [13]. Immune complexes have been observed in plasma and serum of patients with KD since 1977. They are seen within the first week of illness and gradually increase in number before tapering off after 3

Table 1. Diagnostic criteria of Kawasaki disease [59].

<table>
<thead>
<tr>
<th>Classical Kawasaki Disease</th>
<th>Alternative diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever for at least 5 days and at least 4 out of 5 principle clinical features: changes in lips and oral cavity, polymorphous rash, bilateral conjunctivitis, erythema and desquamation of extremities, cervical lymphadenopathy</td>
<td>Fever for at least 5 days and at least 2 -3 principle clinical features, coronary artery abnormalities on echocardiography</td>
</tr>
</tbody>
</table>

Table 2. Incidence of Kawasaki disease in children less than five years old [60].

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence per 100,000</th>
<th>Year</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>308</td>
<td>2014</td>
<td>Nationwide survey</td>
</tr>
<tr>
<td>South Korea</td>
<td>217.2</td>
<td>2014</td>
<td>National health insurance survey</td>
</tr>
<tr>
<td>Beijing</td>
<td>116.6</td>
<td>2014</td>
<td>Questionnaire survey</td>
</tr>
<tr>
<td>Taiwan</td>
<td>82.8</td>
<td>2010</td>
<td>National health insurance survey</td>
</tr>
<tr>
<td>Canada</td>
<td>19.6</td>
<td>2014</td>
<td>National administrative data</td>
</tr>
<tr>
<td>United states</td>
<td>19.1</td>
<td>2015</td>
<td>Nationwide inpatient sample</td>
</tr>
<tr>
<td>Italy</td>
<td>14.7</td>
<td>2013</td>
<td>National administrative data</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>4.55</td>
<td>2015</td>
<td>Prospective Population based study</td>
</tr>
<tr>
<td>Thailand</td>
<td>3.43</td>
<td>2002</td>
<td>Hospital discharge data</td>
</tr>
<tr>
<td>Israel</td>
<td>2.03</td>
<td>2012</td>
<td>Hospital discharge data</td>
</tr>
</tbody>
</table>
– 4 weeks. This may suggest that immune complexes are formed in response to a foreign antigen to enhance the targeted action of other inflammatory cells and stimulate phagocytosis of the antigen to remove it from the circulation. While this is an interesting finding, there has been no significant correlation between immune complexes and the severity of illness in KD patients, likely due to incomplete data collection and difficulties in identifying the phases of illness during which test samples were collected. More recent studies are needed to rectify these issues and investigate the role of immune complexes in the pathogenesis of KD more closely [13]. An exorbitant immune system activation may occur in KD causing macrophage activation syndrome (MAS), a rare complication that can occur at any stage of KD and lead to increased cardiac complications and high mortality, highlighting the importance of timely diagnosis and management [14]. Studies have shown that this immune response is strongest during the first few weeks of infection with many inflammatory molecules such as cytokines and C-reactive protein being released into the bloodstream. This could be related to the increased expression of cytokines such as IL-1, IL-6 and IL-8 [13]. Tumor necrosis factor-alpha (TNF-α) levels are raised more significantly in KD patients who develop coronary artery aneurysms as compared to those without. This could be related to TNF-α triggering the release of chemokines by endothelial cells, increasing permeability of the endothelial lining to other inflammatory cells such as neutrophils, causing more severe damage to the affected arteries [15].

