REVIEW ARTICLE

SARS-CoV-2 Infection and ACE-2 Expression in Children: An Overview

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Abstract

SARS-CoV-2 has marked a new era in the medical field with a wide array of signs and symptoms. The clinical manifestations may vary from simple sore throat to severe multiple organ failure causing death in adults. The severity of the disease was relatively mild in children compared to adults but the preliminary evidence reveals high proportions of asymptomatic infection which contributes to a viral transmission. It still remains ambiguous why children are less severely affected than adults. This literature provides a comprehensive review of epidemiology, vulnerability, pathophysiology, organ-specific systemic manifestations of coronavirus disease-2019 (COVID-19), its clinical course similarities and differences between child and adult with a special focus on the reasons behind the reduced disease severity in children.

Keywords: Angiotensin-converting enzyme 2, Clinical manifestations, Coronavirus disease-2019 in children, SARS-CoV-2.

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Introduction

Severe acute respiratory syndrome (SARS) of viral origin (SARS coronavirus) was first reported in 2003 characterized by influenza-like symptoms. This coronavirus was uncertainly emerged from bats, transferred to humans, and burst as an epidemic affecting around 8,100 persons approximately. Appropriate traditional infection control practices brought the global outbreak to an end within a span of 8 months. The SARS has revisited (SARS-CoV-2) as a cluster of idiopathic pneumonia cases in the month of December 2019 in Wuhan, China. World Health Organization (WHO) has declared a novel coronal virus outbreak as Public Health Emergency of International Concern and was named coronavirus disease-2019 (COVID-19). It has rapidly spread globally affecting millions of people and still continues to spread rapidly around the world and became a pandemic.[1]

Epidemiology

A cumulative total of about 59.8 million people have been infected globally of which 1.4 million (3.4%) deaths were reported. India has a cumulative total of over nine million cases, which accounts for 87.5% of all southeast Asian regions (Table 1).[2] Coronavirus disease-2019, a highly infectious disease has been reported in all age groups of children including neonates making up to 1–5% of the total reported cases. Most of the children infected with SARS-CoV-2 presented mild symptoms or are asymptomatic, scarcely developed life-threatening disease.[3] Ogimi et al. observed that young age, especially younger than school age, children with underlying disease and immunosuppression are the only predictors of disease severity in children.[4]

Pathophysiology

SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE-2) receptors present on the biciliated epithelial cells of human lungs. These ACE-2 receptors are also distributed along with the tissues of the gastrointestinal system (ileum), heart, kidney, urinary bladder, etc., and also on cells like dendritic cells, macrophages, vascular endothelial cells, etc.[5,6] (Table 2). After the spike protein of SARS-CoV-2 binds to ACE-2 receptors on the cell surface, the virus enters the cell via proteolytic cleavage through endocytosis involving two proteases, the transmembrane protease serine 2 (TMPRSS2) and cathepsin L (CTSL). After invading, proinflammatory cytokine

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Table 1: Confirmed cases and fatalities in the top 10 affected countries as of February 24, 2021[2]

Country/region/ sovereignty	*Confirmed cases*	*Fatalities*	*Case fatality (%)**
US	28,259,88	502,594	17.7
India	11,016,434	156,463	1.42
Brazil	10,257,875	248,529	2.42
United Kingdom	4,146,756	121,536	2.93
Russia	4,142,126	82,666	1.99
France	3,689,534	85,195	2.31
Spain	3,161,432	68,079	2.15
Italy	2,832,162	96,348	3.40
Turkey	2,655,633	28,213	1.06
Germany	2,405,263	68,785	2.86
Colombia	2,233,589	59,118	2.65

*Crude rates not adjusted for age, sex, existing comorbidities, etc.

