Review article

Exploring the causes of mild COVID-19 involvement in pediatric patients

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Abstract

In December 2019, emergence of a novel coronavirus, which rapidly turned into a pandemic, posed a public health threat of global concern that has had a huge impact on the health of millions of people around the world. Existing evidence indicates relatively low incidence and mild severity of COVID-19 in children as compared to adults. Although the precise underlying reasons for such disparity remain obscure. The article provides general information about the COVID-19 and epidemiological data of the disease in children and their clinical manifestations and multisystem inflammatory syndrome in children (MIS-C). The main aim of this article is to exploring the reasons given for the mildness of the disease in pediatric patients. Several theories related to immunosenescence, vaccination and trained immunity, coinfection, ACE-2 maturation and expression, viral exposure, overall health and smoking have been proposed so far in recent literature. However, due to the newfound of this virus and lack of information about it, these reasons are not conclusive, but these points are considered as possible reasons for the low prevalence and mildness of the disease in pediatric patients.
**Keywords:** COVID-19; SARS-CoV-2; Pediatric; Children; ACE2; Immunosenescence; Smoking; Vaccination

**Highlights**

- The rapid global spread of COVID-19 has become a major health issue world-wide while children show milder severity and lower incidence than adults.
- Another concern regarding the epidemic of the SARS-CoV-2 around the world in relation to children is the association between the COVID-19 and multisystem inflammatory syndrome in children (MIS-C).
- Alterations in immune system with aging may contribute to such difference.
- Angiotensin-converting enzyme-2 (ACE-2) is a cell receptor for the virus and the factors that cause this receptor to differ between children and adults can be among the underlying factors.
- Trained immunity can be another casual element of milder symptoms in pediatric COVID-19.
- Vaccine-induced enhancement of the immune system may moderate symptoms in children.
1. Introduction

In late 2019 in Wuhan, China, detection of a novel beta-coronavirus, which was subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in pneumonia patients of unknown etiology, initiated the greatest public health issue over the recent years. According to the latest classification of The International Committee on Taxonomy of Viruses (ICTV), Thirty-eight specific species of coronavirus have been classified into four genera by the ICTV (alpha, beta, gamma, delta), of which the SARS-CoV-2 is in the beta genera(1). The coronavirus disease 2019 (COVID-19) spread rapidly to other parts of China and throughout the world which put the global community in a state of emergency and was ultimately declared a pandemic by the World Health Organization (WHO) (2, 3). In the early reports on COVID-19, children were rarely involved and showed a milder disease and a better prognosis than adults. In the first report of 27 patients which was subsequently revised to 41(4) and two following studies in January 2020, concerning patients under 18 (41 cases)(5) and under 21 (99 cases)(6), no pediatric or adolescent cases were revealed (7). Despite the absence of children in the initial studies in Wuhan, China, the current widespread outbreak of the virus has led to more accurate data on the epidemiology of the disease. The first pediatric case was reported on January 20, 2020 in Shenzhen, China (8).
According to preliminary studies conducted by the Chinese Center for Disease Control and Prevention until February 11, 2020, out of 72314 people mentioned in this report, 1% were in the age range of 9 years or younger, 1% were aged 10 to 19 years (9). In one of the greatest statistical studies conducted by Chinese novel Coronavirus Pneumonia Emergency Response Epidemiology Team, out of 44,762 confirmed cases, 2% were children under 19 and 0.9% were under the age of 10 at diagnosis. In this study, only one death was reported which was between ages 10 and 19 (10, 11). Also, children-specific surveys have exhibited mild outcomes. In one of the major review studies performed in China, out of 2143 children aged 0-18, 112 (5.6%) were in severe status, 13 (0.6%) advanced to acute respiratory distress syndrome (ARDS) and up to one third of the children with positive RT-PCR (reverse transcription polymerase chain reaction) test results, developed no symptoms. In this regard fever and cough have also been the most common symptoms among pediatric patients (12, 13). Exploring the underlying mechanisms for this varying distribution of COVID-19 clinical manifestations in different age groups, as will be elaborated in this article, may expand the existing knowledge of the pathogenesis of the disease, offer potential treatment targets and open a window into the pandemic control.
2. Clinical manifestations

As suggested by the above data, children are normally asymptomatic or mild, presented with fever, cough and fatigue, which can be accompanied by a few symptoms of upper respiratory tract infection, such as nasal congestion, rhinorrhea and sputum production(2).

Some pediatric patients may experience gastrointestinal symptoms, including abdominal pain, diarrhea, nausea and vomiting. Septic shock, metabolic acidosis, coagulation dysfunction and specifically acute respiratory distress syndrome (ARDS) as the leading cause of death, may occur at severe stages (14, 15). Severe cases of COVID-19 infection in pediatric patients have symptoms such as: dyspnea, central cyanosis and an oxygen saturation of less than 92% (16, 17).