Management and outcomes

Treatment of Kawasaki disease has evolved over the years. Aspirin was first used to treat coronary aneurysms and to prevent coronary artery thrombosis. There is no evidence currently showing the benefit of high dose aspirin over low dose aspirin to prevent coronary aneurysms in Kawasaki Disease [16]. Aspirin was combined with intravenous immunoglobulin (IVIG) in 1983 and demonstrated a significant reduction in coronary artery complications with the combination therapy. Since then, IVIG has replaced aspirin to become the standard treatment of Kawasaki Disease [17]. Given the lack of high-quality randomized control trials in pediatrics, current KD guidelines recommend use of IVIG and aspirin as the mainstay of treatment. However, there is a small group of patients who do not respond well to immunoglobulins. While steroids were thought to portend poor outcomes [17], there may be benefit of high dose intravenous methylprednisolone in patients who did not respond to IVIG. These patients did not have significant complications or worsening of coronary aneurysms on follow-up and established the role of corticosteroids as the second line treatment for the condition [18]. The possible involvement of tumor necrosis factor-alpha (TNF-alpha) in the pathogenesis of coronary artery lesions in KD raises the question of the possible role of infliximab as a viable treatment option. Pooled data from 16 studies involving 429 patients was analysed, with infliximab treatment causing less complications such as fever, mucosal lesions and lymphadenopathy in the cervical region as compared to traditional immunoglobulin treatment. Laboratory results also showed more significant improvement in platelet count and inflammatory markers such as C-reactive protein and white cell counts in the infliximab groups as compared to the immunoglobulin groups [15]. Similar benefits were noted in groups receiving combination therapy with infliximab and immunoglobulins, further supporting the potential benefit of infliximab in KD treatment [16].

COVID-19 disease

Diagnosis and epidemiology

In contrast to KD that preferentially affects the pediatric population, COVID-19 predominantly affects the adult population. In an epidemiological study published by the Chinese Center for Disease Control comprising of 44,672 confirmed COVID-19 cases, only 1% occurred in children younger than ten years old, and another 1% in those aged between 10-29 years. Most patients were aged 30 years and above, with advanced age being a risk factor for more severe disease [19]. Incubation period of COVID-19 infection is estimated to be up to 14 days; thus it is widely accepted that a quarantine period of 14 days is reasonable to monitor for the development of symptoms in people suspected for COVID-19 infection [20]. While this may indicate a lower detection rate in children rather than lower susceptibility to the infection [21], the vast majority of cases in children aged 18 years or less were mild, or asymptomatic. In the United States, by Oct 2020, up to 1.6 million cases of COVID-19 were reported in children, making up 12.2% of total cases in the country [22]. COVID-19 cases reported in children less than 10 years old made up 5% of total cases in Australia, 0.9% in China (out of a sample of 44,000 cases), 2.7% in South Korea and 0.18% in the United Kingdom. Canada reported 15.7% of COVID-19 cases in patients aged less than 20 years old. Though these are just a few examples and the different age brackets used make it
difficult to compare directly between countries, it does show that children tend to make up a minority of the total number of COVID-19 cases globally [23].

Pathogenesis and complication

In general, viral infections induce a response from the innate immune system by producing inflammatory molecules. While this response helps combat the disease, when the inflammatory response is excessive, a “cytokine storm” ensues, leading to various complications in the host [24]. The critical role of the innate immune system has been reported in other coronaviruses such as Middle East Respiratory Syndrome (MERS) [25] as well as Severe Acute Respiratory Syndrome (SARS) [26]. This concept of immune system dysfunction has naturally generated quite a bit of interest in COVID-19. In COVID-19 disease, the infection of immune cells such as monocytes, macrophages and dendritic cells promotes the production of IL-6, which then acts via the cis or trans signaling pathways to activate the adaptive immune system, leading to more inflammation [27]. There is increased production of vascular endothelial growth factor (VEGF) causing increased leakage from blood vessels, excess of which may then result in drop in blood pressure and respiratory failure [28]. Higher levels of cytokines and chemokines have been shown to correspond with the severity of disease with COVID-19 [29]. Evolving data has shown a drop in the leucocyte levels while the virus multiplies in the initial ten days of COVID-19. There is an initial delay in the production of inflammatory molecules followed by a surge in the levels of cytokines such as IL-6 and TNF-α, as well as chemokines such as macrophage inflammatory protein 1. This implies that the virus may possess a mechanism of evasion of the immune system to facilitate virus replication in the early stages of infection [26]. It is also possible that more than 90% of COVID-19 patients develop antibodies targeted at SARS CoV2 following infection, though the duration of such immunological protection needs to be quantified with further studies [30]. IgG antibodies targeted at SARS CoV1 and memory B cells did not last as long as memory T cells, which were detected up to 6 years after initial infection [31]. The similarities between SARS CoV1 and SARS CoV2 make it possible that the immunological defense against COVID-19 may follow a similar trajectory as well. The angiotensin-converting enzyme (ACE) 2 receptor has been identified as a receptor for the SARS coronavirus [32], found throughout the body in heart and lungs as well as immune cells such as macrophages [28]. The effect of SARS CoV2 on the ACE-2 receptor causes a reduction in the levels of ACE-2 and thus less protective effect on the linings of the pulmonary endothelium due to less inhibition of the action of ACE-1 [33]. This then leads to acute respiratory distress syndrome (ARDS) [34] due to the death of cells in the lung epithelium and blood vessels, causing edema in the alveoli and leakage of the pulmonary capillaries [24]. Studies in mice showed that the binding of SARS-CoV-2 to ACE-2 receptors could trigger activation of the Stimulator of Interferon Genes (STING) pathway, promoting the release of factors like interferon-beta, causing hypercoagulability. This may explain the thrombotic effects of COVID-19, leading to thrombosis, embolism and stroke in severe cases [35].

