MINI-REVIEW

Claims and reasons about mild COVID-19 in children

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Abstract

The elderly form the main risk group in the coronavirus disease 2019 (COVID-19) pandemic, and age is recognized as a major risk factor for the severity of infection and mortality of COVID-19. The severity of the infection in children is milder than in adults. Although the pathophysiology of COVID-19 is not fully understood, several possible factors and mechanisms have been suggested for the lower severity of infection in children.
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Introduction

The coronavirus disease 2019 (COVID-19) pandemic is still continuing and millions of infections have been reported [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with its high transmissibility, has put a lot of stress on the world since late 2019, and the effects of this infection on the human population are still being studied [2,3].

Reinfection with SARS-CoV-2 remains to be fully clarified. Children from a broad spectrum of ages can be infected by SARS-CoV-2 but most infected children do not show symptoms of COVID-19, or their disease is less severe than in adults and they recover 1–2 weeks after symptom onset [4,5].

According to CDC data, in the USA children <18 years of age represent 1.7% to 12% of all COVID-19 cases [5,6]. Although serious illness in children with COVID-19 has been reported, their hospitalization rate is also much lower than in adults [5]. Both children and adults are susceptible to COVID-19, but outcomes as well as clinical presentations were more favourable for children [4,7]. According to contact tracing data, children are mostly not the index patients and they become infected with SARS-CoV-2 from adults. Secondary infections from children as the source were also uncommon [4].

Although serious illness in children with COVID-19 has been reported, hospitalization or death is rare [5,8]; however, a small number of deaths have been recorded [9]. Like adults, children with an underlying disease, such as diabetes, obesity, congenital heart disease, genetic conditions or conditions affecting the nervous system or metabolism have higher risk for serious complications of COVID-19 [10,11].

It is now accepted that COVID-19 is less severe in children and infants than in adults. Several hypotheses and possible mechanisms that may cause mild disease in children have been proposed.

Angiotensin-converting enzyme 2

Angiotensin-converting enzyme 2 (ACE-2) is the SARS-CoV-2 receptor. It seems that ACE-2 expression in the respiratory tract of children is less than in that of adults [12]. In addition, in adults, because of underlying problems and the use of some

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drugs such as ACE inhibitors, ACE-2 expression increases, which in turn increases the virus entry into cells [13], although some researchers believe in protective effects of ACE-2 in lung disease [14].

There are two forms of ACE-2: a membrane-bound form and a soluble form. Some researchers believe that soluble ACE-2 is more common in children than adults, and that this form of ACE-2 acts like a neutralizing antibody and neutralizes SARS-CoV-2, in other words, the soluble ACE-2 in children has a protective role [15,16].

Bradykinin and angiotensin-converting enzyme

A group of researchers suggested that a bradykinin storm in individuals with COVID-19 is responsible for many of the clinical symptoms of the disease, and that changes in the renin–angiotensin system in individuals with COVID-19 lead to increased bradykinin levels. Bradykinin is one of the important components in regulating blood pressure and reduces blood pressure with its vasodilatory role. In addition, bradykinin increases vascular permeability and oedema in lung tissue. Increased bradykinin levels in the body cause pain and induce neutrophils to inflammatory tissue. Increased bradykinin has been reported to cause symptoms such as dry cough, an initial decrease in oxygen saturation, and increased vascular permeability [17]. Bradykinin is further degraded and inactivated by ACE. Children have more ACE in the serum than adults, so it can be hypothesized that children break down bradykinin more than adults, so they do not show the adverse effects of elevated bradykinin levels.

Endothelial system

The endothelium and the coagulation system are also different in children compared with adults, which makes children less susceptible to thrombotic complications [18]. Activation of coagulation pathways and formation of microthromboses as a result of endothelial damage due to SARS-CoV-2 infection of endothelial cells, as well as angiogenesis, play an important role in the pathogenesis of SARS-CoV-2 infection.

