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COVID-19 AND KAWASAKI DISEASE- A FOCUSED REVIEW

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ABSTRACT
The incidence of Kawasaki disease (KD) has significantly increased since the outbreak of coronavirus disease 2019 (COVID -19) pandemic across the globe, posing a major challenge among pediatricians and health care authorities. COVID-19 is currently recognized as a multisystem disorder that can cause systemic vasculitis which shares clinical features of Kawasaki disease and reflects a particularly strong immunological reaction described as an inflammatory multisystem syndrome (MIS-C) in children with lab evidence of SARS-CoV-2. The main features of cytokine syndrome include high fever, multi-organ dysfunction, and inflammation with clinical features that mimic Kawasaki Disease, toxic shock, and macrophage activation syndrome (MAS) requiring pediatric intensive care admissions for circulatory support. The evidence from various studies suggested that COVID-19 can trigger Kawasaki-like disease. However, much remains to be understood about the potential association between covid-19 and increasing incidence of Kawasaki disease-like features as the disease process is still unclear. This review highlights the need to screen Covid-19 in patients diagnosed with classic Kawasaki disease. Recommended guidelines should be followed along with administration of intravenous immunoglobulins (IVIG), IV methylprednisolone, IL-6, and IL-1 inhibitors in midst of the COVID-19 pandemic as early as possible to decrease the frequency of coronary artery lesions.

INTRODUCTION
Kawasaki disease (KD), a rare acute systemic vasculitis of medium-sized arteries with unknown/inconsistent etiology was first defined by Tomisaku Kawasaki in 1967, affecting children ≥5 years of age. Based on clinical, immunological, and epidemiological evidence, it is suggested that KD is triggered by viral infections[1] and is considered a leading cause of acquired heart disease in children in Europe, North America, and Japan.[2] Although there is no definitive test to diagnose KD, diagnosis is mainly based on a constellation of clinical presentation.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) causing coronavirus disease 2019 (COVID-19) was first reported from Wuhan, China in December 2019 and is an ongoing global pandemic. It has currently affected more than 112,649,371 confirmed cases with 2,501,229 confirmed death globally as of February 26, 2021.[3] Children have been less commonly affected by Covid-19 than adults, accounting for <2% of infection as reported from the first 72,000 cases in the Chinese Center for Disease Control[4]. The epidemiological data from different countries report that children typically

account for up to 13% of laboratory-confirmed cases.[5] The surveillance data from different countries demonstrate that severe illness and death due to Covid-19 is rare among children.[6,7]

Children aged <18 years have a benign course of illness, ranging from asymptomatic to mild or moderate infection as compared to adults who predominantly are vulnerable to more severe forms of the disease especially older adults with underlying comorbidities.[8,9] However, a diverse range of Covid-19 symptoms has been observed across the pediatric population in previous studies, including acute upper respiratory tract infection, gastrointestinal symptoms, and pneumonia.[10] Besides this, a systemic inflammatory response with clinical features resembling Kawasaki disease and toxic shock syndrome in the pediatric population have posed an emerging challenge to this age group[11,12] and underlines the need for careful consideration of the presenting features of COVID-19 in children and adolescents.[13,14] Recent studies reported high rates of children hospitalized in intensive care units (ICUs) in Europe and North America due to multisystem inflammatory syndrome with overlapping Kawasaki disease features and toxic shock syndrome.[15] Although it remains unclear whether patients who had positive serology had true Kawasaki disease or it's the manifestation of coronavirus that resembled KD. Due to a highly unusual yet similar presentation to KD, this condition has temporarily been associated with COVID-19 infection, based on the positive serology in the laboratory investigation of these patients.[16]

Etiopathogenesis of Kawasaki Disease

The etiological agent for Kawasaki disease is unknown but the risk of KD is higher in genetically predisposed children,[17,18] and one or more infectious agents are thought to reflect an abnormal and exaggerated inflammatory response in genetically susceptible children.[19] Recent gene-wide association studies (GWAS) identified specific chromosomal loci and single nucleotide polymorphism (SNPs)[20] in various genes to be linked with susceptibility to develop KD[21] and are considered to contribute to diagnosis and treatment of the disease.[18]

Multiple viral infections have been suggested as the trigger of KD, including parainfluenza virus, coxsackievirus, respiratory syncytial virus, cytomegalovirus, human metapneumovirus, and chikungunya.[22] Subsequent studies showed that up to half of all patients with KD had one or more respiratory RNA viruses as the causative agents, but the etiological role is unclear.[23] Bacterial superantigens mainly staphylococcal enterotoxin A, B, and C, TSST-1, and SPE-A,[24] can lead to exaggerated immune response; hence considered to contribute to KD etiology.[25]