Management and outcomes

Treatment options that have been examined in clinical trial setting include chloroquine [36], hydroxychloroquine [37] and a combination of antiretroviral drugs lopinavir and ritonavir [38]. Remdesivir is another antiviral medication that appears to be promising for treatment of COVID-19. Studies have showed improvement in symptoms and reduction in mortality in COVID-19 patients with remdesivir, though further studies are still required to delineate potential side effects and confirm the therapeutic benefits [39]. Multiple drug trials are still ongoing at this point, aiming towards finding a cure for COVID-19, though likely the best way to terminate the spread of the virus would be the development of a vaccine. In the meantime, supportive treatment such as steroids, monoclonal antibodies, or IVIG targeted at reducing the immune response in COVID-19 are also being tested [40]. With no clear answer for effective treatment, for COVID-19 patients demonstrating symptoms similar to KD, IVIG could still be considered as it is the standard of care for Kawasaki disease.

Kawasaki-like disease in COVID-19

Case reports

Both KD and COVID-19 infection have been shown to have increased activation of the immune system. There has been a rising number of children diagnosed with both COVID-19 and KD in various countries, including the United Kingdom [41] and USA [42]. Marie Pouletty et al. reported 16 cases of Kawasaki-like disease following SARS-COV-2 infection. This study suggests Kawasaki-like symptoms tend to occur several weeks after SARS-COV-2 infection, causing severe illness requiring intensive care intervention due to inflammation of the myocardium in almost half of the patients studied. Poor prognosis
Factors include age older than 5 years and ferritin levels more than 1,400mg/l [43] (Table 3).

**Associations between KD and COVID-19**

The tendency of COVID-19 to bring about an overdrive of the immune system makes it a potential trigger of KD [43]. The involvement of CD8 T-cell lymphocytes with an elevated CD8:CD4 ratio in KD also point towards a viral cause [44], further supported by the apparent lack of efficacy of antibiotics in the treatment of Kawasaki patients, making it less likely to be due to a bacterial pathogen [45]. It has been suggested that children with COVID-19 infection and genetic pre-disposition to KD may have a lower level of the ACE-2 receptor in the body at baseline, thus resulting in an even lower expression of ACE-2 receptor due to the down-regulatory effects of the SARS COV-2 virus [9]. Activation of STING pathway has also been found to have a role in the formation of coronary aneurysms through inflammation, apoptosis and weakening of vessel walls, which could be one of the mechanisms involved in cardiac complications associated with Kawasaki disease. This overlapping pathway could explain the associations between KD and COVID-19 observed thus far [35]. SARS-COV-2 is known to induce the formation of immune complexes that may accumulate and result in a type III hypersensitivity reaction similar to that seen in KD, especially in patients with compromised immunity [46]. While many cases are pointing towards a possible positive association between KD and COVID-19, there is insufficient evidence to prove that the two conditions share a causal relationship at this stage [47].