The uncommon severe cases of pediatric COVID-19 are mainly observed in children with comorbidities such as developmental disabilities, congenital cardiovascular or respiratory diseases, type I diabetes, cancer, malnutrition and chronic lung diseases (for example asthma) that result in pulmonary function impairments (2, 18).

Another concern regarding the epidemic of the SARS-CoV-2 around the world in relation to children is the association between the COVID-19 and multisystem inflammatory syndrome in children (MIS-C). Recently, patients with COVID-
19 have been observed with syndrome that is very similar to Kawasaki syndrome (KD)(19).

In previously healthy children between the ages of 5 and 19, severe cases associated with COVID-19 were found, many of these cases, which had a positive COVID-19 antibody test, had toxic shock-like syndrome or Kawasaki-like syndrome characteristics. After that the term of Multisystem Inflammatory Syndrome (MIS-C) was given to this condition by the Centers for Disease Control and Prevention (CDC)(20).

Similar cases have been reported around the world and warnings have been issued. MIS-C affects various organs(21). Prolonged fever, skin rash, lymphadenopathy, diarrhea, and elevation of inflammatory biomarkers are the common symptoms between MIS-C and Kawasaki disease (KS)(19).

Also, left ventricular systolic dysfunction and acute heart failure, and less cases with abdominal disorders, are symptoms of MIS-C. One of the most common causes of acquired heart disease in developed countries is Kawasaki syndrome(22). Various factors have been suggested as a trigger of KD but the most important trigger is some infectious agents. Some infectious agents in people with specific genetic predisposition prompt the clinical manifestations of the disease(19, 21).

Unfortunately, the exact cause of Kawasaki Syndrome has not been determined. The lately general idea expressed about this syndrome, which is related to source of it, is that an
immunologic response to an exposure in the respiratory system or gastrointestinal tract or both can lead to KD in children who are susceptible in genetics(23). Systematic inflammation is a result of the immunologic cascade in multiple organs and in medium sized arteries at the moment the syndrome is in acute phase(19, 22).

3. Suggested explanations

There are some particularities in children’s immune system which makes the symptoms of COVID-19 milder(24). Generally, maturation of immune system initiates and improves continuously from the birth, in such a way that the child’s immune system is completely relies on its own function after six months, by waning the maternal antibodies form the blood(25). Milder symptoms of COVID-19 in children could be related to many factors. Innate immune responses as the first line of defense seems to play important role in eradication of viral infections(26). Efficient innate immune responses after virus entry in children are comparable to adults. These responses are mediated by production of type 1 interferons which could block viral replication in early stages of infection. In addition, function of macrophages, neutrophils, natural killer (NK) cells and even, T lymphocytes (γδ) cells were impaired with age advance (27), which can lead to severe manifestations in adult patients. Children are more exposed to respiratory viral infections (e.g. respiratory syncytial virus; RSV) which leads to
trained immunity and therefore, robust immune responses against other viruses (28).

Some theories relate this difference to the general idea that the immune system varies across the lifespan, both in terms of constitution and function, particularly during the phenomenon of immunosenescence, which is defined as the gradual deterioration of the immune function associated with natural aging process (29). A steady decline in the number of naïve T-cells as a result of thymus atrophy, reduction of naïve B-cells, an increase in both memory B and T cells, exhaustion of T-cell repertoire (TCR) which limits the antigenic diversity, and modifications in the expression of costimulatory ligands (for instance CD28) are some changes impairing the adaptive immune responses. The innate arm of immunity is also remodeled with aging. Neutrophils, monocytes, macrophages and dendritic cells suffer from diminished phagocytosis (30). Also, the expression of MHC (major histocompatibility complex)-II is reduced on the surface of macrophages, which result in diminished ability of these cells for inducing T cell activation. Along with these changes, NK cells show a decrease in their cytotoxic ability. In addition, enhanced levels of pro-inflammatory cytokines, like IL-6, Tumor Necrosis Factor-alpha (TNF-α) and Interferon-gamma (IFN-γ), along with a rise in the number of mast cells contribute to inflammation, the major complication of immunosenescence.
which is referred to as an intensified inflammatory condition
with age advancement that seems to be implicated in cytokine
storm and therefore, ARDS.