Table 2: COVID-19 systemic manifestations

Type	*Mechanism of injury*	*Features*	*Source*
Pulmonary manifestations	• Viral invasion through ACE-2 in type I and II alveolar cells • Proinflammatory cytokine cascade reaction	• Cough • Dyspnea • Hemoptysis • Shortness of breath • Sputum production	• Conti et al. • Li et al.[7] Meta-analysis by • Rodriguez-Morales et al.[8] • Yang et al.[9] • Cao et al.[10]
Gastrointestinal manifestation	ACE-2 in GI epithelial cells	• Nausea • Vomiting • Diarrhea • Abdominal pain	• Wang et al.[11] • Kopel et al.[12] • Chen et al.[13]
Hepatic manifestation	• Virus entry through ACE-2 on hepatic endothelial cells Abnormal high serum levels of cytokines (serum IL-1, IL-6, IL-10, etc.) derange liver chemistries.	Increased serum levels of • Alanine transaminase (ALT) • Aspartate transaminase (AST) • Bilirubin Decreased levels of serum albumin Microvascular steatosis	• Meta-analysis by Lippi and Plebani[14] • Duan et al.[15]
Cardiovascular manifestations	Viral invasion through ACE-2 receptors in myocardial cells Cytokine storm can lead to Stress-induced cardiomyopathy Hypoxemia can elevate calcium ion influx further leads to cardiac myocyte apoptosis	• Cardiac arrhythmias • Ventricular tachycardia/ventricular fibrillation • Fulminating myocarditis • Pericarditis • Acute coronary syndrome • Heart failure • Cardiogenic shock • Cardiac arrest Elevated levels of cardiac markers like troponins	Li et al.[16] Zhou et al.[17]
Renal manifestations	• ACE-2 receptors are highly expressed in proximal tubules and urothelial cells of the bladder • Hypovolemia, rhabdomyolysis, hypoxemia, sepsis, septic shock in critically ill patients • Cytokine storm cause multiorgan failure	Acute kidney failure	• Zhou et al.[17] • Yang et al.[18] • Meta-analysis by Wang et al.[13]
Central nervous system manifestations	ACE-2 receptors on dendritic cells	• Headache • Confusion • Reduced levels of consciousness • Dizziness • Encephalopathy, meningitis • Agitation • Seizure • Cerebral venous sinus thrombosis/cerebral hemorrhage • Cerebrovascular Disease	Mao et al.[19] Poyiadji et al.[20] Wang et al.[11]

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Type	*Mechanism of injury*	*Features*	*Source*
Peripheral nervous system manifestations	ACE-2 receptors on dendritic cells	• Hypogeusia	Mao et al.[19]
		• Hyposmia, polyneuropathy	Cui et al.[21]
		• Neuralgia	Villalba et al.[22]
Hematological manifestations	ACE-2 receptors on vascular endothelial cells	• Petechiae	Xu et al.[23]
		• Systemic vasculitis (Kawasaki)	
Ocular manifestations	Neurotropic and mucotropic effects	• Chemosis	Qing et al.[24]
		• Epiphora	Ma et al.[25]
		• Conjunctival congestion	
		• Conjunctivitis	
Cutaneous manifestations	Neurotropic and mucotropic effects	• Erythematous rash	Recalcati[26]
		• Vesicular lesions	Tang et al.[27]
		• Urticaria most commonly on the trunk, which resolved within few days	
Oral manifestations	Neurotropic and mucotropic effects	• Sore throat	Xu et al.[28]
		• Unspecific oral ulcerations petechiae	Lovato et al.[29]
		• Geographic tongue	Sabino-Silva et al.[30]
		• Dysgeusia	Dziedzic and Wojtyczka[31]
		• Gingivitis	Yuen et al.[32]
		• Opportunistic infections like	Amorim Dos Santos et al.[33]
		• Candidiasis	
		• Oral thrush	
		• Recurrent oral herpes simplex virus (HSV-1) infection, etc.	

cascade is initiated with increased levels of IL-1β, IL-6, TNF, etc., resulting in a cytokine storm.[7,34] The incubation period observed has been ranged between 2 days and 14 days.[5]

Viral mRNA replicates and produces new viral particles contributing to the viral load and secreted in tears, saliva, feces, etc.[35] Real-time polymerase chain reaction (RT-PCR)/viral genome sequencing to detect 2019-nCoV nucleic acid is the main method of laboratory diagnosis.[36] This can be tested using nasopharyngeal swabs, throat swabs, sputum, stool, or blood samples. Real-time polymerase chain reaction has revealed that there is no significant difference in the viral loads between young children and adults. Even a considerable percentage of pre- or mild-symptomatic carry viral loads likely to represent infectivity.[37] False-negative results were frequently reported with a nucleic acid test in children.[38]