**Differences between KD and COVID-19**

Despite their similarities, there are still some fundamental differences between KD and COVID-19. Kawasaki-like symptoms being associated with COVID-19 infection have been mostly reported in Western countries so far. This is a significant change from the traditional understanding of KD, which has always been more common in Asian countries [45]. In fact, there has been very limited data from China, the birthplace of the pandemic, regarding Kawasaki-like symptoms emerging in COVID-19 patients. This could indicate a possible genetic predisposition in the

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of cases diagnosed with Kawasaki-like disease and COVID-19 infection</th>
<th>Age range</th>
<th>Gender ratio</th>
<th>Presenting symptoms</th>
<th>Investigation findings</th>
<th>Treatment</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>[41]</td>
<td>8</td>
<td>4-14</td>
<td>62.5% male, 37.5% female</td>
<td>Fever – 100%, Diarrhea and vomiting – 87.5%, Conjunctivitis – 87.5%, Odynophagia – 37.5%</td>
<td>Raised CRP/ferritin (100%), raised BNP (62.5%)</td>
<td>Intensive care support – 100%, Immunoglobulins – 100% Systemic corticosteroids – 62.5% Intra venous antibiotics – 100% Intensive care support – 80% Mechanical ventilation – 20% Extracorporal membrane oxygenation – 4% Immunoglobulins – 100% Systemic glucocorticoids – 53% Anticoagulation – 37% Intensive care support – 44% Immunoglobulins – 93% Aspirin – 53% Systemic corticosteroids – 25% IL-1 antagonist – 6% IL-6 antagonist – 6% Hydroxychloroquine – 6% Intensive care support – 100% Immunoglobulins – 71% Systemic corticosteroids – 34% IL-1 antagonist – 8% Anticoagulation – 65% Intensive care support – 93% IL-6 antagonist – 80% Immunoglobulins – 80% Systemic corticosteroids – 20% Remdesivir – 13%</td>
<td></td>
</tr>
<tr>
<td>[42]</td>
<td>167</td>
<td>&lt;21</td>
<td>62% male, 38% female</td>
<td>Fever – 90% had fever for at least 4 days or more Respiratory symptoms – 70%, Respiratory failure or insufficiency – 59%, Gastro-intestinal symptoms – 92%, Muco-cutaneous symptoms – 74%</td>
<td>Raised BNP (73%), raised trops (50%), aneurysms on echocardiogram (9%), raised CRP/neuropilis/ferritin (92%)</td>
<td>Intensive care support – 100%, Immunoglobulins – 100% Systemic corticosteroids – 62.5% Intra venous antibiotics – 100% Intensive care support – 80% Mechanical ventilation – 20% Extracorporal membrane oxygenation – 4% Immunoglobulins – 100% Systemic glucocorticoids – 53% Anticoagulation – 37% Intensive care support – 44% Immunoglobulins – 93% Aspirin – 53% Systemic corticosteroids – 25% IL-1 antagonist – 6% IL-6 antagonist – 6% Hydroxychloroquine – 6% Intensive care support – 100% Immunoglobulins – 71% Systemic corticosteroids – 34% IL-1 antagonist – 8% Anticoagulation – 65% Intensive care support – 93% IL-6 antagonist – 80% Immunoglobulins – 80% Systemic corticosteroids – 20% Remdesivir – 13%</td>
<td></td>
</tr>
<tr>
<td>[43]</td>
<td>16</td>
<td>4-12</td>
<td>50% male, 50% female</td>
<td>Fever – 100%, Respiratory symptoms – 12%</td>
<td>Raised CRP/procalcitonin – 100%, Raised ferritin – 50%, Acute kidney injury – 56%, Raised trops – 48.7%, Echocardiogram findings of myocarditis 44%, pericarditis 25%</td>
<td>Intensive care support – 100%, Immunoglobulins – 100% Systemic corticosteroids – 25% IL-1 antagonist – 6% IL-6 antagonist – 6% Hydroxychloroquine – 6% Intensive care support – 100% Immunoglobulins – 71% Systemic corticosteroids – 34% IL-1 antagonist – 8% Anticoagulation – 65% Intensive care support – 93% IL-6 antagonist – 80% Immunoglobulins – 80% Systemic corticosteroids – 20% Remdesivir – 13%</td>
<td></td>
</tr>
<tr>
<td>[57]</td>
<td>35</td>
<td>2-16</td>
<td>51% male, 49% female</td>
<td>Fever – 100%, Respiratory distress – 65%, Gastrointestinal symptoms – 83%, Rash – 57%</td>
<td>Raised CRP/procalcitonin – 100%, Raised pro-BNP – 100%, Raised trops – 45%, Echocardiogram findings of coronary artery dilation – 17%</td>
<td>Intensive care support – 100%, Immunoglobulins – 100% Systemic corticosteroids – 25% IL-1 antagonist – 6% IL-6 antagonist – 6% Hydroxychloroquine – 6% Intensive care support – 100% Immunoglobulins – 71% Systemic corticosteroids – 34% IL-1 antagonist – 8% Anticoagulation – 65% Intensive care support – 93% IL-6 antagonist – 80% Immunoglobulins – 80% Systemic corticosteroids – 20% Remdesivir – 13%</td>
<td></td>
</tr>
<tr>
<td>[58]</td>
<td>15</td>
<td>5-20</td>
<td>53% male, 27% female</td>
<td>Fever – 100%, Gastrointestinal symptoms – 87%, Rash – 47%, Conjunctivitis 27%</td>
<td>Raised trops/BNP – 87%, Raised CRP – 100%, Raised procalcitonin – 60%, Raised ferritin – 87%</td>
<td>Intensive care support – 100%, Immunoglobulins – 100% Systemic corticosteroids – 25% IL-1 antagonist – 6% IL-6 antagonist – 6% Hydroxychloroquine – 6% Intensive care support – 100% Immunoglobulins – 71% Systemic corticosteroids – 34% IL-1 antagonist – 8% Anticoagulation – 65% Intensive care support – 93% IL-6 antagonist – 80% Immunoglobulins – 80% Systemic corticosteroids – 20% Remdesivir – 13%</td>
<td></td>
</tr>
</tbody>
</table>
Western population associated with the development of KD in COVID-19. It is also possible that there is a difference in the virus variant found in Western countries compared to Asian countries [48]. It is thought that symptoms of KD are mediated by immune complexes, thus explaining the efficacy of intravenous immunoglobulin in its treatment. On the other hand, Kawasaki-like syndrome in COVID-19 may be more closely linked with the generation of a cytokine storm and hyperinflammatory state in response to the viral infection, potentially leading to suppression of the bone marrow and resulting in a low platelet count [49].

