Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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

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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 [1]. Recent epidemiological studies have also confirmed that children/adolescents are less likely to test positive for SARS-CoV2 than adults [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 [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) [3]. Like SARS-CoV and coronavirus NL63, recent evidence indicates that SARS-CoV-2 entrance into cells requires the presence of ACE2 protein [4]. ACE2 receptors are expressed in human airway epithelia and lung parenchyma. ACE2 are more abundant on cells of the lower respiratory tract [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 [6]. ACE2 is less mature in young children and thus may not function properly as a SARS- CoV-2 receptor [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 [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 [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 [3]. Actually, T-cells are especially important in clearing viruses from mice infected with SARS-CoV [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.

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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.

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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

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References

[1] https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino/sorveglianza-integrata-COVID-19_23-giugno-2020.pdf.
[2] Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the icelandic population. N Engl J Med. 2020;382:2302–15.
[3] Zhu L, Lu X, Chen L. Possible causes for decreased susceptibility of children to coronavirus. Pediatr Res. 2020 Apr 8. doi:10.1038/s41390-020-0892-8. [Epub ahead of print].
[4] Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3.
[5] Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203:631–7.
[6] Jia HP, Look DC, Shi L, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. J Virol 2005;79:14614–21.
[7] Fang F, Lu XP. Facing the pandemic of 2019 novel coronavirus infections: the pediatric perspectives. Zhonghu a Er Ke Za Zhi 2020;58:81–5.
[8] Cruz AT, Zeichner SL. COVID-19 in children: initial characterization of the pediatric disease. Pediatrics 2020::e20200834.

[9] Rawat M, Chandrasekharan P, Hicar MD, Lakshminrusimha S. COVID-19 in newborns and infants-low risk of severe disease: silver lining or dark cloud? Am J Perinatol 2020;37:845–9.
[10] Day CW, Baric R, Cai SX, Frieman M, Kumaki Y, Morrey JD, et al. A new mouse-adapted strain of SARS-CoV as a lethal model for evaluating antiviral agents in vitro and in vivo. Virology 2009;395:210–22.
[11] Ploton MC, Sommet J, Koehl B, Gaschignard J, Holvoet L, Mariani-Kurkdjian P, et al. Respiratory pathogens and acute chest syndrome in children with sickle cell disease. Arch Dis Child 2020. https://doi.org/10.1136/archdischild-2019-317315. pii: archdischild-2019-317315.
[12] Arvia R, Corcioli F, Ciccone N, Della Malva N, Azzi A. Detection of 12 respiratory viruses by duplex real time PCR assays in respiratory samples. Mol Cell Probes 2015;29:408–13.
[13] Killerby ME, Biggs HM, Haynes A, Dahl RM, Mustaquim D, Gerber SI, et al. Human coronavirus circulation in the United States 2014–2017. J Clin Virol 2018;101:52–6.
[14] Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol 2020;92:418–23.
[15] Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol 2020;92:424–32.
[16] Hofmann H, Pyrc K, van der Hoek L, Geier M, Berkhout B, Pöhlmann S. Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. Proc Natl Acad Sci U S A 2005;102:7988–93.
[17] Enjuanes L, Zuñiga S, Castaño-Rodriguez C, Gutierrez-Alvarez J, Canton J, Sola I. Molecular basis of coronavirus virulence and vaccine development. Adv Virus Res 2016;96:245–86.
[18] Tilocca B, Soggiu A, Musella V, Britti D, Sanguinetti M, Urbani A, et al. Molecular basis of COVID-19 relationships in different species: a one health perspective. Microbes Infect 2020;22:218–20.
[19] Tilocca B, Soggiu A, Sanguinetti M, Musella V, Britti D, Bonizzi L, et al. Comparative computational analysis of SARS-CoV-2 nucleocapsid protein epitopes in taxonomically related coronaviruses. Microbes Infect 2020;22:188–94.
[20] Li W, Sui J, Huang IC, Kuhn JH, Radoshitzky SR, Marasco WA, et al. The S proteins of human coronavirus NL63 and severe acute respiratory syndrome coronavirus bind overlapping regions of ACE2. Virology 2007;367:367–74.
[21] Devulapalli CS. COVID-19 is milder in children possibly due to cross immunity. Acta Paediatr 2020 Jun 10. https://doi.org/10.1111/apa.15407. 10.1111/apa.15407.
[22] Devulapalli CS. Immune responses to coronaviruses with emphasis in children. Int J Pediatr Neonat Care 2020;6:165.
[23] Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, Xia X, Lv T. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol 2020. https://doi.org/10.1002/jmv.25882.
[24] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80.