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Minireview

Clinico-Pathogenesis of COVID-19 in children

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The recent pandemic by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causing Coronavirus disease-2019 (COVID-19) affects mainly adults and to a lesser extent children. The major route of spread is *via* droplets where the virus is released into the air in the form of droplets by an infected individual during coughing and sneezing. The virus primarily infects the respiratory tract epithelium. Its spike protein interacts *via* ACE-2 receptor and facilitates the entry of the virus into the cells by membrane fusion. The activated Cytotoxic T cells and other cells cause an exaggerated inflammatory response releasing huge amounts of pro-inflammatory cytokines like interleukins and interferon. Due to this surge in the cytokine levels leading to a storm like state, there is significant endothelial injury causing hyper-coaguable state and disseminated intravascular coagulation. The common presentation in children include involvement of respiratory system leading to pneumonia, severe pneumonia, acute respiratory distress syndrome and rarely multiorgan involvement.

Keywords: Children, COVID-19, Disseminated Intravascular coagulation (DIC), Hyper-inflammatory State, SARS-CoV-2

Introduction

The worldwide spread of novel Coronavirus disease-19 (COVID-19) has created an unprecedented panic among common people as well as the healthcare workers. As per the latest data on 18 May, 2020 WHO reported worldwide 4628903 confirmed cases and 312009 deaths[1]. On same dates in India a total of 102032 confirmed cases and 3167 deaths had been reported[2]. The spread of this novel virus started as a small outbreak in Wuhan, China in December 2019, which has now evolved as a pandemic affecting individuals of all ages. COVID-19 is caused by a respiratory virus named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which belongs to coronaviruses family (CoV)[3]. It affects individual of all ages, especially adults and elderly, relatively sparing the children. It enters *via* the upper respiratory tract epithelium and causes flu like illness-fever cough, sore throat, difficulty in breathing, headache, myalgia and gastro-intestinal symptoms. Mild symptoms are present in majority of cases, however, it can progress to cause severe pneumonia requiring oxygen and other forms of respiratory support, both invasive and non-invasive support[4]. The disease can progress to cause varied complications like Acute Respiratory Distress Syndrome (ARDS), septic shock, multiorgan dysfunction, myocardial injury and acute kidney injury (AKI)[5]. This virus has similarity with viruses causing Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), whose immune-pathogenesis is known[6]. Because of this peculiar similarity, a possible pathogenesis of SARS-CoV-2 has been explained in various literatures. Various case reports and case series of atypical presentations in children has gained curiosity for in-depth understanding of the pathogenesis in children. There have been meticulous efforts to understand the clinicopathological presentation of this disease in children. This review is aimed at highlighting various different possible pathophysiological aspects in children and the shift of the pathogenesis as new literature is evolving.

Virology

SARS-CoV-2 belongs to the β-coronaviruses (β-CoV) family of enveloped, positive single-stranded Ribo-nucleic acid (RNA) viruses which can cause respiratory, enteric, hepatic, and neurologic diseases[6,7].

These include hundreds of members that infect humans and other animals such as bats, snakes, birds, and other[3]. SARS coronavirus (SARS-CoV) and MERS coronavirus (MERS-CoV) also belongs to β-CoV[6]. Phylogenetic analysis show that SARS-CoV-2 shares 79.5% sequence identity to SARS-CoV and 50% sequence identity to MERS-CoV[8-10].

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SARS-CoV-2 is a round or oval shaped virus with a diameter of 60-100 nm and a genomic size of 29.9 kb. Its nucleocapsid is buried inside phospholipid bilayers and is covered by 2 different types of protein. The Spike protein is present in all the viruses of coronavirus family giving it crown like appearance and hence the name; another Haemaglutinin-esterase protein is present in some members of the family. Other proteins are Membrane protein (M protein) and Envelope protein (E protein)[10]. Human angiotensin converting enzyme-2 (ACE–2) receptors facilitates its entry into the cell by interacting with the spike protein[9,11]. These receptors are present on cells of human organs including lung, kidney, liver, nervous system, and skeletal muscle[12].

Epidemiology: Origin and natural host

SARS-CoV-2 was first isolated from Bronchoalveolar lavage fluid of three COVID-19 infected patients from Wuhan, China[8]. Moreover, these are zoonotic viruses with bats as the primary natural host[13]. The possible origin of this virus was from seafood market in Huanan, China. It has been seen that Pangolin origin CoVs have 99% similarity with SARS-CoV-2[14]. Animal to human transmission of infection is rare, however this transmission can occur if the infective dose is very high, called the spillover phenomena[15].