Screening and surveillance

In view of the potentially severe complications of KD, it is essential that screening is done promptly so that treatment can be initiated. Changes in the coronary arteries may not be detectable within the first seven days of illness; thus, a normal echocardiogram at the time of diagnosis does not rule out KD and will require follow-up at around 2 weeks followed by 4-6 weeks after treatment [3]. Whether it would be beneficial to perform screening CT coronary angiogram in young COVID-19 patients with KD-like symptoms to identify coronary aneurysms early [36] needs to be answered by future studies. More frequent follow-ups may be necessary for patients already found to be developing aneurysms to detect thrombosis in time, with increasing size of aneurysms corresponding to a higher risk of thromboses and lumen narrowing [50]. In patients with KD, inflammation of the cardiac myocytes has been found to improve on follow-up echocardiograms and usually patients regain normal systolic function over time [51].

Kawasaki-like syndrome in COVID-19: a different entity?

Some have proposed using a different label to differentiate the traditional definition of KD from the widespread systemic inflammation induced in COVID-19 patients. This serves as a recognition of the differences between traditional KD and the Kawasaki-like symptoms that have been emerging in COVID-19 patients, in order to avoid confusion especially in cases where symptoms may not entirely fit KD’s clinical diagnostic criteria [52]. The fact that Kawasaki-like symptoms are manifesting in association with a concurrent COVID-19 infection also indicate that it is not a disease on its own but rather part of a syndrome triggered by infection that can be more serious than traditional KD and calls for early recognition and more aggressive treatment [53]. Various names such as Multisystem Inflammatory Syndrome in Children (MIS-C) and Pediatric Inflammatory Multisystem Syndrome Temporarily associated with SARS CoV2 (PIM-TS) were suggested by the Centers for Disease Control and Prevention (CDC) and the Royal College of Pediatrics and Child Health (RCPCH) respectively [54-55]. MIS-C is a diagnosis of exclusion and the diagnostic criteria, as described by the CDC, is shown in Table 4.