The vasculitis begins with neutrophilic infiltration of the arterial wall followed by infiltration of CD8+Tcells, plasma cells, and monocytes releasing elevated levels of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNFα), resulting in an aneurysm. High levels of Th17 and regulatory T cells in KD patients indicate the involvement of adaptive immunity.[26,27]

Principle Clinical findings, Diagnosis, and Management of Kawasaki disease

American Heart Association devise clinical criteria in 2017 for diagnosis of KD which requires ≥5 days of persistent fever plus at least four of the five major features for the diagnosis of complete and less than four for incomplete KD

Table 1. The 2017 American Heart Association (AHA) criteria for Diagnosis of Kawasaki Disease.

Persistent high Fever with ≥ 4 of 5 principal clinical features
1. Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
2. Bilateral bulbar conjunctival injection without exudate
3. Erythema and edema of the hands and feet in the acute phase and/or periungual desquamation in the subacute phase
4. Maculopapular rash, diffuse erythroderma, or erythema multiforme-like rash
5. Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral

Further lab findings that support KD diagnosis are high levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), raised white blood cell count, and thrombocytosis. Less frequently, elevated levels of serum transaminases or gamma-glutamyl transpeptidase, and hypoalbuminemia are also commonly found along with pyuria and high cell count in cerebral spinal fluid. Electrocardiogram and echocardiography are necessary for the evaluation of coronary artery abnormalities.

Incomplete KD is diagnosed with unexplained fever with fewer than 4 of 5 principal clinical manifestations, with

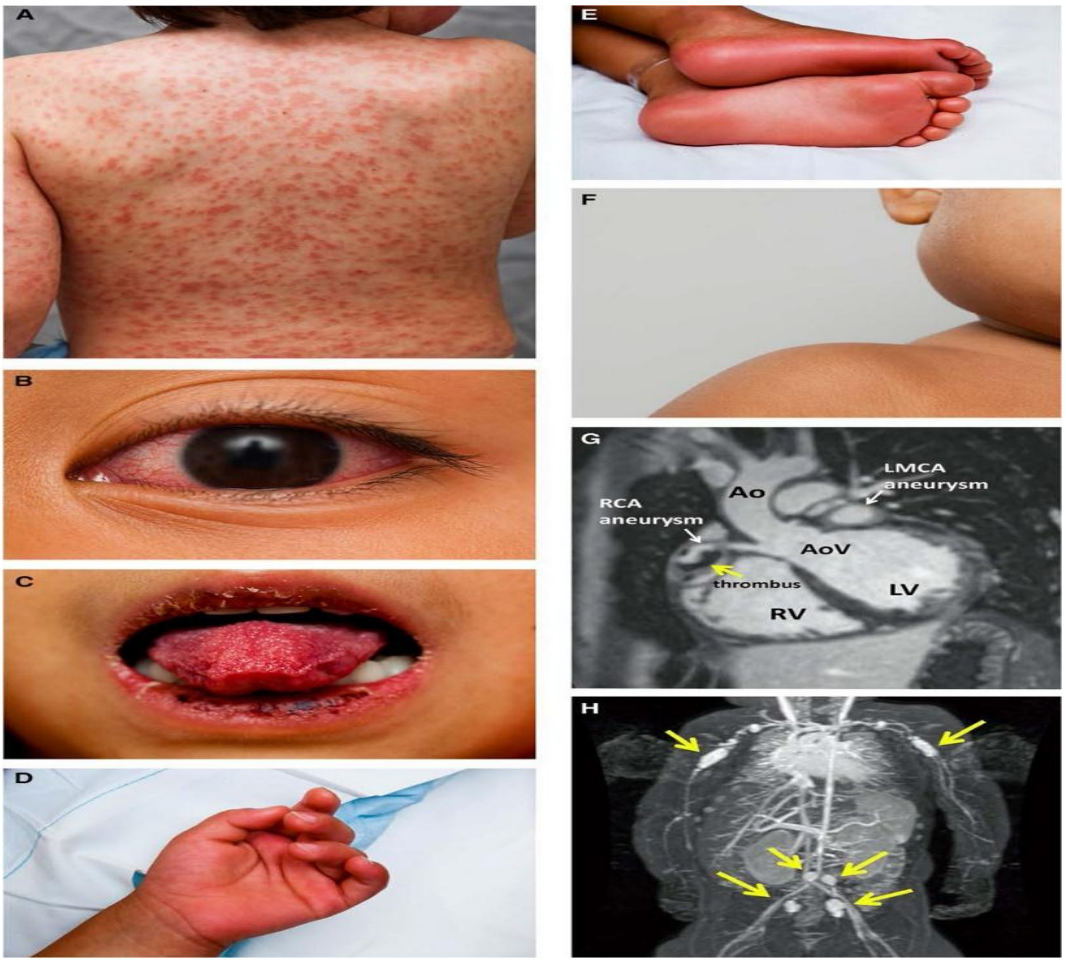
comparable laboratory and echocardiographic findings.[28]

