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

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Abstract

In December 2019, the emergence of a novel coronavirus, which rapidly turned into a pandemic that posed a public health threat of global concern and 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 coronavirus disease 2019 (COVID-19) in children compared with adults; although the precise underlying reasons for such disparity remain obscure. The article provides general information about COVID-19 and epidemiological data of the disease in children, its clinical manifestations and multisystem inflammatory syndrome in children. The main aim of this article is to explore the reasons given for the mildness of the disease in pediatric patients. Several theories related to immunosenescence, vaccination and trained immunity, co-infection, angiotensin-converting enzyme-2 maturation and expression, viral exposure, overall health and smoking have been proposed in recent literature. However, due to the novelty of this virus and the lack of information about it, these reasons are not conclusive; however, these points are considered as possible reasons for the low prevalence and mildness of the disease in pediatric patients.

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Introduction

In late 2019 in Wuhan, China, detection of a novel β-coronavirus, which was subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in individuals with pneumonia of unknown aetiology, initiated the greatest public health issue in recent years. According to the latest classification of The International Committee on Taxonomy of Viruses, 38 specific species of coronavirus are classified into four genera (α, β, γ, δ); SARS-CoV-2 is in the β genus [1]. Coronavirus disease 2019 (COVID-19) spread rapidly to other parts of China and throughout the world, placing the global community in a state of emergency and ultimately being declared a pandemic by the 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 [1] and two following studies in January 2020, concerning patients under 18 years (41 cases) [5] and under 21 years (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 20 January 2020 in Shenzhen, China [8]. According to preliminary studies conducted by the Chinese Centre for Disease Control and Prevention until 11 February 2020, out of 72 314 people mentioned in the report, 1% were aged <9 years and 1% were aged 10–19 years [9]. In one of the largest 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 between ages 10 and 19 [10,11]. Child-specific surveys have exhibited mild outcomes. In one of the major review studies performed in China, out of 2143 children aged 0–18 years, 112
Left ventricular systolic dysfunction and acute heart failure, and fewer abdominal disorders, are symptoms of MIS-C. One of the most common causes of acquired heart disease in developed countries is Kawasaki syndrome [21]. Various factors have been suggested as a trigger of Kawasaki syndrome but the most important trigger is some infectious agents. In people with a specific genetic predisposition some infectious agents can prompt the clinical manifestations of the disease [18,20]. Unfortunately, the exact cause of Kawasaki syndrome has not been determined. The current idea is that an immunological response to an exposure in the respiratory system or gastrointestinal tract or both can lead to Kawasaki syndrome in children who are genetically susceptible [22]. Systemic inflammation is a result of the immunological cascade in multiple organs and in medium-sized arteries when the syndrome is in acute phase [18,21].

Suggested explanations

There are some particularities in children’s immune systems that makes the symptoms of COVID-19 milder [23]. Generally, maturation of the immune system starts at birth and continues in such a way that by 6 months of age the child’s immune system is completely reliant on its own function through the waning of maternal antibodies in the blood [24]. Milder symptoms of COVID-19 in children could be related to many factors. Innate immune responses as the first line of defence seem to play an important role in eradication of viral infections [23]. Efficient innate immune responses after virus entry in children are comparable to those in adults. These responses are mediated by the production of type I interferons, which could block viral replication in the early stages of infection. In addition, the function of macrophages, neutrophils, natural killer cells and even T lymphocytes (γδ) becomes impaired with age [25], which can lead to severe manifestations in adult patients. Children are more exposed to respiratory viral infections (e.g. respiratory syncytial virus), which leads to trained immunity and therefore, robust immune responses against other viruses [26].