Endothelial cells maintain vascular health with anticoagulant and anti-inflammatory activities. Endothelial cells have ACE-2, and SARS-CoV-2 enters them. Endothelial cell damage with the entry of SARS-CoV-2 and subsequent inflammation and the creation of a prothrombotic environment is another pathophysiological mechanism of COVID-19. Both the entry of SARS-CoV-2 into the endothelium and the decrease in ACE-2 on endothelial cells, which is followed by an increase in angiotensin 2, increase inflammation and coagulation. Children generally have healthy vascular systems and less endothelial damage. In adults, the endothelium is more vulnerable and the presence of cardiovascular disease exacerbates vascular damage [19].

Respiratory tract

The characteristics of the respiratory tissues of children and adults are also different. In adults, reduction of ciliary movement of cells in the respiratory tract can be an important factor in the rapid access of the virus to the lower respiratory tract, a feature that is not present in the respiratory systems of children. In addition, children's lungs may have a greater capacity for repair after infection [20].

Frequency of underlying diseases

One of the important risk factors for the severity of COVID-19 is underlying diseases, and the prevalence of underlying diseases is higher in adults than in children [21,22].

Vaccines and vaccination

Immune system differences are probably one of the main reasons for the difference in disease severity between children and adults [19]. Some infections and vaccinations can provide extensive protection against other infectious agents through innate immune mechanisms. This process is called trained immunity. Trained immunity is the memory of an innate immune system that acts non-specifically without producing antibodies. Although reversible and short-lived [23], the frequency of childhood vaccinations causes sufficient trained immunity in this period. Vaccines, such as bacillus Calmette–Guérin (BCG) for tuberculosis, can increase the basal level of innate immunity and stimulate resistance to other pathogens like COVID-19 (known as trained innate immunity). As a result, a child's immune system is ready to respond quickly to pathogens [19].

Some live vaccines have non-specific immunomodulatory effects rather than giving protection against their target pathogens. It has also been postulated that this contributes to age-

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related differences in COVID-19 severity [24,25], supported by the fact that children have also generally been vaccinated with BCG and other live-attenuated vaccines more recently and frequently than adults [24,26].

Immune system in children and adults

The presence of natural antibodies is higher in children; they are part of the innate immune system and cause a faster response to infectious agents. Natural antibodies can contain the infection until the acquired immune system is activated and antigen-specific antibodies are produced [27]. Another point is cross-immunity, it is also possible that common cold coronaviruses in children have caused cross-protection against SARS-CoV-2 [15].

Like other organs and systems, the immune system can be affected by aging. According to several studies, aging causes changes in the body's immune factors and may lead to a decrease in the strength of immune responses, a phenomenon called immunosenescence. In addition, inflammation is beneficial if it is short-lived and controlled, but harmful if it is severe and uncontrollable. One possible mechanism of SARS-CoV-2 pathogenesis is the overproduction of inflammatory cytokines called cytokine storms. In children, the production of inflammatory cytokines is lower than in adults, and the amount of pro-inflammatory cytokines increases with age. Cytokine storms are more likely to occur in adults than in children. In general, inflammation increases with age, a phenomenon also known as 'inflame-aging' or 'inflammaging'. The production of interleukin-6 increases with age, and interleukin-6 is the major cytokine in the formation of cytokine storms. Increased production of inflammatory cytokines, especially interleukin-6, in adults compared with children leads to a higher chance of developing a cytokine storm in adults than in children [28]. In addition, the hyperinflammation underlying paediatric inflammatory multisystem syndrome is different to that observed in adults with severe COVID-19, which includes higher levels of interleukin-7 and interleukin-8 and lower levels of effector $CD4^+$ T cells. It has been shown that SARS-CoV-2 infection in children leads to a less robust activation of T cells against virus spike protein [29]. Immunosenescence is promoted by ageing, refers to the gradual deterioration of the immune system by natural ageing [30], and probably contributes to partly reduced SARS-CoV-2 clearance. Inflammaging is another age-related conversion in the immune response of elderly individuals and has been linked to some inflammatory conditions, which can correlate with severe outcome of SARS-CoV-2 infection [31,32]. Interferons play an important role in innate antiviral defence. This third part of the immune system plays a probable role in the age-related severity of COVID-19; increases in autoantibodies against type I interferon through life are correlated with the severe outcome of COVID-19 pneumonia [33,34].