Disease abruptly begins with a high fever (>39°C to 40°C) which can last for 1-3 weeks along with the presence of ≥4 of the 5 principal clinical manifestations (figure 2).

1. Diffuse maculopapular or erythematous rash with early desquamation is a characteristic feature, usually appears early within the first 5 days of fever onset.
2. Bilateral non-purulent conjunctivitis sparing the limbus is considered a characteristic sign as well.
3. Extremity changes include painful swelling of hands and feet, erythema of hands and soles often happen in acute phase followed by peeling off of the periungual region (desquamation) which can extend to palms and soles.
4. Oral lesions include the strawberry tongue, cracking, fissuring, or bleeding of the lips, and diffuse oropharyngeal erythema.
5. Cervical lymphadenopathy is present in 60% of patients, usually unilateral, ≥1.5 cm in diameter, and confined to the anterior cervical triangle. Sometimes, it is the only notable initial finding in KD patients.[29]

Other multisystem manifestations include gastrointestinal symptoms (abdominal pain, vomiting, diarrhea, hepatitis, gallbladder hydrops), and musculoskeletal symptoms (arthritis or arthralgias) which are seen in the first week of the disease;[30] visual (uveitis, retinal vasculitis), genitourinary tract (pyuria, urethritis, phimosis), respiratory tract (lung infiltrates) are the other commonly involved systems. Neurological symptoms originate in 5% of patients and include headache, extreme irritability, seizures, aseptic meningitis, peripheral unilateral or bilateral facial nerve palsy, and sensorineural hearing loss.[31] Macrophage activation syndrome is less frequent and is usually associated with IVIG resistance.[32] Infants may not develop a full disease spectrum and may present only with pyuria or irritability, whereas older children may have delayed presentation.

Coronary artery aneurysm (CAA) is evident after one week of disease onset. Children >10 years of age are at increased risk of CAA.[33] Coronary artery dilations with Z-scores >2.5 are highly specific (specificity 98%) for the left coronary artery or the right coronary artery.[34] Pericarditis can develop in 18% whereas myocarditis is indicated in 3% of patients, can lead to cardiogenic shock.[35]



(Figure 2).

The standard treatment is intravenous immunoglobulin (IVIG) plus high dose acetylsalicylic acid (ASA) in the acute phase of the disease. It reduces inflammation and prevalence of coronary artery abnormalities from 25% to ~4%.[28, 36]

In resistant cases where fever persisted for > 36 hours of IVIG infusion, a second dose of IVIG infusion is administered along with IV methylprednisolone and/or etanercept,[28] cyclophosphamide, anakinra, cyclosporine, or even plasma exchange or combination of anakinra with etanercept can be considered as additional treatment options to prevent the unfavorable progression of the disease.[37]

In the case of coronary artery aneurysm development, triple treatment with low-molecular-weight heparin (LMWH) or warfarin plus low-dose ASA and clopidogrel (second antiplatelet agent) is suggested. For coronary artery thrombosis, Alteplase can be used as thrombolytic therapy. Thrombosis prophylaxis is given for long-term management in patients with coronary artery abnormalities.[38]