Inflammation is an integral part of effective immunological
responses, and it is difficult to eradicate an infection without
the help of inflammation. Nevertheless, in the COVID-19, the
virus causes over-production and release of cytokines in some
patients, called as Cytokine storm(31). Cytokine storm could
result from different pathological contexts. For example, in
malignancy, infections, sepsis, ARDS and even though in auto-
inflammatory diseases, maybe we have some forms of cytokine
storms(32). In other words, Cytokine storm is a systemic
inflammatory response initiated by the release of excessive
quantities of pro-inflammatory cytokines, can result in ARDS
and multi-organ failure (33). Thus, the loss in defensive
function and alterations in inflammatory reactions can
cooperatively be possible reasons for higher mortality rates
among the elderly (34). Clinical observations have shown that
in patients with severe conditions, cytokine storm has been
detected(35). One way to successfully control and treat patients
is to control cytokine storm in a timely manner through
immunomodulators and cytokine antagonists(31).

Another causal element of milder symptoms in pediatric
COVID-19 can be trained immunity, a new model in
immunology which emphasizes on shaping of memory in
innate immune cells after antigen challenges. Based on this theory, the use of obligatory vaccines in children could induce particular cellular epigenetic and metabolic modifications which results in more efficient immune responses of innate immune cells when challenges with other pathogens (34, 36). On the other hand, it has been reported that COVID-19 patients show lymphopenia and a decrease in cytotoxic CD8+ T cell counts (37). In addition to cytotoxic T cells, expression of exhaustion markers are upraised on the surface of NK cells (38). Vaccination can modify this induced lymphopenia through stimulating CD4+ helper T helper 1 cells to secrete various cytokines encouraging the maturation of cytotoxic CD8+T cells. (39). Bacillus Calmette–Guérin vaccine (BCG), MMR (Measles, Mumps, and Rubella), PPD (Purified Protein Derivative-tuberculin) and Candida vaccines are used to improve the capacity of the immune system to detect specific viral antigen, as most vaccines act in this way. Although these vaccines are used to prevent and control their own specific diseases, they also provide non-specific immunity to other diseases; one common example is the use of these vaccines in dermatology, they are applied intralesionally to amend verruca wart caused by human papillomavirus (HPV)(39). BCG vaccine that has been used for many years against tuberculosis, especially in most Asian countries where children are vaccinated regularly with BCG(40), also trains innate immunity
to generate immune memory and fortifies the human "frontline"
innate immunity in the long-term vaccination(39). Researches have shown that the BCG vaccine provides non-specific
protection against influenza virus infection in mice, most likely by the induction of trained immunity. Similar to COVID-19,
influenza has been shown to increase ARDS more in adults but much less in children (41). Hence, researchers hope that the BCG vaccine, which could be responsible for milder COVID-19 in children, will also be effective in preventing COVID-19. Pursuant to a study by Miller, A. et al., which looked at the correlation between global Vaccination Policy and mortality and morbidity reduction for COVID-19, countries with long-standing global vaccination policies, such as South Korea and Japan, showed lower mortality rates than countries without a policy of universal BCG vaccination, such as Italy and USA (42). To examine these findings, researchers in Australia are vaccinating more than 4,000 health workers with BCG to find out whether it protects against COVID-19 or reduces symptoms. Similar studies are being conducted in the USA and the Netherlands (43). Contrary to Miller, A. et al., in another analysis by Szigeti et al., there was no significant association between daily rates of COVID-19 case fatality per days of the endemic and the presence of BCG vaccination policy before 1980, the launch of global vaccination program (44). Also, in a study by R. Root-Bernstein in some countries where BCG
vaccination has been carried out since 2010 and even in countries where vaccination has not been carried out, mortality rates vary widely from low to high. However, a variety of factors besides vaccination policy may affect mortality rates (45). More importantly, according to a scientific summary published by the World Health Organization on April 12, 2020, there is no evidence to support the protective effect of the BCG vaccine on COVID-19. Meanwhile, two clinical trials are underway to find out (46). However, the BCG vaccine is not the only vaccine that may have such a positive effect on the COVID-19. The positive effects of other vaccines, such as measles and oral poliovirus vaccine (OPV), may be concluded in the upcoming clinical trials (47). Considering children along with the above-mentioned facts, some positive effects of vaccination in the face of COVID-19 are worth taking into consideration. Gathered data from China states that children older than one year experience less serious symptoms than children under one (48). Since MMR is given after the age of one, it could be an implication of the advantageous effects of vaccination (39). In short, boosting the immune system by vaccination in children 1 to 8 years of age can stimulate their immune system to moderate the clinical manifestations. With all the findings, more evidence is needed to validate the notions.
Additionally, children (younger children in particular) are often predisposed to contracting several viral infections which may reinforce the immune response by raising the circulating antibody levels to a higher point than adults. Besides, competition between concurrent viruses in the respiratory mucous membrane could inhibit SARS-CoV-2 cycle, which is consistent with recent findings demonstrating association of viral load with disease severity. Accordingly, exposure to higher doses of the virus could be a plausible explanation for some medical staff mortalities (11, 48, 49).