Transmissibility

In dentistry, salivary spatters or respiratory droplets infected with the virus can transmit the disease when they come in contact with conjunctival, nasal, or oral mucosa.[39] Salivary glands in COVID-19 patients are the potential reservoir even in asymptomatic patients and hence infected saliva could be the source of infectivity.[40] It can also occur through contaminated fomites as SARS-CoV-2 can reside on the surfaces for 72 hours.[41] Xu et al. observed long-lasting viral shedding in the fecal matter even after nasopharyngeal testing was negative, thus increasing the chances for feco-oral transmission.[42] Coronavirus disease-2019 is a highly infectious disease, but the role of children in its transmission is still unclear. Children were more likely to be infected from a household contact with COVID-19 adult patients.

Systemic Manifestations

The clinical manifestations are primarily related to the pulmonary system and its impact extends far beyond the respiratory system to other parts of the human body (Table 2). The symptoms of COVID-19 are almost similar in children and adults, but the frequency of symptoms varies. Although the clinical findings in children are diverse, the most commonly reported symptoms are fever, cough, rhinitis, myalgia, sore throat, and headache and less commonly vomiting, abdominal pain, diarrhea, and febrile seizures.[43] The recovery period was noticed within 1–2 weeks after the onset of the disease.[44]

Dong et al.[3] in their retrospective study observed that the clinical manifestations of COVID-19 infection in children were less severe than adults. However young children, especially infants are more vulnerable to COVID-19 infections.[4] The clinical severities were stratified based on symptoms, laboratory abnormalities, chest imaging, and RT-PCR/genomic analysis in Table 3.

Laboratory findings display mostly normal leukocyte counts but few cases reported with lymphopenia and neutrophilia/neutropenia. Thrombocytopenia may occur. Inflammatory markers like IL-6, C-reactive protein (CRP), and procalcitonin were found elevated in adults,[45] but it is uncommon in children suggestive of the reduced inflammatory response to infection.[42] Elevated levels of liver enzymes, lactate dehydrogenase, muscle enzymes, myoglobin, D-dimer, and abnormal coagulation might be seen in severe cases.[36]

Multisystemic Inflammatory Syndrome

Few children were reported with a multisystemic inflammatory condition similar to Kawasaki–a systemic vasculitis disease. It usually

Table 3: COVID-19 staging of clinical severity in children

Clinical severity according to Dong et al.[3]	*Proportion*	*Signs and symptoms*
Asymptomatic	4.4%	• No clinical signs and symptoms, normal chest imaging.
Mild	51%	• Fever, cough, sore throat, runny nose, sneezing, fatigue, and myalgia. • Digestive symptoms, such as nausea, vomiting, abdominal pain, and diarrhea. • Physical examination reveals congestion of the pharynx. • No auscultatory abnormalities.
Moderate	38.7%	• Pneumonia, frequent fever, and cough (mostly dry cough, followed by productive cough). • Wheezing, but no obvious hypoxemia (shortness of breath), snoring. • Chest computed tomography shows subclinical lung lesions. (milder form of ground-glass opacities).
Severe	5.3%	• Fever, cough, diarrhea, dyspnea, central cyanosis, oxygen saturation <92%, hypoxia.
Critical	0.6%	• Acute respiratory distress syndrome, respiratory failure, shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, or acute kidney injury.

manifests itself 3–4 weeks after the child recovers from SARS-CoV-2 infection associated with elevated inflammatory markers.[23]

Neurotropic and Mucotropic Effects of SARS-CoV-2

Cutaneous Manifestations

Exanthematous eruptions potentially related to SARS-CoV-2 infection are heterogeneous, widely distributed, and were primarily located on the trunk. They were detected during the prodromal or subclinical phase and mainly appeared as erythematous, urticarial,[46] chickenpox-like/varicelliform-like vesicular lesions,[47] petechiae rash, and also reactivation of herpes simplex virus 1 lesions were noticed. Vesicular lesions and peculiar (perniosis-like) skin lesions are few reported critical lesions. The latency period from systematic symptoms to exanthema has been ranged from 2 to 21 days.[27,48]