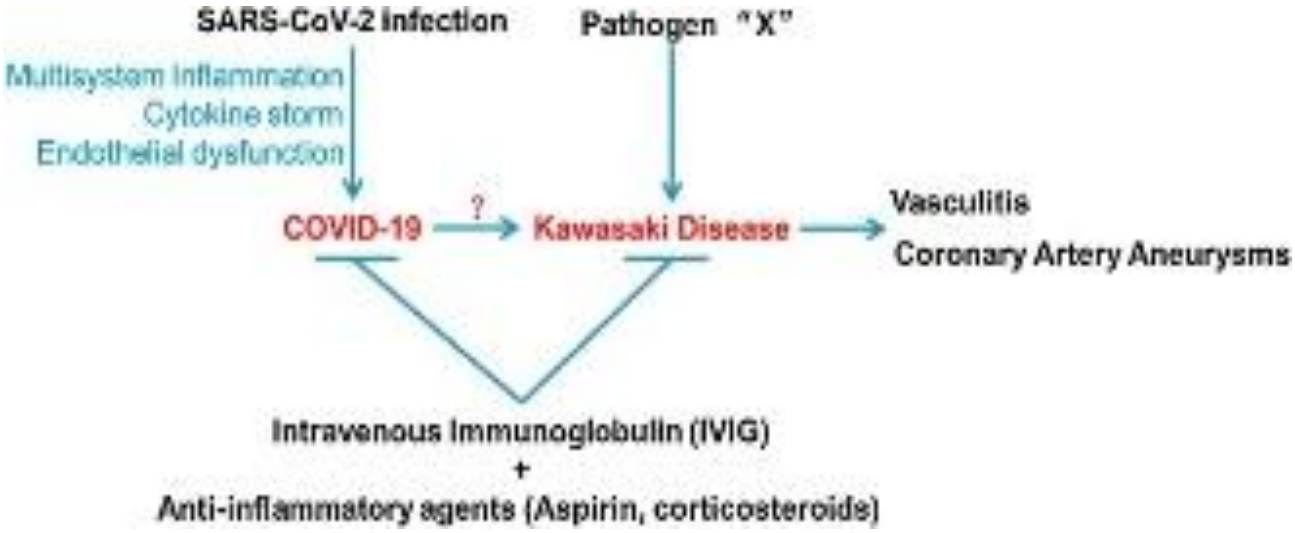
Relationship with COVID-19

The incidence of COVID-19 was 1.7% in the USA among children <18years of age,[39] 2% in UK[40], and 0.8% in Iceland.[41] Several studies have reported the benign course of illness for COVID-19 in children with one-fifth had asymptomatic infections and two-third had only one symptom at the time of testing.[42] However, data from different countries reported Inflammatory Multisystem Syndrome associated with SA RS-CoV-2, requiring hospitalization and intensive care admissions.[10,43] In the USA, 15 cases of the multisystem inflammatory syndrome with similar characteristics of KD were reported by the department of health of New York City on May 4, 2020.[44] A study from south London UK hospital reported 8 children with toxic shock syndrome with atypical KD features and KD shock syndrome, and five children out of them were tested positive for SARS-CoV-2. Clinical findings included high fever, rash, abdominal pain, vomiting, diarrhea, peripheral edema, conjunctivitis which progressed to cardiogenic shock necessitating hemodynamic support.[16]

Verdoni et al. presented 10 (aged 7.5 years [SD 3.5]) cases of Kawasaki-like disease from Bergamo, Italy with a 30 fold higher monthly incidence of KD during the COVID-19 pandemic (Feb 18 to April 20, 2020), across

the previous 5 years.[45] Eight of the 10 patients had been SARS-CoV-2 exposed, six of 10 had cardiovascular system involvement, five of 10 developed macrophage activation syndrome while five of 10 progressed to KD-shock syndrome (KDSS). It is estimated that similar outbreaks of KD occurred in other countries involved in the pandemic.[46] Toubiana and colleagues described a similar outbreak of KD with unusual higher gastrointestinal involvement in patients from African ancestry during the pandemic between April 27 and May 7, 2020 in Paris, France. Among 17 included patients, 14 had SARS-CoV-2 infection, 11 presented with KDSS, and 12 had myocarditis necessitating intensive care admission. The incidence of KD is 13 fold higher as compared to previous years over 2018-2019 (average 1 per 2 weeks) in France.[47] The multiple inflammatory responses (MIS-C) linked with SARS-CoV-2 infection can affect multiple organs/systems including respiratory, gastrointestinal, cardiovascular, hematological, mucocutaneous with overlapping features of KD and toxic shock syndrome leading to increase pediatric intensive care unit (PICU) admissions.[48]

