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REVIEW ARTICLE

ARE THE NEW KAWASAKI-LIKE SYNDROMES IN THE CHILDREN ASSOCIATED WITH COVID-19?

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ABSTRACT

COVID-19 has become a significant public health problem since December 2019, and despite vaccination, people are still infected and have died because of COVID-19. COVID-19 mainly affects older adults and people with comorbidities like cancer, obesity, metabolic syndrome, diabetes, endocrine disorders, cardiovascular diseases, and immune disorders. On the other hand, some young adults infected by COVID-19 show severe symptoms similar to Kawasaki Disease (KD) called Kawasaki-like syndrome (KLS), incomplete Kawasaki disease, atypical Kawasaki disease, SARS-CoV-2-induced Kawasaki-like Hyper-inflammatory Syndrome (SCiKH Syndrome) and Kawa-COVID-19. Children with KD-like syndromes and cardiovascular complications, including aneurysms, left ventricular dysfunction, pericarditis, myocarditis, valvular regurgitation, or coronary arterial ectasia, tested positive for the COVID-19 virus, up to two-thirds of cases. On the other hand, people with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more vulnerable to COVID-19 infection, and KD with G6PD deficiency has been reported previously. Therefore, children with G6PD deficiency or KD disease can be more vulnerable to COVID-19; thus, we discuss the possible role of COVID-19 in KD-like syndrome and G6PD deficiency associated with severe symptoms in children. Also, the possible correlation between COVID-19 infection and Kawasaki disease-like syndromes should be further investigated.

Keywords: COVID-19, children, hyper-inflammatory state, Kawasaki disease, G6PD deficiency

INTRODUCTION

COVID-19 has been a major public health problem since December 2019, affecting millions of people's lives; however, vaccines developed by different companies reduced the mortality and severity of the infection. COVID-19 mainly affects older adults and people with comorbidities like cancer, obesity, metabolic syndrome, diabetes, endocrine disorders, cardiovascular diseases, and immune disorders. On the other hand, thousands of young populations and children without comorbidities reported severe symptoms during the COVID-19 pandemic (1–4). For instance, news about some COVID-19-positive children has started showing Kawasaki disease-like syndromes with a 1-3% mortality rate, and National Health Service (NHS) has warned medical doctors about these syndromes among children. Additionally, WHO has investigated the correlation between COVID-19 and Kawasaki disease-like syndromes in children since April 2020 (5–7).

COVID-19-triggered Kawasaki-like syndromes in children have been named Kawasaki-like syndrome (KLS), incomplete Kawasaki disease, atypical Kawasaki disease, SARS-CoV-2-induced Kawasaki-

like Hyper-inflammatory Syndrome (SCiKH Syndrome) and Kawa-COVID-19 (8). Kawasaki disease, also known as mucocutaneous lymph node syndrome, was first described in 1967 by Tomisaku Kawasaki and defined by a hyper-inflammatory state with several symptoms, including persistent fewer (more than five days), redness in the lips, mouth, and throat, rash, swollen lymph glands, redness in the whites of the eyes and swelling of the hands and feet. KD is described as a rare systemic medium-vessel vasculitis occurring in children between 5 months and 5 years of age. The reason for Kawasaki disease is unknown; however, it is hypothesized that a pathogen, probably a virus, may trigger this disease (9).

Thousands of children and adults have developed COVID-19-induced severe health effects mimicking KD disease, such as a hyperinflammatory state, cardiac dysfunction, respiratory failure, and enhanced inflammation (10). Also, a case report has revealed that COVID-19 triggered a recurrence of Kawasaki disease with symptoms including fever, maculopapular rash, altered sensorium, elevated inflammatory markers, and dilated coronary arteries (11). On the other hand, some HIV-positive patients have been shown Kawasaki disease-like syndromes supporting the correlation between the current COVID-19 infection and Kawasaki symptoms in children (12). Additionally, we have reported that people with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more vulnerable to COVID-19 infection (13), and KD with G6PD deficiency has been reported previously. Therefore, children with G6PD deficiency or KD disease can be more vulnerable to COVID-19 associated with severe symptoms (14,15). In this review, we discuss the possible role of the COVID-19 disease in KD, KD-like syndrome, and G6PD deficiency associated with severe symptoms.

Kawasaki-like syndrome in COVID-19-infected children

KD primarily affects instants and young children between 6 months and 4 years of age, and the causes of this are unknown (16). KD is a multisystem acute inflammation of coronary blood vessels and aorta (17), also known as lymph node disease because this syndrome highly affects lymph nodes (18). In this disease, a classical pathogen response is localized to the coronary arteries, and one of the critical initial symptoms is high fever. KD causes infiltration of inflammatory cells in the arteries, especially the coronary arteries for instance, 25% of KD patients develop coronary artery aneurysm (CAA). Therefore, stopping cardiovascular complications and maintaining hemodynamic stability are vital for KD patients (19).