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 immune function associated with the natural aging process [27]. A steady decline in the number of naive T cells as a result of thymus atrophy, reduction of naive B cells, an increase in both memory B and T cells, exhaustion of T-cell repertoire, which limits the antigenic diversity, and modifications in the expression of co-stimulatory ligands (for instance CD28) are some changes that impair the adaptive
immune responses. The innate arm of the immune system is also remodelled with aging. Neutrophils, monocytes, macrophages and dendritic cells suffer from diminished phagocytosis [28]. Also, the expression of major histocompatibility complex class II is reduced on the surface of macrophages, which results in diminished ability of these cells for inducing T-cell activation. Along with these changes, natural killer cells show a decrease in their cytotoxic ability. In addition, enhanced levels of pro-inflammatory cytokines, like interleukin-6, tumor necrosis factor-α and interferon-γ, along with a rise in the number of mast cells contribute to inflammation, the major complication of immunosenesence, 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 COVID-19, the virus causes over-production and release of cytokines in some patients, the so-called cytokine storm [29]. Cytokine storms can occur in different pathological contexts: malignancy, infections, sepsis, ARDS and even in autoinflammatory diseases [30]. In other words, Cytokine storm is a systemic inflammatory response initiated by the release of excessive quantities of pro-inflammatory cytokines, and can result in ARDS and multi-organ failure [15]. The loss in defensive function and alterations in inflammatory reactions can cooperatively be possible reasons for higher mortality rates among the elderly [31]. Clinical observations have shown that in patients with severe conditions, cytokine storm has been detected [32]. One way to successfully treat patients is to control the cytokine storm in a timely manner through immunomodulators and cytokine antagonists [29].

Another causal element of milder symptoms in pediatric COVID-19 can be trained immunity, a new model in immunology that emphasizes the 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 that result in more efficient immune responses in innate immune cells when challenged with other pathogens [31,33]. On the other hand, it has been reported that individuals with COVID-19 show lymphopenia and a decrease in cytotoxic CD8+ T-cell counts [34]. In addition to cytoxic T cells, the expression of exhaustion markers is raised on the surface of natural killer cells [35]. Vaccination can modify this induced lymphopenia through stimulation of CD4+ T helper type 1 cells to secrete various cytokines, encouraging the maturation of cytotoxic CD8+ T cells [36]. Bacillus Calmette–Guérin vaccine (BCG); Measles, mumps and rubella vaccine; Purified protein derivative-tuberculin and Candida vaccines are used to improve the capacity of the immune system to detect specific viral antigens; 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 amed verruca warts caused by human papillomavirus [36]. The BCG vaccine has been used for many years against tuberculosis, especially in most Asian countries where children are routinely vaccinated with BCG [37]. It also trains innate immunity to generate immune memory and fortifies the human ‘frontline’ innate immunity in the long-term vaccination [36]. Research has shown that the BCG vaccine provides non-specific protection against influenza virus infection in mice, most likely through the induction of trained immunity. Similar to COVID-19, influenza has been shown to increase ARDS much more in adults than in children [38]. 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 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 [39]. To examine these findings, researchers in Australia are vaccinating more than 4000 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 [40]. Contrary to Miller et al., in another analysis by Szügeti 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 the global vaccination programme [41]. In a study by 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 [42]. More importantly, according to a scientific summary published by the WHO on 12 April 2020, there is no evidence to support the protective effect of the BCG vaccine against COVID-19, but two clinical trials are underway [43]. The BCG vaccine is not the only vaccine that may have such a positive effect on COVID-19. The positive effects of other vaccines, such as that for measles and the oral poliovirus vaccine, may be concluded in the upcoming clinical trials [44]. Considering children along with the above-mentioned facts, some positive effects of vaccination in the face of COVID-19 are worth taking into consideration. Data collected from China indicate that children older than 1 year experience
less serious symptoms than children <1 year old [45]. As the measles, mumps, rubella vaccine is given after the age of 1 year, it could be an implication of the advantageous effects of vaccination [36]. In short, boosting the immune system by vaccination in children aged 1–8 years can stimulate their immune system to moderate clinical manifestations. More evidence is needed to validate these ideas.

