

COVID-19 AND KAWASAKI DISEASE

Confirmatory rapid PCR test was positive for SARS-CoV-2 in few children of KD cases during Covid-19 epidemic.¹ This RNA virus association had been observed with KD few years ago.²⁻⁵ Circulating immune complexes (ICs), triggered by infectious agents, bacteria, or viral or other unknown causes, have been detected in the early phase of KD already known to us, implicating that immune-pathologic mechanisms might be involved in the pathogenesis of vasculitis in KD.⁶⁻¹² SARS-CoV-2 mimicking symptoms and signs of KD where immune-pathological mechanism could be same. Still this is not a particular causative agent to stress over etiopathogenesis on KD, but may consider as a one among the many triggering agents for circulating immune complex producing vasculitis. As far as my understanding no authors published any coronary artery lesions in cases with positive SARS-CoV-2 which is more important to prove coronary artery affinity like in KD. We do not know why particular immune complexes disease attacking mainly coronary endothelium, could be readily triggers a host immune response in genetically susceptible children and genes implicated in susceptibility to KD with replication. Family linkage studies and genome-wide association studies with subsequent validation studies have implicated single-nucleotide polymorphisms in six genes or gene regions.^{6, 12} These polymorphisms likely vary across populations and results suggest that KD susceptibility and disease outcome, including aneurysm formation and response to IVIG, are influenced by variants in several different genes and signalling pathways.¹³

Many authors also noted that Covid-19 can produce myocarditis in children.^{14,15} At the same time all cases with myocarditis didn't manifest signs and symptoms to fulfill the criteria for KD. Myocarditis in children can occur with many viral or bacterial diseases, and also will

manifest in KD prior to epicardial coronary arteritis appear. Published data indicate that myocardial inflammation can be documented in 50% to 70% of patients using gallium citrate Ga 67 scans and technetium Tc 99m-labelled white blood cell scans.¹³ Acute LV dysfunction is generally transient and responds readily to anti-inflammatory treatment. The rapid improvement in LV function differs from that observed in other causes of myocarditis. Myocarditis in KD likely improves rapidly as the inflammatory process subsides because it results from interstitial edema and inflammation and only rarely from myocardial cell necrosis.¹³ Hence LV function study by routine Simpson method or Global longitudinal strain (GLS) by 2-D echocardiography in KD, and also in all other suspected viral illness including Covid-19 positive cases is essential. In such occasion I personally suggest that paediatricians should seek the help of a cardiologist to evaluate LV function by at least two or three follow up.

In this presently study D-Dimer was investigated and which was within normal limit. (D-dimer 3285-7180). In adult cases many clotting issues reported and thrombosis occur in most of the organs including heart results in stroke and myocardial infarction. Thrombotic episodes not published so far in children with Covid-19. All such cases with positive SARS-CoV-2 were well responded to IVIG and Aspirin. So that children with Covid positive, even without Signs and symptoms of KD, you may give a trial of same treatment protocol for KD to prevent or mitigate myocarditis and thrombotic episodes. IVIG will be certainly helpful in myocarditis in at least few cases as per our experiences. Role of HCQ in children yet to be proved. Possible mechanisms of IVIG include the modulation of cytokine production, neutralization of toxins, pathogenic agents. Fc receptors, augmentation of regulatory T cell activity, and suppression of antibody synthesis will certainly help in cases with SARS-CoV-2, and even in the situation of myocarditis.

Finally I conclude that we may add SARS-CoV-2 as one of the differential diagnosis of KD. Once the criteria is fulfilled for KD in Covid-19 cases, treatment protocol will be same as for KD. Veena. G. Jones et.al, in their study, the patient was treated as per treatment guidelines, with intravenous immunoglobulin and high-dose aspirin, and subsequently reduced or resolved clinical symptoms in a case of KD with positive SARS-CoV-2.¹

References

1. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. *Hosp Pediatr*. 2020; doi: 10.1542/hpeds.2020-0123 **DOI:** 10.1542/hpeds.2020-0123.
2. Shirato K, Imada Y, Kawase M, Nakagaki K, Matsuyama S, Taguchi F.J Possible involvement of infection with human coronavirus 229E, but not NL63, in Kawasaki disease. *Med Virol*. 2014;86 :2146-53. doi: 10.1002/jmv.23950. Epub 2014 Apr 24. PMID: 24760654.
3. Rowley AH, Baker SC, Shulman ST, Rand KH, Tretiakova MS, Perlman EJ, Orenstein JM et.al. Ultrastructural, immunofluorescence, and RNA evidence support the hypothesis of a "new" virus associated with Kawasaki disease. *J Infect Dis*. 2011;203 :1021-30. doi: 10.1093/infdis/jiq136. PMID: 21402552.
4. Belay ED, Erdman DD, Anderson LJ, Peret TC, Schrag SJ, Fields BS, Burns JC, Schonberger LB. Kawasaki disease and human coronavirus. *J Infect Dis*. 2005;15;192 :352-3; author reply 353. doi: 10.1086/431609.
5. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. *Hosp Pediatr*. 2020; doi: 10.1542/hpeds.2020-0123 **DOI:** 10.1542/hpeds.2020-0123
6. Kei Takahashi, Tokshiaki, Oharaseki, Yuki Yokouchi. Update on etio and immunopathogenesis of Kawasaki disease. *Current Opin Rheumatol* 2014;26:31-36
7. Naoe S, Shibuya K, Takahashi K, Wakayama M, Masuda H, Tanaka M. Pathological observations concerning the cardiovascular lesions in Kawasaki disease. *Cardiol Young* 1991; 1:212-20.

8. Furuse A, Matsuda I Circulating immune complex in the mucocutaneous lymph node syndrome. *Eur J Pediatr* 1983; 141:50–51
9. Mason WH, Jordan SC, Sakai R, Takahashi M, Bernstein B 1985 Circulating immune complexes in Kawasaki syndrome. *Pediatr Infect Dis* 4:48–51
10. Lehman TJA, Walkwer SM, Mahanovsky V, Mc Curdy D 1985 Coronary arteritis in mice following the systemic injection of group B *Lactobacillus casei* cell walls in aqueous suspension. *Arthritis Rheum* 28:652–659
11. Philip S, Lee WC, Liu SK, Wu MH, Lue HC. A swine model of horse serum-induced coronary vasculitis: an implication for Kawasaki disease. *Pediatr Res* 2004; 55:211-19.
12. Onouchi Z, Ikuta K, Nagamatsu K, Tamiya H, Sakakibara Y, Ando M 1995 Coronary artery aneurysms develop in weanling rabbits with serum sickness but not in mature rabbits: an experimental model for Kawasaki disease in humans. *J Vasc Dis* 46:679–686
13. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, Treatment, and Long- Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation*. 2017;135:927-99.
14. Nianguo Dong, Jie Cai, Ying Zhou, Junwei Liu and Fei Li. End-stage Heart Failure with COVID-19: Strong Evidence of Myocardial Injury by 2019-nCoV. *JACC: Heart Failure* 2020 Apr 1. DOI: 10.1016/j.jchf.2020.04.001
15. Kao CH, Hsieh KS, Wang YL, Wang SJ, Yeh SH. The detection of ventricular dysfunction and carditis in children with Kawasaki disease using equilibrium multigated blood pooling ventriculography and ⁹⁹Tcm-HMPAO-labelled WBC heart scans. *Nucl MedCommun*. 1993;14:539–543.