Some overlapping symptoms between KD and COVID-19, called Kawasaki-like syndromes, include high and persistent fever, gastrointestinal disorders, skin rash, dry and cracked lips, elevated C-reactive protein, and high levels of ferritinaemia (20). On the other hand, COVID-19 infection shares similar symptoms with the multisystem inflammatory syndrome in children (MIS-C), KD, and pediatric inflammatory multisystem syndrome temporarily (21). Multisystem inflammatory syndrome has been observed in most COVID-19 cases of children associated with severe pediatric syndromes such as KD (22). Various viral infections, including retroviruses, enteroviruses, the New Haven coronavirus (HCoVNH), and parvovirus B19, have a significant role in the development of KD (23). Bacterial infections such as Streptococcus pyogenes, Staphylococcus aureus, and Yersinia pseudotuberculosis have been implicated with KD etiology (24). Some HIV-positive patients have been shown Kawasaki disease-like syndromes supporting the correlation between the current COVID-19 infection and Kawasaki symptoms in children (12). Also, the wavelike spread and acute onset of KD have been reported in the winter, a season for viral respiratory illnesses, addressing the correlation of KD with infectious diseases (25–27). Children with KD-like syndromes, along with cardiovascular complications including aneurysms, left ventricular dysfunction, pericarditis, myocarditis, valvular regurgitation, or coronary arterial ectasia, tested positive for COVID-19 virus up to two-thirds of cases (28).

The endothelial dysfunction in COVID-19 and Kawasaki Disease correlated with myocardial dysfunction

COVID-19 and KD induce oxidative stress and inflammation associated with endothelial dysfunction, thrombosis, cytokine storm, organ dysfunction, and myocardial injury in the patients. Endothelial dysfunction is a shared pathogenesis by KD and COVID-19 resulting from enhanced oxidative stress, inflammation, cytokine storm, and coagulopathy, leading to myocardial dysfunction, thrombosis, and multiorgan dysfunction (29). KD is the most common

acquired heart disease in children due to endothelial dysfunction, acute vasculitis, coronary artery abnormalities, and thrombosis. During acute and subacute phases, KD induces inflammatory cell activation, such as monocytes, neutrophils, and natural killer (NK) cells. Activated inflammatory cells induce the secretion of monocyte chemoattractant protein-1 (MCP-1), e-selectin, IL-6, IL-8, IL-37, IL-1, IL1β, ICAM1 (Intercellular Adhesion Molecule 1), and VCAM1 (vascular cell adhesion molecule 1) associated with endothelial damage, thrombosis, artery damage, and vasculitis in KD (30). On the other hand, activated inflammatory cells induce reactive oxygen species (ROS) release, leading to enhanced oxidative stress and endothelial dysfunction, inflammation, thrombosis, altered microcirculation, and myocardial dysfunction (31). Enhanced ROS attacks lipids, protein, and DNA; for instance, oxidative stress causes the oxidation of low-density protein (LDL), which binds to the lectin-like-oxLDL receptor 1 (LOX1) mainly expressed in the endothelial cells, macrophages, dendritic cells, and lymphocytes. The oxidized LDL and LOX1 interaction is the key mechanism for endothelial cell injury (32).

COVID-19 is considered a microvascular and endothelial disease since endothelial dysfunction is the major pathogenesis of the disease. Spike glycoprotein (S protein) of COVID-19 induces endothelial cell activation and endothelial damage directly by binding to the cell. On the other hand, the S protein triggers macrophages secreting ICAM-1, VCAM-1, IL-6, IL-18, PAI1, and MCP-1 correlated with thrombosis, inflammation, vascular leakage, and endothelial dysfunction. Furthermore, the S protein induces the degradation of endothelial junction proteins such as cadherin, connexin-43, PECAM-1, and junctional adhesion molecule-A (33). COVID-19 induces endothelial dysfunction via several mechanisms, including endothelial cell injury, degradation/damage of endothelial glycocalyx/barrier, endothelial hyperpermeability, endothelial to mesenchymal transition (EMT), endothelial inflammation, enhanced angiogenesis, cytokine storm, increased oxidative stress, altered mitochondrial function, virus-induced senescence of the endothelial cells and complement activation (29).