Mode of transmission and spread

SARS-CoV-2 is transmitted from person to person mainly by respiratory droplets, resembling the spread of influenza and other respiratory viruses, and seldom by contact transmission. The virus is released into the air in the form of tiny droplets by an infected individual during coughing and sneezing. These droplets loaded with virus can spread upto 1-2 meters and can deposit on distant surfaces[16]. The virus can remain viable on surfaces for days in favourable atmospheric conditions, but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide *etc*[17]. A healthy individual can get infected by coming in direct contact with COVID-19 positive individual. Also one can acquire infection if the person touches contaminated surface with hands and then touches his eye, nose or mouth. The incubation period is quite variable with a median incubation period of approximately 4 (2-7) days and range up to approximately 14 days[18,19]. The exact duration of viral shedding is still not known. However, the viral shedding occurs predominantly in first week but may persist for few weeks even in an asymptomatic individual. The SARS-CoV-2 virus has also been isolated from the stool samples and thus subsequent transmission *via* feco-oral route has also been hypothesized, but has not been proven till date. These stool samples detected the viral ribo-nucleic acid (RNA) even after nasopharyngeal reverse-transcriptase polymerase-chain-reaction (RT-PCR) was negative[20].

Clinical presentation and spectrum of illness

It infects predominantly adults and elderly with co-morbidities. Children are less commonly affected by this virus, many reasons have been postulated for the same. Among those with COVID-19, children comprised just 2% of the diagnosed cases in China[21], 1.2% of cases in Italy[22] and 5% cases in the United States[23]. The most common symptoms were cough and pharyngeal erythema in 48.5% and 46.2% cases, respectively. Other symptoms include fever (41.5%), diarrhoea (8.8%), fatigue (7.6%), rhinorrhoea (7.6%) and vomiting (6.4%).In children the median age of presentation was 7 years[24]. Among children infected with COVID-19, almost 90% cases were asymptomatic or had only mild to moderate disease, 5.2% cases had severe illness and only 0.6% presented with critical illness requiring intensive care unit (ICU) admission[25]. The prevalence of severe and critical disease was 10.6% in infants, 7.3% in 1-5 years, 4.2% in 6-10 years,4.1% in 11-15 years and 3% in children of 16-17 years of age[25]. During first 5-7 days, children with hyper-acute course presented with severe hypoxemia and respiratory distress requiring ventilatory support. In the more indolent disease children with moderate hypoxemia and respiratory distress requiring oxygen therapy improved gradually over the week. These patients with indolent course may have acute worsening in the form of clinical deterioration and hyper-inflammation in the second week also known as biphasic illness. Thus the spectrum of illness caused by COVID-19 includes asymptomatic cases to mild upper respiratory illness (URI) like symptoms, severe pneumonia, ARDS, multi-organ involvement, hyper-inflammatory syndromes like Kawasaki Disease (KD), KD shock syndrome, Toxic Shock Syndrome, and Macrophage activation Syndrome[26]. Varied complications like myocardial injury, acute kidney Injury, disseminated intravascular coagulation (DIC) and multiorgan dysfunction syndrome can also be seen[5]. Most of the children infected with COVID-19 recover in 2 weeks and mortality is rare[27].

