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Prior infection with intestinal coronaviruses moderates symptom severity and mortality in patients with COVID-19: A hypothesis and preliminary evidence

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A B S T R A C T

The pandemic of acute respiratory illness caused by the novel betacoronavirus SARS-CoV-2, officially designated COVID-19, has attained the proportions of a global health crisis. Though all nations of the world have been affected by this disease, there have been marked cross-national variations in prevalence, severity and mortality rates. Various explanations, based on demographic, social and climatic factors, have been suggested to account for this variability, but these remain unverified to date. Based on recent research findings suggesting that human enterocytes may serve as a point of entry for SARS-CoV-2, leading to intestinal viral replication, this paper puts forward the hypothesis that prior intestinal infection with coronaviruses, either symptomatic or asymptomatic, may moderate this process and minimize the severity of SARS-CoV-2 infection. This hypothesis is supported by evidence on the gastrointestinal manifestations of SARS-CoV-2 and related infections, on the geographical patterns observed in the variability of COVID-19 mortality, and on the occurrence and geographical distribution of outbreaks of diarrheal disease, as well as asymptomatic infection, with human coronaviruses as verified by direct or serological testing. Preliminary supporting evidence based on national and international health statistics is presented, along with suggestions on more robust methods by which this hypothesis may be tested. If the proposal put forth in this paper can be confirmed either wholly or in part, it would have significant implications in terms of strategies aimed at minimizing the severity of COVID-19 in a clinical setting.

Introduction

From its beginnings as a localized outbreak of respiratory illness in Wuhan, China, the global pandemic of acute respiratory illness caused by the novel β-coronavirus SARS-CoV-2, designated COVID-19, has attained the proportions of a global health crisis [1,2]. To date, 12 million cases and over 550,000 deaths due to this disease have been reported worldwide [3]. Several researchers have observed a high degree of variation in the prevalence and mortality associated with COVID-19, both between widely separated countries [4–6] and within the same continent or country [7–9]. A variety of factors have been hypothesized to be responsible for this variability, including prior exposure to other respiratory coronaviruses [4], demographic variations across or within countries [6,9], cultural factors that may influence disease transmission [6], the enforcement of restrictive measures by local and federal governments and the level of trust of the general public in these measures [5–7] and genetic variants of SARS-CoV-2 itself [10]. However, none of these hypotheses have been tested to date, and the evidence supporting some of them is inconsistent [6,10].

Recent evidence has emerged suggesting that apart from direct lung infection, SARS-CoV-2 may also cause gastrointestinal symptoms. Viral RNA has been detected in fecal samples from infected patients, and there are reports of active replication of SARS-CoV-2 within the rectal mucosa [11,12]. Though the evidence for fecal-oral transmission of SARS-CoV-2 to date has been inconclusive [11,13], it has been proposed that gut-lung interactions, mediated via gut microbiota and immune responses, may significantly influence the clinical outcome of COVID-19 [11]. Building on these observations, as well as the above findings, this paper puts forward the hypothesis of an association between prior intestinal infection with coronaviruses, either symptomatic or asymptomatic, and the spread and severity of COVID-19 during the current pandemic.

The hypothesis

The hypothesis advanced in this paper is that prior intestinal viral infection, and more specifically infection with intestinal coronaviruses – which generally occurs in early childhood – may lead to the development of local immunity and/or alterations in gut microbiota. In turn, this minimizes or inhibits the intestinal replication of SARS-CoV-2, with beneficial effects on the clinical manifestations and outcome of COVID-19. An expanded version of this hypothesis would depend on the possibility of fecal-oral transmission of COVID-19, in which case it could be invoked to account for variations in local disease spread as well. This

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hypothesis does not exclude a role for the other factors enumerated above, such as demographic or social variables or prior infection with respiratory coronaviruses, in influencing the spread and prognosis of this disease; instead, it should be viewed as complementary to them.