COVID-19 infection triggers the innate immune system, leading to an enhanced inflammatory response and oxidative stress associated with severe symptoms and increased mortality risk in patients. Biomarkers associated with endothelial dysfunction, thrombosis, coagulopathy, vascular dysregulation, and oxidative stress have been reported in COVID-19 patients associated with disease severity and mortality risk (29,31,34). For instance, circulating neutrophils, many pro-inflammatory effector cytokines, including TNF, IL-1β, IL-6, IL-8, ICAM-1, VCAM-1, G-CSF, and GM-CSF, chemokines such as MCP1, IP10, and MIP1α levels significantly elevated in the severely ill patients infected by COVID-19 compared control to the healthy individuals (35).

On the other hand, syndecan-1 and heparanase are biomarkers of glycocalyx damage correlated with endothelial damage, thrombosis, and microcirculation. The glycocalyx consists of glycoprotein and proteoglycan covering endothelial cells to maintain vascular homeostasis. Altered glycocalyx structure leads to enhanced oxidative stress and inflammation that causes syndecan-1 release. Increased syndecan-1 levels are correlated with elevated levels of thrombomodulin, TNF-α, IL-6, and heparinase, a degrading enzyme of glycocalyx (36). Moreover, some patients infected by COVID-19 showed a hyper-inflammatory state followed by a cytokine storm like KD syndrome due to the overactivation of the innate immune response. Cytokine storm leads to multi-organ dysfunction via enhanced inflammation, thrombosis, and endothelial dysfunction. Thus, hyper-inflammatory state and Kawasaki-disease-like syndromes in COVID-19-positive children may result from COVID-19-infection-induced over-activation of inflammatory responses and altered oxidative stress metabolism (37,38).

Glucose-6-phosphate dehydrogenase enzyme deficiency and COVID-19

G6PD enzyme deficiency is the most common blood disorder and enzymopathy worldwide, affecting 400 million people with 160 variants (39–41). G6PD is the rate-limiting enzyme of the pentose phosphate pathway (PPP) and reduces $NADP^+$ to $NADPH^+ + H^{+.}$ The reduced form of $NADP^+$ plays a vital role in detoxification reactions, redox signaling, oxidative stress, cell proliferation, migration, differentiation, and growth (42,43). $NADPH^+$ is used to convert oxidized glutathione (GSSG) to reduced glutathione (GSH) via the glutathione reductase (GR) enzyme. GSH/GSSG ratio is the major biomarker of oxidative stress, and G6PD deficiency causes depletion of GSH associated with increased oxidative stress in individuals. Since G6PD is one of the most crucial enzymes in antioxidant metabolism, infectious

diseases such as COVID-19, which induce oxidative stress, may cause severe symptoms via enhanced hemolysis in G6PD-deficient individuals (2,14,15).

G6PD enzyme gene locus is found on the X-chromosome; therefore, males are much more affected than females (44,45). On the other hand, COVID-19 infection has gender-based differences and has much more adverse effects on male patients than female patients, according to the literature (46). Recent studies have revealed that COVID-19 results in hematological alterations because of altered heme and hemoglobin metabolism, leading to hemolysis and dysregulated oxygen transport (47). Since G6PD deficiency is described by the dysfunction of RBCs leading to hemolysis, children with G6PD deficiency can be more vulnerable to COVID-19 infection because of increased hemolysis and impaired oxygen transport (48). Therefore, hyper-inflammatory state and severe symptoms in G6PD-deficient children infected by COVID-19 may result from increased hemolysis and hyperactivation inflammatory response (49). Also, the impact of the G6PD enzyme on KD pathogenesis should be further investigated in KD patients with and without G6PD deficiency.

CONCLUSION

World has been struggling with COVID-19 and its adverse effects since December 2019. Despite vaccination, thousands of people are still infected by COVID-19, and our knowledge is increasing daily via new studies. Older individuals and people with comorbidities like cancer, diabetes, endocrine disorders, metabolic syndrome, cardiovascular diseases, and immunological disorders are reported risk groups. On the other hand, younger individuals and children infected by COVID-19 showed severe symptoms, including KD-like syndromes characterized by endothelial dysfunction, myocardial damage, thrombosis, and cytokine storm. COVID-19 and KD induce endothelial dysfunction as common pathogenesis correlated with enhanced oxidative stress, inflammation, vascular damage, and thrombosis. The exact mechanism or reason for KD-like syndromes in COVID-19-infected children is unknown; however, COVID-19-induced endothelial damage can be the possible reason behind the indicated symptoms. On the other hand, G6PD-deficient individuals showed severe symptoms of COVID-19 because of enhanced oxidative stress and inflammation. No data address the role of the G6PD enzyme in KD pathogenesis; thus, the impact of the G6PD enzyme can be further investigated in KD and KD-like syndromes.

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