Additionally, children (younger children in particular) are often predisposed to contracting several viral infections that may reinforce the immune response by raising the circulating antibodies levels to a higher point than in adults. Besides, competition between concurrent viruses in the respiratory mucous membrane could inhibit the SARS-CoV-2 cycle, which is consistent with recent findings demonstrating an 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 [11,45,46].

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 as facilitating invasion for SARS-CoV-2, in view of their homologous structures. In theory, the difference in the maturation and function of ACE-2 between children and adults, such as binding ability, may explain the relatively low pediatric incidence [45,47]. 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 [46,48]. However, a study on rat lung indicated a substantial decline in ACE-2 expression with aging [49,50] and a survey by Chen et al. reported an age-dependent ACE-2 repression due to inflammation and reduced sex hormone levels [51,52]. In contrast to preclinical trials, Schouten et al. found no considerable difference in pulmonary ACE-2 across the age spectrum [53,54]. Nonetheless, ACE2 is an anti-inflammatory constituent of the renin–angiotensin system, a vital regulatory system for homeostatic maintenance that induces inflammation and increases blood pressure via angiotensin II. ACE-2, which antagonizes the effects of the renin–angiotensin system by degrading angiotensin II, is widely distributed in several tissues including lungs, intestines, kidneys and heart. 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 [55,56]. In addition, Chen et al. suggested an inverse relationship between ACE-2 expression and COVID-19 severity [51]. Similarly, receiving recombinant human ACE-2 injection alleviated acute lung injury in wild-type and ACE-2 knockout mouse models [52,57] and Gu et al. described a protective effect of ACE-2 against respiratory syncytial virus-induced lung failure in mice and pediatric patients [49,58]. Therefore, it could become a potential future treatment for hypertension, diabetes, cardiovascular disease and ARDS, as well as COVID-19. Validation of this therapy, which focuses on the 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 co-morbidities can be other possible explanations for such disparity. Another possibility can be having a healthier respiratory tract as they are not exposed to so much air pollution and cigarette smoke as adults [49]; although statistics did not indicate a significant correlation with smoking [59]. Chronic smoking is frequently accompanied by some co-morbidities prone to severe COVID-19 progression (e.g. diabetes, emphysema, atherosclerosis and diminished immune function) [60,61]. Interestingly, a study concluded that cigarette smoke 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 [52,62]. More importantly, smoking can promote pulmonary and mucosal inflammation, a rise in epithelial permeability, mucus hypersecretion, expression of inflammatory cytokines including tumour necrosis factor-α, and hyperplasia of ciliated epithelium which disrupts mucociliary protection, rendering smokers susceptible to viral respiratory infections [52,60]. Additionally, ACE-2 expression has been declared to have a positive association with degrees of epithelial differentiation, implying that ciliated cells harbour more ACE-2 than non-ciliated cells. Considering the protective role of ACE-2, the destruction of ciliated cells could be involved in disease severity [52,63]. Furthermore, nicotine has been confirmed to down-regulate ACE-2 [64]. Conversely, recent evidence pointed to ACE-2 up-regulation with cigarette exposure, which could put this population at higher risk for SARS-CoV-2 infection, because ACE-2 acts as a binding site for the virus [65,66]. Future research is warranted to address this argument.

Conclusion

In conclusion, differences in immune system, degrees of ACE-2 maturation and expression, viral exposure and overall health are some proposed theories that could explain the discrepancy between pediatric and adult COVID-19. 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 [46]; so, regardless of their apparent resistance, they should be managed with intense care as part of the pandemic control plan. The ideas presented in this article are not conclusive and, as mentioned in the text, there are contradictions and different opinions among researchers for some of them. The lack of knowledge of this new virus makes more research on various aspects of the disease imperative, including the relationship between age and COVID-19 and the reasons for the mild and low prevalence of COVID-19 involvement in children.

Transparency declaration

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