Biological plausibility of the hypothesis

The entry of SARS-CoV-2 into host cells is accomplished via certain receptor proteins, most notably angiotensin-converting enzyme 2 (ACE-2) [14,15], but also the transmembrane serine proteases TMPSS2 and TMPSS4 [14,16]. High levels of expression of these proteins have been observed in lower gastrointestinal epithelial cells [17], and infection of mature human enterocytes by SARS-CoV-2, through viral fusion and entry via these receptors, has been demonstrated *in vitro* [16]. Fecal shedding of SARS-CoV-2 RNA has been detected in over 25% of a sample of patients recovering from COVID-19 [18], as has evidence of SARS-CoV-2 replication in a rectal biopsy sample [12]. A significant proportion of patients with COVID-19 experience diarrhea, which has been putatively linked to intestinal inflammation following viral entry into small and large bowel epithelial cells through the aforementioned receptor proteins [19].

Evidence of acute diarrheal disease associated with human coronavirus infection dates back to 1975. [20] Though some researchers have found little evidence of a link between this group of organisms and diarrheal disease [21], others have found evidence of a role for intestinal coronaviruses in causing outbreaks or sporadic cases of childhood diarrhea in India [22], Costa Rica [23] and Africa [24]. Another group from India found evidence of fecal shedding of coronaviruses in 23% of a control group of healthy children, suggesting that asymptomatic infections with such organisms may also be common [25]. Besides these geographical variations, ethnic variations in the presence of antibodies to enteric coronaviruses have been described, with high levels being found in Australian Aboriginal children and low to undetectable levels in children of European origin [26]. It is plausible that such antibodies may cross-react with SARS-CoV-2 to a certain extent, thereby inhibiting viral fusion and replication in the bowel.

Findings explained by this hypothesis

- From the earliest stages of the COVID-19 pandemic, a marked variability has been observed in mortality and case fatality rates, with paradoxically higher rates being reported from European countries such as Italy, France and Spain [5]. This may be explained by the low prevalence of diarrhoeal disease, including enteric coronavirus infections, in children in these countries [27]. Similarly, countries from which cases of sporadic or epidemic diarrhoea associated with coronaviruses have been reported, such as India, Costa Rica, and African countries [22–24], tend towards lower fatality rates despite having lower levels of health infrastructure [3,28].
- The occurrence of diarrhea as a symptom in COVID-19 has been associated with higher rates of multi-organ damage and prolonged hospitalization [29], as well as longer durations of symptoms such as fever and dyspnea [30]. This is consistent with the proposal that a “gut-lung axis interaction”, mediated by intestinal inflammation and immune dysfunction, could lead to such complications [11]. Similarly, abdominal pain, which has been hypothetically linked to gut viral replication, has been associated with a significant increase in the severity of COVID-19 [31]. Additionally, patients with severe illness had a nearly two-fold higher rate of detection of SARS-CoV-2 RNA in fecal samples [30,32], lending support to the contention that intestinal replication of SARS-CoV-2 could significantly contribute to illness severity and progression [16]. Prior immunity acquired via intestinal infection with coronaviruses, even if partial, could potentially reduce intestinal SARS-CoV-2 replication and the resultant inflammation, and thereby improve patient outcomes.
- COVID-19 outcomes have been observed to be relatively favourable in children when compared with adults [33,34]. In regions where intestinal coronavirus infections occur in young children, such infections may confer partial protection against intestinal replication of SARS-CoV-2, thereby leading to more favourable outcomes. In this context, it is perhaps significant to note that antibodies against human coronaviruses, including those implicated in intestinal infection, are more frequently detected in children than in adults [35].

Preliminary supporting evidence from health statistics

As a preliminary test of this hypothesis, two data analyses were carried out using population-level statistics. In the first, information on mortality rates for COVID-19 for the 50 countries reporting the highest number of cases was extracted from the Johns Hopkins Medical University interactive dashboard for COVID-19 [3] on July 1, 2020. The correlation between these parameters and World Health Organization statistics on disability-adjusted life years for diarrheal disease in the total population and in children under five years of age [36] was examined. Significant negative correlations were obtained between DALYs for all diarrheal disease and mortality rates ($\rho = -0.32$, $p = 0.023$) and between DALYs for diarrheal disease in children under 5 and mortality rates (ρ for mortality rate $= -0.41$, $p = 0.003$). It is noteworthy that a stronger relationship was noted in the case of childhood diarrheal disease. In the second analysis, government data on COVID-19 prevalence and mortality across twenty-four states in India [37] was correlated with information on DALYs for diarrheal disease for these states obtained from a multi-centre study [38]. A significant negative correlations was again noted between DALYs for diarrheal disease and COVID-19 mortality rates ($\rho = -0.5$, $p = 0.013$) across states. Though these results are based on estimates of diarrheal disease as a whole rather than on measures of intestinal infection with coronaviruses, they provide indirect support of a link between prior intestinal infections, particularly in childhood, and a reduced impact of COVID-19 at the international and national levels.

