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Why do children seem to be more protected against COVID-19? A hypothesis

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**Article Info**

**Keywords:** COVID-19, Infection, Children, Coronavirus

**Abstract**

Today it remains unclear why children seem to be less likely to get infected by COVID-19 or why they appear to be less symptomatic after infections. All individuals, especially children, are exposed to various viruses including human coronavirus (CoVs) that can generally lead to respiratory infections. We hypothesize that recurrent CoVs exposure may induce an effective antiviral B and T-cell-mediated adaptive immune response, which could also be protective against COVID-19. Based on the high-homology between the Spike protein epitopes of taxonomically-related coronaviruses, we theorize that past/recurrent contact with CoVs might shield children also against the circulating COVID-19 through a possible neutralizing antibody response previously CoVs-induced. This would open up possible lines of research for the development of live-attenuated virus vaccines from CoVs. Future research is desirable to confirm or disprove such hypothesis.

**Introduction**

Coronavirus disease 2019 (COVID-19) is caused by a novel strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was first found in Wuhan, China, in December 2019. The virus rapidly spread around the world and was declared a global pandemic by the World Health Organization. As of June 28, 2020, there were 10.2 million confirmed cases of COVID-19 with about 502,000 deaths. Reports from China, US and Italy indicated that COVID-19 causes an illness of various degrees in children and adults, with children being underrepresented in all cases, especially concerning severe and fatal events. Only 4,933 children/adolescents aged 0 to 17 years were found COVID-19 positive in Italy up to 23 June 2020. In fact, just 2.1% of them were hospitalized (0.043% of all hospitalizations) with only 4 death cases\textsuperscript{[1]}. Recent epidemiological studies have also confirmed that children/adolescents are less likely to test positive for SARS-CoV2 than adults\textsuperscript{[2]}. This may be due to a lower incidence of positive subjects in the above said groups as a result of minor exposures to SARS-CoV2\textsuperscript{[2]} because of lockdown restrictions. However, a probable biologic resistance should not be excluded.

Some authors assert that one of the possible reasons for children’s very low susceptibility to SARS-CoV2 might be the result of their lower angiotensin-converting enzyme 2 (ACE2) activities (compared to adults)\textsuperscript{[3]}. Like SARS-CoV and coronavirus NL63, recent evidence indicates that SARS-CoV-2 entrance into cells requires the presence of ACE2 protein\textsuperscript{[4]}. ACE2 receptors are expressed in human airway epithelia and lung parenchyma. ACE2 are more abundant on cells of the lower respiratory tract\textsuperscript{[5]}, which is the typical site of severe COVID-19 disease. In fact, undifferentiated cells expressing little ACE2 were found to be poorly infected with SARS-CoV, while well-differentiated cells expressing more ACE2 were quickly infected\textsuperscript{[6]}. ACE2 is less mature in young children and thus may not function properly as a SARS-CoV-2 receptor\textsuperscript{[3,7]}. In addition, the intracellular response induced by ACE2 in children’s alveolar epithelial cells may be lower than in adults. Consistent with this observation, recent data indicate that children experience more SARS-CoV-2 infections in the upper than the lower respiratory tract\textsuperscript{[8]}. Another possibility may be related to higher numbers of CD4 cells (due to the thymus activity) and to lower numbers of CD8 T lymphocytes in children compared to adults\textsuperscript{[3,9]}. This may be protective because it has been reported that SARS-CoV-2 infection is related to a decrease in CD4 cells in older men when compared with younger men and women’s higher CD4 cell numbers\textsuperscript{[3]}. Actually, T-cells are especially important in clearing viruses from mice infected with SARS-CoV\textsuperscript{[10]}. Nevertheless, it remains unclear why children are less likely to be infected by SARS-CoV-2 or why it is more improbable for them to become symptomatic after infection.
Hypothesis.

