Pathogenesis of COVID-19 and multi-system inflammatory syndrome in children

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ABSTRACT

World health organization declared COVID-19 caused by SARS CoV-2 virus as a pandemic in early 2020. The target cells facilitating viral entry are ACE-2 receptor bearing cells like bronchial epithelial cells and pneumocytes. Children pose a less risk compared to adults in acquiring this disease and mortality in them is low due to protective pathogenesis. Children with COVID-19 are also at risk of developing unique immunological phenomena, known as multi-system inflammatory syndrome in children. MIS-C is considered to be hyperimmune state resulting from cytokine storm and circulating immune complexes. This mini-review reflects the most recent understanding of the pathogenesis in children with special emphasis on MIS-C.

Keywords: COVID-19, SARS CoV-2, Multi-system inflammatory syndrome in children, Pathogenesis, Children

INTRODUCTION

The novel corona virus disease caused by SARS CoV-2 virus was first reported in December 2019 from Wuhan, Hubei province, China.\textsuperscript{1} World health organization (WHO) named the virus 2019 novel coronavirus (2019-nCoV) on 7 January 2020 and 4 days later rechristened the resultant disease as COVID-19. As the virus started spreading rapidly across counties WHO declared a public health emergency of international concern (PHEIC) and later as a pandemic.\textsuperscript{2} The virus responsible for this devastating pandemic was first isolated from bronchoalveolar lavage (BAL) fluid of a patient on 3 January 2020 in Wuhan which was confirmed by center for disease control and prevention of China (CDC China) as the cause of this disease. As per the latest data on 11 October, 2020 WHO reported 37,340,151 confirmed cases and 1,074,500 deaths worldwide with an overall mortality of 3.06%.\textsuperscript{3} India reported 71,18,770 confirmed cases with 1,02, 179 deaths.\textsuperscript{4} Children account for small proportion of total COVID cases ranging from 1.2% in China to 5% in United States.\textsuperscript{5} Approximately 90% of children with COVID-19 were asymptomatic or suffered from mild to moderate disease, 5.2% had severe disease and barely 0.6% manifested with critical illness demanding admission to intensive care unit (ICU). Among children, infants have more severe illness than older children.\textsuperscript{6} SARS CoV-2 predominantly affects adults and children are less affected or show mild symptoms due to differences in pathogenesis. As COVID-19 is a relatively new disease, the data and our understanding about the disease is constantly evolving every day. This mini-review will reflect the most recent evidence on pathogenesis of COVID-19 in children with a special emphasis on multi-system inflammatory syndrome in children (MIS-C).

THE VIRUS

SARS CoV-2 is an enveloped, positive single stranded ribonucleic acid (RNA) virus belonging to \( \beta \)-
Coronavirus family. It is capable of causing respiratory, enteric, neurologic and hepatic diseases.\(^7\) Phylogenetic analysis showed that SARS CoV-2 shares 79.5% sequence identity to SARS coronavirus (SARS CoV) and 50% sequence identity to and MERS coronavirus (MERS-CoV).\(^8\) It is oval or round virus of 60-100 nm diameter with a genomic size of 29.9 kb. The phospholipid bilayer which encloses nucleocapsid is covered by two types of protein. The spike (S) protein is found in all viruses of coronavirus family and gives it “crown” like appearance, which is responsible for its nomenclature. In some viruses of this family is another protein called Haemagglutinin esterase protein. Other proteins known to be part of phospholipid layer includes membrane (M) protein and envelope (E) protein.\(^5\)

HOSTS AND TRANSMISSION

SARS CoV-2 is a zoonotic virus with bat being the primary host. Animal to human transmission is very rare, but can occur if the infective dose is markedly high, known as spillover phenomena.\(^9\) Humans can also be infected via intermediate host like pangolin.\(^10\) Person to person transmission of virus is by respiratory droplets produced while coughing or sneezing, similar to other respiratory viruses. The droplets loaded with virus can spread up to 1-2 meters and can also deposit on surfaces and survive for days in favourable conditions.\(^11\)