Testing and refining the hypothesis

There are numerous means by which the various components of this hypothesis can be tested and refined. First, the possibility of active intestinal replication of SARS-CoV-2 must be confirmed *in vivo*, preferably in prospective samples of confirmed cases, using methods such as tissue biopsies where this is ethically and clinically feasible. Second, the link between intestinal replication of the virus, local inflammation, immune dysfunction and distal effects on other organs, such as the lung and kidney, can be verified by correlating such findings with alterations in markers of immune and inflammatory function, as well as with clinical, radiological and laboratory evidence of end-organ dysfunction. Third, surveillance studies in uninfected patients could be carried out to assess the frequency of symptomatic or asymptomatic intestinal infection with coronaviruses in different geographical relations, as well as the prevalence of antibodies to these viruses in different regions and at specific ages. The results of these studies could then be correlated with measures of regional and cross-national variations in the clinical severity and outcomes of COVID-19, which would include not only mortality but other adverse outcomes such as multiple organ dysfunction or the need for assisted ventilation. Fourth, *in vitro* or animal models could be used to test the effect of prior intestinal infection with coronaviruses on the morbidity and mortality associated with SARS-CoV-2 infection, and to elucidate the molecular mechanisms underlying this phenomenon. Finally, if a significant effect of prior intestinal coronavirus infection can be demonstrated using the above methods, its relative magnitude and its interaction with other factors – such as the demographic and social factors discussed earlier – could be quantified in prospective samples across distinct geographical locations.

Potential objections to the hypothesis

The first and most significant objection to the above hypothesis is the contention that the role of human coronaviruses in causing intestinal infection and diarrheal disease is still undetermined. Some authors have claimed that the "coronavirus-like particles" observed on electron microscopy in human stool samples are not true coronaviruses [39] or are incidental "passengers" which do not cause diarrhea [40]. The first of these points probably reflects methodological limitations in earlier research: more advanced techniques, such as immunofluorescence, have confirmed the presence of coronaviruses in stool samples of patients with gastrointestinal symptoms [41]. The second remains legitimate [42]; however, it does not invalidate the hypothesis proposed, as even asymptomatic or subclinical infections might result in a substantial host immune response.

The second objection that can be raised is that even if coronaviruses cause human gastrointestinal disease, they may be antigenically distinct from respiratory coronaviruses such as SARS-CoV-2, and thus fail to induce any significant level of cross-reactive or cross-protective immunity. While a definitive answer to this objection requires further study of putative human enteric coronaviruses, preliminary evidence suggests that there is some antigenic similarly between enteric and respiratory coronaviruses in humans [41].

Finally, it may be argued that prior exposure to respiratory, rather than intestinal, coronaviruses may be responsible for the existence of partially protective immune responses hypothesized above [4]. Such a possibility certainly needs to be tested, but the two hypotheses are not mutually exclusive, given the evidence that intestinal replication of SARS-CoV-2 appears to influence the severity of COVID-19.

Implications

The implications of the hypothesis proposed above extend far beyond explaining the geographical variations in severity and fatality associated with COVID-19. If the above proposals can be verified even partially, they would confirm the postulated existence of a "gut-lung axis" that influences outcome in severe viral respiratory infections [11], and would lead to a better understanding of the mechanisms through which such an "axis" might operate. Further, this could lead to the development of therapies aimed at minimizing intestinal SARS-CoV-2 replication, or to modulate the immune response to this phenomenon by means of immunomodulatory or probiotic agents [43]. Finally, this model would need to be expanded if evidence of fecal-oral transmission of SARS-CoV-2 can be definitively obtained [13]; in this case, the implications of the hypothesis would extend beyond treatment to preventive strategies, such as the development of oral vaccines based on live or attenuated intestinal coronaviruses. Even if parts of this hypothesis ultimately require revision or rejection, the research required to answer these questions would deepen our understanding of the link between the gut, the immune system, and local and systemic disease in the context of COVID-19 and related respiratory illnesses.

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Declaration of conflict of interest

The author reports no actual or potential conflicts of interest concerning the work presented in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110116.

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