Pathogenesis

SARS-CoV2 virus primarily infects the epithelium of upper respiratory tract and further replication may occur in lower respiratory tract as well. The spike protein interacts *via* ACE-2 receptor and facilitates the entry of the virus into the cells by membrane fusion. The viral RNA genome is then released into the cytoplasm and is translated into 2 polyproteins and structural proteins, this triggers the viral replication leading to viremia[28]. Other entry mechanisms includes clathrin-dependent and clathrin-independent endocytosis[29]. In high viral load, replication of virus starts in lower respiratory tract especially bronchioles and alveoli causing severe pneumonia[3]. Since many other organs also express ACE-2 receptor, hence symptoms suggesting other organs involvement may also be present[30]. Due to COVID-19 infection, lymphopenia especially decrease in CD4+ and CD8+ T cells have been reported in adults. The level of fall in CD8+ T cells predicts the severity of the illness[31]. However no such findings have been seen in the children. A large case series in children demonstrated only 3.5% children presented with lymphopenia[25]. These viral antigenic peptides are presented by major histocompatibility complex especially MHC-1[32], and then gets recognized by virus-specific cytotoxic T lymphocytes (CTLs). Various HLA polymorphisms have been seen to be associated with susceptibility to SARS-CoV-2 infection such as HLA-B*4601, HLA-B*0703, HLA-DR B1*1202[33] and HLA-Cw*0801[34]. These peptides stimulate virus-specific B and T cells. The SARS-specific IgM antibodies disappear at the end of week 12, while the IgG antibody can last for long time. The SARS-specific IgG antibodies primarily are S-specific and N- specific antibodies[35]. Rapid viral replication induces cellular damage and antibody dependent enhancement (ADE), leading to aggressive inflammation[36]. The activated Cytotoxic T cells and other cells cause an exaggerated inflammatory response releasing huge amounts of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFb, *etc*.) and chemokines by effect or immune cells causing interstitial inflammation, exudates and severe pneumonitis[37]. The pathological T cells also release granulocyte monocyte colony stimulating factor (GM-CSF) that attract circulating CD14+ and CD16+ monocytes that expresses interleukin, IL-6, which is responsible for accelerating inflammatory responses[38]. Although the exact pathogenesis in children is not known, this violent cytokine storm triggers a systemic inflammatory response causing multiorgan involvement, ARDS and shock. Among the studies from critically ill patients with ARDS requiring mechanical ventilation, it has been observed that in spite of managing ARDS adequately there is higher mortality in those with COVID-19[39]. The surprising fact is that these patients with ARDS demonstrate a relatively spared lung compliance and higher alveolar-arterial oxygen gradient as compared to conventional ARDS cases[40,41]. Lung histopathology revealed findings of diffuse pulmonary micro-vascular thrombi which are consistent with these ARDS cases suggesting a vascular occlusive cause of ARDS as compared to a low compliance cause of ARDS. A large autopsy series of COVID-19 infected patients showed pattern of exudative and early proliferative phases of diffuse alveolar damage with diffuse thrombosis of the peripheral small vessels on histopathological examination[42]. The suggested etio-pathogenesis can be cytokine storm leading to significant endothelial injury causing hyper-coaguable profile. A study by Tang *et al*. showed that a procoagulant profile was observed in severe cases of COVID-19 with elevated D-dimer and fibrin degradation products (FDPs) levels. It further demonstrated coagulopathy as a hallmark finding in severe COVID-19 cases with 71.4% of non-survivors having disseminated intravascular coagulation (DIC)[43].

Atypical presentations associated with COVID-19 in children

There are few reports of hyper-inflammatory shock like illness in children which is probably due to cytokine storm. There were eight children who presented with fluid refractory shock requiring inotropes like noradrenaline and milrinone. In these children, the laboratory parameters showed elevated C reactive protein (CRP), erythrocyte sedimentation rate (ESR), elevated procalcitonin and high serum ferritin levels suggestive of a hyper-inflammatory state[44]. Other inflammatory manifestations in children includes Kawasaki disease (KD) like illness (typical or atypical), KD shock syndrome[45] and cutaneous vasculitis chilblain like lesions[46]. There are various reports of KD and toxic shock syndrome (TSS) like illness in children from Italy[47] and New York City[48]. From India one published case report of KD like illness with hyper-inflammatory shock had been

reported. This report highlights the use of Tocilizumab, IL-6 antagonist (under clinical trials) in cases not responding to IVIG[49]. Some of the adult reports suggest an immune based response in the form of Guillian-Barre syndrome (GBS) associated with COVID-19, however no such reports have been identified in children[50].

Why Children have milder illness than Adults?

Children have milder illness as compared to adults with COVID-19. The exact reason for this is not known but a possible explanation can be given owing to the characteristics of the immunity in children. There could be multiple reasons playing a role in decreasing the severity of illness in children. The first possibility is that children may have less viral loads as compared to adults. It is also hypothesised that the epithelial cells may have reduced expression of ACE-2 receptors due to immaturity. It is due to the fact that ACE-2 receptors are fully expressed on well differentiated epithelial cells. The third possibility is that children have a stronger innate response and a relatively weak adaptive response. The strong innate response can be due to the fact that children have exposure to influenza and many other viruses due to recurrent viral infections. The adaptive response is naïve and lacks memory cells like adults, so is unable to mount a vigorous inflammatory response. Fourth possibility could be the simultaneous presence of other viruses which let SARS-CoV-2 virus compete with them and limit its growth.

Conclusion

SARS-CoV-2 is an enveloped RNA virus which belongs to the β-coronaviruses (β-CoV). It has a high affinity to ACE-2 receptors in humans. It is transmitted mainly by droplets and primarily infects the respiratory epithelium. The spectrum of illness caused by COVID-19 ranges from asymptomatic cases, mild to moderate illness, severe pneumonia, ARDS, multi-organ involvement, to hyper-inflammatory syndromes like Kawasaki Disease (KD), KD shock syndrome, Toxic Shock Syndrome, and Macrophage activation Syndrome. Rapid viral replication induces cellular damage and aggressive inflammation which causes release of myriad of cytokines and chemokines. This cytokine storm leads to significant endothelial injury causing hyper-coaguable profile culminating into widespread thrombi formation[44]. Children can also present with Kawasaki Disease (KD) like illness (typical or atypical), KD shock syndrome and cutaneous vasculitis and chilblain like lesions. Pediatric population overall has a milder clinical course as compared to adults.

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