Interestingly, a cohort study of over 135 thousand pediatric COVID-19 patients done by Bailey et al. indicated a lower number of KD diagnoses made during the COVID-19 pandemic starting from early 2020 as compared to 2018-2019. This may be a reflection of an actual reduction in the numbers of KD cases due to social distancing measures and personal hygiene habits promoted during the pandemic, which likely reduced the transmission of infectious agents associated with KD. However, there could be an under-reporting of Kawasaki-like syndrome in COVID-19 pediatric patients due to a lack of awareness and recognition, as well as reduced access to healthcare during the pandemic leading to missed diagnoses and thus an under-estimate of the true prevalence of Kawasaki-like syndrome in COVID-19 [56].

Early diagnosis and treatment

According to French surveillance studies, there was a peak in the diagnosis of PIM-TS or MIS-C cases about 4-6 weeks following a rise in COVID-19 diagnoses, suggesting a delayed presentation of COVID-19 infection [54-55]. It has also been noticed that MIS-C in COVID-19 patients tends to occur in older children, leading to symptoms predominantly involving the skin, gut and heart [54, 57]. There was also increased production of IL-6 and IL-8 in MIS-C compared to IL-

Table 4. CDC diagnostic criteria of MIS-C [58].

<table>
<thead>
<tr>
<th>Diagnostic criteria for Kawasaki-like disease in COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Clinical</td>
</tr>
<tr>
<td>Laboratory</td>
</tr>
<tr>
<td>Positive test result for SARS-CoV2 (antigen, serology or PCR)</td>
</tr>
</tbody>
</table>
1 in classic KD [58]. Treatment recommendations include IVIG, corticosteroids and anticoagulation to damp down the hyperinflammatory response and reduce complications from thrombosis [52]. More time would be required to study the long-term effectiveness of various treatment options for MIS-C, though it is encouraging to see that the majority of patients who underwent treatment recovered [42]. While MIS-C or PIM-TS may be rare in COVID-19 infection, the potential severe complications makes it important for early diagnosis and treatment. We would like to propose a framework to facilitate active screening and early recognition of KD-like disease in COVID-19: Recognition, Early surveillance, administering treatment and Prevention (REAP). Recognition of symptoms can be facilitated by disseminating information regarding MIS-C to healthcare workers and offering virtual telehealth consults for parents to reduce late presentations of children due to fears of transmission risk in hospitals. Early surveillance can then be implemented on wards by distributing pictorial charts on Kawasaki-like symptoms to improve recognition of such symptoms in COVID-19 patients. A screening echocardiography can also be performed on COVID-19 patients upon diagnosis and at 2 weeks post diagnosis to detect coronary ectasia. Treatment can be administered once diagnosis of Kawasaki-like symptoms in COVID-19 patients is suspected. In addition to supportive management with fluids and oxygen, IVIG with high dose aspirin may be considered as first line, with IV steroids as second line therapy for those who fail to respond to IVIG. Last but not least, prevention of COVID-19 infection is essential in reducing the spread of the virus. Effective social distancing measures and quarantine protocols will need to be implemented nationwide, as well as public health education campaigns to improve public understanding of COVID-19 and the potentially severe complications.

Conclusions

COVID-19 is rare in children, and study sample sizes to date are not sufficient for the results to be extrapolated to a broader population. Differential diagnoses should still be explored before diagnosing KD-like disease in COVID-19. The fact that MIS-C or PIM-TS only occurred in a small proportion of patients suggests a possible genetic component with age as one of the risk factors. Prospective data are awaited to disentangle the immunological link between KD and COVID-19. Mechanistic studies that explore the crosstalk between immune cells and endothelial cells right from the outset of the infection are needed.

References


Corresponding author
Dr. Fang Yulin MBBS (Australia)
Medical officer, MOHH holdings
Woodlands Health Campus, Khoo Teck Puat Hospital
90 Yishun Central, Singapore 768828
Phone: +65 6555 8000
Email: yulin.fang@mohh.com.sg

Conflict of interests: No conflict of interests is declared.