CORRELATION OF IMMUNE RESPONSE IN PEDIATRIC COVID-19 and CYTOKINE SYNDROME



The KD development is accelerated by the hyperimmune response to pneumonia which may heighten the systemic inflammatory response within coronary arteries, leading to endothelial dysfunction, multi-organ failure, and high frequency of myocarditis.[53] This potential life-threatening post-viral severe inflammatory reaction which shares clinical features with atypical KD[48,54] and Staphylococcus aureus toxin-mediated toxic shock[55] has been described as a multisystem inflammatory syndrome in children (MIS-C) by the World Health Organization (WHO) and the Centre for Disease Control (CDC),[56] and as pediatric multisystem inflammatory syndrome-temporally associated with SARS-CoV-2 (PIMS-TS) by the Royal College of Paediatrics and Child Health in UK[57,58]

A rapid increase in the incidence of Kawasaki disease is noticed with severe acute coronavirus respiratory syndrome coronavirus 2 (SARS-CoV-2) infection outbreak, supporting the viral etiology of KD.[49] SARS-CoV-2 can infect endothelial cells by binding to angiotensin-converting enzyme (ACE-2) receptor, present on the surface of lung epithelium and enterocytes of the small intestine,[50] leading to endothelial cell injury/dysfunction and thrombosis. After binding to ACE2-a receptor, the Angiotensin II pathway is excessively activated which in turn over-activates STING, cytosolic DNA sensor, nuclear factor(NF)-κB, and adaptor protein in type I IFN pathways leading to monocyte-macrophages production, triggering the release of tissue factor and interferon β, which promotes thrombotic coagulopathy and systemic inflammation associated with COVID-19.[51] It is crucial to notice that inflammatory cytokines, white blood cells, and activation of platelets cause fibrin deposition via thrombin activation with subsequent tissue damage and development of microangiopathic pathology both locally (eg in the lungs of a patient with severe pneumonia) and systemically.[52]

It has been observed that the Novel coronavirus for unknown reasons activates type2-helper T cells instead of Th-1 cells, which keeps the infection under control in intensive care unit patients.[59] Immune complexes formation results in the deposition of complement anaphylatoxins (component C3A and C5A) inside the blood vessels, rendering the release of histamine from mast cells and phagocyte chemotaxis leading to the development of a cytokine storm,[60] the sequential increase in vascular permeability and non-striated muscle

contraction can cause progressive stenosis of vascular walls.

Subsequent markedly damaged endothelial wall induces the uncontrolled release of pro-inflammatory cytokines which resembles MAS, including IL-6, IL-10, soluble IL-2 receptor, ferritin levels, and D-dimers,[61] developing septic coagulopathy, activating blood clotting system, and hence disseminated intravascular coagulation (DIC) syndrome.[62]

Accumulation of platelets further leads to a hypercoagulable state, thrombocytopenia, and thrombosis. IL-1 and IL-8 are found to be markedly increased in MAS as opposed to MIS-C; mild elevations of IL-18 and IFN-γ are also present. [61] MIS-C is evident in older children as compared to KD which happens in early childhood; 1-4 clinical features overlap to KD. Coagulopathy, thrombocytopenia, lymphopenia, myocarditis, left ventricular systolic dysfunction including acute heart failure are observed more commonly in MIS-C[63] whereas, coronary artery aneurysm (CAA) is also reported in MIS-C patients without KD features. It is important to rule out bacterial infections causing myocarditis (enterovirus), staphylococcal, and streptococcal toxic shock syndrome bacterial sepsis.

Although, there is no specific treatment for MIS-C; IVIg and intravenous methylprednisolone is considered standard treatment approach.[63] Low dose ASA and enoxaparin are considered for anticoagulation therapy while few patients also received remdesivir.[61] IL-1 and IL-6 inhibitors can also be used.[64] Mortality is less with MIS-C as compared to adult severe COVID-19 disease.

CONCLUSION

A multisystemic inflammatory syndrome in children (MIS-C) is a cytokine syndrome that can lead to toxic shock syndrome, KD, and MAS in patients exposed to SARS-CoV-2 infection, resulting in serious cardiac complications requiring inotropic support, hemodynamic support, and PICU admissions. The relationship between the multisystem inflammatory syndrome in children (MIS-C) associated with the SARS-CoV-2 pandemic (also known as Kawasaki-like disease or Kawa-CoVID-19) is not yet adequately characterized but overlapping clinical features, immunopathogenesis, and laboratory findings emphasize the need for further long-term follow-up studies to better understand the dynamics of the temporal association between Multisystem inflammatory syndrome and COVID-19 outbreak. Also, Children diagnosed with KD should be tested for COVID-19, to differentiate the etiology and avoid missing underlying COVID-19 and treat it accordingly.

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