We all know that human coronavirus (CoVs) are endemic and cause typical respiratory infections. In childhood, above all, all individuals are exposed to different viruses such as rhinovirus, adenovirus, respiratory syncytial virus, parainfluenza virus and even to coronavirus and that they can all be responsible for similar clinical manifestations of respiratory (and in some cases also gastrointestinal) infections [11-15]. CoVs belong to the Coronavirinae subfamily and include four genera: Alpha-, Beta-, Gamma- and Delta-coronavirus. Alpha- and Beta-CoVs genera (Human CoVs 229E, NL63, HKU1, OC43) are known to be able to infect humans [14] with NL63 using the same receptor angiotensin converting enzyme 2 (ACE2) to enter the cell as in SARS-CoV-2 and SARS-CoV [16]. CoVs (whose diffusion is favored in the school environment) cause respiratory infections in children only during winter [11,12]. In some viral studies comparing adults and children, authors have highlighted that in adult patients (by PCR performed on throat swab in real-time) influenza A virus is the most frequently detected respiratory virus followed by rhinoviruses. On the contrary, respiratory syncytial virus is the most common in children, followed by enteroviruses, influenza A virus, NL63 and OC43 coronaviruses [11,12,13]. A study has shown that among 854,575 human CoV throat swab tests, 2.2% were positive for HCoV-OC43, 1.0% for HCoV-NL63, 0.8% for HCoV-229E, and 0.6% for HCoV-HKU1 [13]. The percentage of positive tests reached its highest point yearly during December-March and involved particularly children and adolescents but no subjects aged over 65 years [13]. 20% of 30 children with positive samples to at least 1 virus were also positive to CoVs [12]. According to another study, CoVs have been detected by throat swab tests in 17% of children [11]. The prevalence of these viruses ranges between 3% and 16% of the general population [8]. As these viral infections recur cyclically every year in the winter months, many children may progressively get infected with CoV, which may probably lead to a specific immunity of a significant number of them against these viruses. In fact, it is estimated that about 70% of the population is infected from CoVs during childhood, with recurring infections throughout life [17]. These continuous CoVs infections may induce an effective antiviral B and T-cell-mediated adaptive immune response for CoVs through a possible neutralizing antibody response (previously CoVs-induced), which could also be protective against COVID-19. Supportive of this hypothesis is that CoVs and SARS-CoV-2 have genetic sequence and structural similarities. The sequence analysis shows that SARS-CoV-2 possesses a typical CoV genome structure which belongs to the beta-coronaviruses cluster. Analysis of the aminoacidic sequence of the spike protein from SARS-CoV-2 revealed some similarities with 36.93%, 38.42% and 37.68% of the homology with the spike protein sequence not only for canine and bovine respiratory CoVs, but also for human enteric CoVs [18]. In addition, the homology analysis of the aminoacidic sequence of nucleocapsid protein (a highly conserved protein involved in the active phase of the viral infection) also shows 38.348% of identity with human enteric CoVs [19]. Instead, the analysis restricted to some epitope sequences of the receptor binding domain (RBD) of SARS-CoV-2 spike protein (S) and nucleocapsid proteins revealed high percentage homology (between 50 and 83%) towards taxonomically related beta-coronaviruses [18]. Furthermore, the spike proteins of HCoV-NL63 and SARS-CoV, taxonomically much closer to SARS-CoV2, bind at the same three sites on ACE2 receptor [20]. Therefore, it is possible that antibodies against CoV protein S may have an immunogenicity also against SARS-CoV2.

Consequences of the hypothesis and discussion

In this view, a previous “contact” with these viruses might provide at least a partial/basal immunization (through the production of neutralizing antibodies) shielding humans also against the circulating SARS-CoV-2. Recently, other authors have agreed with this hypothesis in which a cross-immunity can be induced by seasonal infections by human coronaviruses especially in children [9,21,22]. This may explain their modest involvement both in the number and severity of the infection. We have to consider that neutralizing monoclonal antibodies represent a promising therapeutic strategy against emerging CoV infections. In fact, convalescent plasma therapy, rich in IgG and IgM antibodies, is effective and specific for COVID-19 [23]. Most of these antibodies may neutralize the receptor-binding domain of the spike (S) glycoprotein [23]. CoVs may also induce a possible neutralizing antibody response addressed to different epitopes of the spike protein or probably also to other viral proteins (like nucleocapside protein) which are capable of producing protective immunity also against COVID-19. Recently, a study has found that convalescent serum from patients who survived SARS could neutralize the binding of SARS-CoV-2 to ACE2, thus blocking SARS-CoV-2 uptake into the cells [24]. This suggests that there is distinct possibility of cross immunity, wherein immunity and antibody responses to one virus can have a significant effect also on other viruses.

If such hypothesis is confirmed, CoVs-induced immunity might be also prolonged over the years (through memory T and/or B cells), given that the most affected population is the one over 50–60 years. Adults with CoVs contact, induced by living or working with children, may either be protected against COVID-19 or develop less severe symptoms.

Further research is needed, firstly, to study the presence of similar epitopes among the various viruses (Human CoVs and SARS-CoV-2) and secondly, to confirm their immunogenicity, leading to improve serological diagnostics and develop possible vaccines by using human CoVs against COVID-19. Infectious cDNA clones have already been engineered for the three human CoVs (HCoV-229E, HCoV-OC43, and HCoV-NL63) [18], providing an excellent basis for the rational development of live-attenuated vaccines based on recombinant viruses.

Future research is desirable to confirm or disprove such hypothesis.

Funding sources

The article has no funding sources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110151.

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Medical Hypotheses 143 (2020) 110151