Furthermore, some studies have raised controversial speculations regarding angiotensin-converting enzyme-2 (ACE-2), the previously established cell receptor for SARS-CoV, which has been identified to facilitate invasion for SARS-CoV-2 as well, in view of their homologue structures. In theory, The difference in the maturation and function of ACE-2 between children and adults, such as binding ability may explain the pediatric relatively low incidence (48, 50). Moreover, drug-stimulated hyper regulation of ACE-2 in patients with diabetes and hypertension, who have been reported to face greater risk of fatal COVID-19, prompted the idea that elevated levels of this receptor, which could also be a consequence of aging, may increase the chance of infection and contribute to the development of critical illness in adults (49, 51); however, a study on rat lung indicated a substantial decline in ACE-2.
expression with aging (52, 53) and a survey by Chen et al. reflected an age-dependent ACE-2 repression due to inflammaging and reduced sex hormone levels (54, 55), while contrary to preclinical trials, Schouten et al. found no considerable difference in pulmonary ACE-2 across the age spectrum (56, 57). Nonetheless, ACE2 is an anti-inflammatory constituent of the renin–angiotensin system (RAS), a vital regulatory system for homeostatic maintenance which induces inflammation and increases blood pressure via angiotensin II (Ang II). ACE-2, which antagonizes RAS effects by degrading Ang II, is widely distributed in several tissues including lungs, intestines, kidneys and heart where it has a protective effect on these organs against diseases with decreased ACE-2 levels, including hypertension, diabetes, cardiovascular disease, ARDS and probably COVID-19, as it has been observed to down-regulate ACE-2 after cell entry (58, 59). In addition, Chen et al suggested an inverse relationship between ACE-2 expression and COVID-19 severity (54). Similarly, receiving recombinant human ACE2 (rhuACE2) injection alleviated acute lung injury in wild-type and ACE-2 knockout mouse models (55, 60) and Gu et al. issued a protective effect of ACE-2 against RSV-induced lung failure in mice and pediatric patients (52, 61).

Therefore, it could become a potential future treatment for the hypertension, diabetes, cardiovascular disease, ARDS as well as COVID-19. Validation of this therapy which focuses on
protective function of ACE-2 could lead to a contradiction to the previous theory respecting its role merely as a receptor.

Lower chances of exposure to the pathogen, as children spend less time outside, and fewer age-related comorbidities can be other possible explanations for such disparity. Another possibility can be having healthier respiratory tract since they are not exposed to much air pollution and cigarette smoke (CS) as compared to adults (52); although statistics did not indicate a significant correlation with smoking (62). Chronic smoking is frequently accompanied by some comorbidities prone to severe COVID-19 progression (for instance diabetes, emphysema, atherosclerosis and diminished immune function) (63, 64).

Interestingly, a study concluded CS-induced down-regulation of CXCL-10, an essential chemokine for the recruitment of macrophages, neutrophils and natural killer cells, suppressing the innate immune response against viral growth (55, 65). More importantly, Smoking can promote pulmonary and mucosal inflammation, rise in epithelial permeability, mucus hypersecretion, expression of inflammatory cytokines including TNF-α, and hyperplasia of ciliated epithelium which disrupts mucociliary protection, rendering smokers susceptible to viral respiratory infections (55, 63). Additionally, ACE-2 expression has been declared to have a positive association with differentiation degrees of the epithelia, implying that ciliated cells harbor more ACE-2 than the non-ciliated ones; thus,
considering the protective role of ACE-2, destruction of the ciliated cells could be involved in disease severity (55, 66). Furthermore, nicotine has been confirmed to down-regulate ACE-2 (67). Conversely, recent evidence pointed ACE-2 upregulation with cigarette exposure which could put this population at higher risk for SARS-CoV-2 infection, since ACE-2 acts as a binding site for the virus (68, 69). Future research is warranted to address this argument.

4. Conclusion

In conclusion, differences in immune system, degrees of ACE-2 maturation and expression, viral exposure and overall health are some proposed theories which could elucidate the perplexing discrepancy between pediatric and adult COVID-19; nevertheless, further research is required to determine the precise mechanisms. It should be noted that children probably play a key role in the transmission chain for they have been reported to contain copious viral loads and yet remain asymptomatic (49); so, regardless of their apparent resistance, they should be managed with intense care as a part of pandemic control plan. At the end, these reasons presented in the article are not necessarily conclusive, and as mentioned in the text, there are contradictions and different opinions among the researchers in some of these reasons. Therefore, due to the lack of full knowledge of this newfound virus, more research should be done on various aspects of the disease, including the
relationship between age and COVID-19 and the reasons for
the mild and low prevalence of COVID-19 involvement in
children.

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