Co-infections in childhood

Children may be co-infected with other viruses, especially human coronaviruses, that could interfere with the replication of a possible SARS-CoV-2 infection. On the other hand, periodic repeated infections with such viruses can enhance the activation of the immune response, ranging from innate immunity to epigenetic changes in trained immunity, resulting in possible clearance of SARS-CoV-2 infection [35,36]. Although some arguments proposed that pre-existing cross-reactive antibodies from recurrent human coronavirus infections might protect children against COVID-19, these data must be interpreted and used with caution. Most people have antibodies for circulating human coronaviruses which originate from childhood [37,38]. However, levels of cross-reactive antibodies and T cells increase with age as a result of re-infection with human coronaviruses over a lifetime. SARS-CoV-2 can bind to these cross-reactive non-neutralizing antibodies, that facilitate the entry of the virion to macrophages and other cells through an antibody-dependent enhancement mechanism and followed by productive replication of virions [39,40]. Children have lower defective neutralizing activity antibody than adults, resulting in less antibody-dependent enhancement of virus infection of cells. This phenomenon may explain the greater susceptibility of adults to severe COVID-19 [21,29].

Child microbiome

Differences in the microbiome and immune microenvironment of oro/nasopharyngeal, lung and gastrointestinal systems may act as an alternative potential player for modulation of COVID-19 outcome in children [41,42].

Host–microbiome systems and their composition with specific interest in the microbial community at various body sites play a basic role in the induction and regulation of systemic or local immune responses and inflammation in mucosal tissues, and of its homeostasis against other microbial pathogens [43,44].

The naso/oropharynx of children is often colonized with communities of viruses and bacteria, more so than adults. The interactions between and competition with invading organism

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might limit the growth and spread of infecting organism such as SARS-CoV-2 [45,46].

Viral load and exposure

As in many other infections, viral load affects the severity of outcome in COVID-19, so lower viral exposure dose may be another factor responsible for the less severe outcome [47–49]. Children may have had lower dose exposure to SARS-CoV-2 in comparison with adults. For SARS-CoV-1 and Middle East respiratory syndrome coronavirus, later generations of virus progeny were reported to have lower virulence compared with the first generation of viruses [50], and children are routinely infected by adults—parents or family members—carrying a second- or third-generation SARS-CoV-2 with probably lower pathogenicity.

Thymus activity

The thymus is a lymphoid organ that degenerates with age. Its activity changes during childhood into adulthood and differences in its activity may affect the severity of COVID-19 in children and adults [51]. Thymus atrophy is one of the aetiologies of immunosenescence in elderly individuals that leads to inflammaging [52]. As the thymus degenerates in the elderly, production of naive T cells and T-cell receptor repertoire diversity decrease, which can lead to weakened immune responses, especially to new infectious agents [51,52].

Sex hormones

Sex hormones have been proposed as one of the possible factors affecting the differences in severity of SARS-CoV-2 infection between male and female individuals. Female sex hormones appear to have a protective effect against COVID-19 by acting on the immune system and in their anti-inflammatory role [16,53].

Although it should be noted that, generally, the level of sex hormones in children is lower than in adults, further research efforts are required to investigate the putative effect and mechanism of sex hormones on disease severity. SARS-CoV-2 entry depends on ACE-2 through employing TMPRSS2 serine protease activity for S protein priming [28,54]. Androgen hormones increase the expression of *TMPRSS2*; given that levels of sex hormones in children are significantly lower than in adults, they may have lower expression of *TMPRSS2* and as a result SARS-CoV-2 entry and replication in children might be limited [54]. In addition, the relationship between sex hormones and the renin–angiotensin system is complex and controversial and sex hormones appear to affect ACE-2 expression [55,56]. Differences in levels of these hormones in children and adults may affect the severity of disease between them.

Conclusion

Although there are several factors responsible for less severe SARS-CoV-2 infection in children, especially age-related differences in immune responses and different endothelial system function or physiology, the exact mechanisms/determinants of COVID-19 outcome in children and adults are still unclear. Many more investigations based on well randomized case–control studies are needed to explain in more detail the less severe outcome of SARS-CoV-2 infection in children.

Conflicts of interest

The authors have no conflicts of interest to declare for this study.

Author contributions

All authors contributed to study design and conceptualization, writing the original draft, review and editing, and discussion.

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