PATHOGENESIS

Entry into host cell: the target cells for SARS CoV-2 are nasal and bronchial epithelial cells and pneumocytes. The S protein of virus binds to angiotensin converting enzyme 2 (ACE 2) receptor. Type 2 transmembrane serine proteinase (TMPRSS2) located in target cells facilitates viral entry by cleaving ACE2 and activating viral S protein.\(^12\) ACE-2 is situated on oral, nasal, and oropharyngeal mucosa, alveolar epithelium, endothelium of heart and vessels, small intestine enterocytes and renal tubules.\(^13\) Glucose regulated protein-78 and CD-147 are recently identified receptors of SARS CoV-2 which favour cell entry.\(^14\) Once infection is established, lymphopenia results in reduction of CD4+ and CD8+ T cells. The severity of disease can be predicted by the level of fall in CD8+ T cells.\(^15\) Susceptibility to COVID-19 is associated with HLA-BX4601, HLABX0703, HLA-DR B1X120233 and HLA-CwX0801.\(^16\)

Proliferation inside Host cells and inflammatory response: after viral entry into host cells, rapid viral proliferation results in antibody dependent enhancement leading to aggressive inflammation. The activated inflammatory cells triggers an exaggerated inflammatory response which results in release of excess amounts of cytokines like IL-1b, IFN-α, IFN-γ, TGF-α, IL-6, IL-12, IL-18, IL-33. This cytokine storm results in systemic inflammatory response causing ARDS, shock and multiorgan dysfunction.\(^17\)

As disease progresses, the virus infects pulmonary capillary endothelial cells resulting in disruption of epithelial- endothelial barrier. This ultimately leads to hyaline membrane disease characterised by alveolar wall thickening, pulmonary edema and interstitial mononuclear infiltrate.\(^18\) In severe infection, exuberant coagulation activation and consumption of clotting factors results in diffuse intravascular coagulation.\(^19\) Disseminated microthrombi formation may occur resulting in deep vein thrombosis, pulmonary embolism and arterial thrombotic complications leading to stroke or myocardial infarction.\(^20\)

Pathogenesis of COVID in children: there are multiple factors which play a role in decreasing the severity of COVID-19 in children compared to adults. These include differences in mediators required for viral entry into target cells and immune mediated response in children.\(^21\) ACE 2 receptor and TMPRSS2 expression in respiratory epithelium and type 2 alveolar cells increases with age. Thus their low expression in children protects them from serious pulmonary consequences by restricting the viral entry.\(^22\) Children have robust innate response, but reasonably weak adaptive response. The strong innate response is children in due to repeated exposure to influenza and other viral infections whereas adaptive response is immature as they lack memory cells. Thus, children are incapable of mounting a strong inflammatory response. The presence of other respiratory tract viruses may compete with SARS CoV-2 and may limit its proliferation in children.\(^7\) Decreased Toll-like receptor (TLR) induced response, increase in regulatory T cells in pediatric lungs suppress immune response preventing cytokine storm.\(^23\)

Mice models have shown that imbalance between production of pro and anti-inflammatory cytokines are responsible for COVID-19 manifestations. Neutrophil response markers like MPO and IL-6 which are hallmarks of ARDS are markedly lower in children and neonates compared to adults. Thus, the absolute neutrophil count was observed to be lower in juveniles and hence neutrophil extravasation was limited in young in comparison to adult animals. This could be due to lower expression of adhesion molecules like P- selectin, which is similar to human studies.\(^24\) Lymphocytopenia and increased neutrophil count was reported to be associated with ARDS in SARS CoV-2 infected individuals and incidence of lymphocytopenia in children suffering from COVID-19 was barely 3.5%.\(^25\)

Microvascular maturation and alveologenesis is a continuous process unique for pediatric lung which is absent in adults.\(^26\) Endothelial cell dysfunction and apoptosis leads to break in pulmonary barrier resulting in pulmonary edema. However, in children, increased focal adhesion kinase-1 (FAK-1) expression leads to preservation of this barrier.\(^27\) These factors could contribute to lesser morbidity in children with ARDS.
The differences in the pathogenesis in adults and children are depicted in (Figure 1).