Ocular Manifestations

Ma et al.[25] observed increased conjunctival discharge (55.1%), yellow-green purulent discharge (22.4%), white mucoid (18.4%), or thin watery eyes (14.3%), and with conjunctival congestion (10.2%). Other ocular manifestation includes eye rubbing (38.8%), ocular pain (8.2%), eyelid swelling (8.2%), tearing (4.1%), and allergic conjunctivitis (4.1%). Eye rubbing and conjunctival discharge were observed in children of all age groups, whereas tearing was only reported in children aged 1–5 years, and eyelid swelling was only recorded in children aged 10–16 years.[25] It is entirely conceivable that cough can lead to ocular infection through unavoidable hand-eye contact in children.

Oral Manifestations

Angiotensin-converting enzyme 2 receptors are also distributed in the oral tissues like the tongue, oral mucosa, salivary glands, etc.[6,28] The susceptible tissues with these receptors can host SARS-CoV-2 virus can potentially affect the salivary gland function, olfactory disorders, taste disorders, and oral mucosal integrity due to certain neurotropic and mucotropic effects.[29,30] The oral manifestations most commonly reported in adults include unspecific oral ulcerations, petechiae, geographic tongue, dysgeusia, gingivitis, etc.[31] Acute COVID-19 infection with associated co-morbidities or intensive therapeutic measures might increase the susceptibility to various opportunistic infections like candidiasis, oral thrush, recurrent oral herpes simplex virus (HSV-1) infection, and fixed drug eruptions.[30–32] Deterioration of systemic health with the impaired immune system may result in secondary lesions.[33] There still exists a paucity of information regarding the oral manifestations in COVID-19 positive children. But, it is always suggestive to be cautious during oral health examinations.

Reasons behind Milder Course of COVID-19 in Children

From the physiological point of view, COVID-19 in children have milder clinical course compared to adults could be due to the following reasons[49–55]

- The presence of more protecting cilia prevents the virus entry into the respiratory system.[35,49]
- Children have a weaker ability to trigger an acute inflammatory response to SARS-CoV-2. In contrast to adults, the coronavirus that infects children with common cold down-regulates the expression of ACE-2 receptors further reducing the expression of associate inflammatory modules. Hence, there is a reduced chance for initiation of "cytokine storm".[50,51]
- In India, exposure to various vaccines as part of Universal immunization program [like Bacille Calmette-Guerin (BCG), influenza vaccine, etc.] may modulate the course of COVID-19 in children with protective immune response.[52]
- Less exposure to pollutants and lack of comorbidities that compromise lung function.[53] These specific features can underestimate the rate of COVID-19 infected children.
- Expression of ACE-2 and TMPRSS2 is relatively low in children compared to adults, but the maturation of receptors may vary with age.[54,55]
- Viral interference: Children frequently exposed to more than one viral agents, thus adaptive immune response in children initiate an intriguing protective mechanism to lower respiratory tract infections.[55]
- Human T helper cells provide a protective benefit to children against COVID-19 via Th2 immune response. Th2 associated

with allergic diseases in children dramatically reduced ACE-2 expression in the respiratory tract. Th2 cytokines drive also increases eosinophilic count which presents an unknown protective mechanism against SARS-CoV-2 infection.[55]

- Children have lower risk levels for developing acute respiratory distress syndrome due to decreased production of thrombin and fibrin.[50]

From the epidemiological perspective, the reason for the low prevalence rate in children could be due to under-sampling, under-reporting of the disease, and also, not attending to schools could be a confounding factor.[3]

Conclusion

Globally, SARS-CoV-2 infection presented a milder course of disease in children to date. The disease severity in children differs from that of adults and the reasons behind it may be differential defense mechanism with trained immune response in children, low density of ACE-2 which provide a portal of entry for SARS-CoV-2, viral interference, and competition limiting the growth of SARS-CoV-2 and their limited ability to produce inflammatory cytokines. Even though children tend to have COVID-19 in milder/asymptomatic form, they have been found to harbor high levels of the virus and become silent carriers of the virus through nasopharyngeal secretions and even feces. Considering the risk of contagion, proper monitoring, early detection, and intervention, emphasis on infection control measures for infected children to reduce transmissibility and subsequently mitigate the pandemic.

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