![Pathogenesis of pediatric and adult COVID-19.](image)

**Figure 1: Pathogenesis of pediatric and adult COVID-19.**

**MULTI-SYSTEM INFLAMMATORY SYNDROME IN CHILDREN**

In the initial days of pandemic it was noted that children had milder disease compared to adults, but later in mid-April 2020 a severe inflammatory disease was described which resembled Kawasaki disease (KD) and had temporal association with SARS CoV-2. This novel syndrome in children and adolescents was termed “multi-system inflammatory syndrome in children” (MIS-C). 28 Royal college of pediatrics and child health (RCPCH), center for disease control and prevention (CDC) and WHO definitions of MIS-C include fever, multi-organ (two or more) involvement without alternative plausible diagnoses, laboratory evidence of inflammation, evidence of COVID-19 infection or recent exposure to a COVID-19 case.29-31 These children often present with persistent fever, erythematous rash, conjunctivitis, mucosal involvement, respiratory, gastrointestinal symptoms, and neurocognitive symptoms.32 A proportion of them presented with hypotension and shock due to acute myocardial dysfunction or hyperinflammatory state similar to the pathology of Kawasaki syndrome (KS) and toxic shock syndrome (TSS) respectively.28

Even though KS and MIS-C are two different conditions, diagnostic confusion can occur due to the overlapping findings like mucocutaneous involvement, myocarditis and coronary artery dilation. More than 70% of children with MIS-C were previously healthy and common comorbidities seen in the remaining were obesity and hyper-reactive airway disease.33 Laboratory investigations in children with MIS-C reveal highly elevated inflammatory markers like C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), ferritin and IL-6 indicating a hyper-inflammation state. [34] Leucocytosis, neutrophilia with shift to left, lymphopenia and thrombocytopenia were also detected in many such cases and D-dimer and fibrinogen also showed a significant increase.28 Around 20-53% patients of MIS-C had positive SARS CoV-2 reverse-transcriptase protein chain reaction (RT-PCR), but 75-100% demonstrated IgG antibodies suggesting post infectious immune dysregulation.35

**PATHOGENESIS OF MIS-C**

Pathogenesis of MIS-C is not very clear and many hypothesis have been put forth by experts but none proven till date. Many speculate that it is a delayed immunological phenomenon coupled with inflammation subsequent to asymptomatic or symptomatic COVID-19 infection presenting after one to six weeks subsequent to COVID-19 infection.36,37

In children, early infection (phase I) with SARS CoV-2 is mild or asymptomatic. The pulmonary stage (phase II) in adults is severe but mild or absent in paediatric age group. Early infection activates macrophages followed by T-helper cell stimulation leading to release of cytokines. In addition, B-cells and plasma cells are activated leading to antibody production resulting in a hyper-immune state (phase III). This immune dysregulation results in inflammatory syndrome called MIS-C in affected children.36 This immune dysregulation hypothesis is supported by the fact that majority of children with MIS-C have positive serology and negative PCR testing. The other probable mechanism would be antibody or T-cell recognition of self antigens (molecular mimicry) leading to synthesis of autoantibodies and formation of circulating immune complexes.38 Occurrence of autoantibodies against immune cells, endothelial and gastrointestinal cells have also been reported in MIS-C patients.39 There are also evidences which imply that genes also a play role in MIS-C and some racial groups like Africans have strong association with it.40 It is also hypothesized that neutrophil extracellular traps (NETs) are involved in pathophysiology of MIS-C. Viruses stimulate the formation of NETs whose main function is to entrap virus. This virus induced NETs are known to elicit uncontrolled immunological and inflammatory reactions resulting in hyperinflammatory state. These are increased in plasma of patients with severe COVID-19 and associated with respiratory failure and DIC.41

The exact mechanism of myocardial injury seen in MIS-C is not known. Few postulated hypotheses include injury from systemic inflammatory response, stress cardiomyopathy, acute myocarditis and ischemia due to coronary arteritis.28 The pathogenesis of MIS-C is summarized in (Figure 2). Further studies are needed to...
understand the complete spectrum of pathogenesis in MIS-C.

Figure 2: Pathogenesis of MIS-C in children.

CONCLUSION

Children are less prone to COVID-19 and less mortality compared to adults due to multiple factors including reduced expression of ACE 2 receptor and TMPRSS2 restricting viral entry, relatively weak adaptive and strong innate response, decreased TLR response and high regulatory T cells preventing cytokine storm and ARDS. Immune dysregulation plays a key role in the genesis of MIS-C resulting from exaggerated hyperimmune response. Our understanding about COVID-19 pathogenesis is continuously evolving. It is important for the treating pediatricians to understand the pathogenesis to interpret the symptoms, anticipate progression of disease and contemplate development of therapeutic targets.

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