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COVID-19: Can the symptomatic SARS-CoV-2 infection affect the homeostasis of the gut-brain-microbiota axis?

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A B S T R A C T

COVID-19 is associated with acute and lethal pneumonia, causing the severe acute respiratory syndrome (SARS), which is not confined to the respiratory tract, as demonstrated by clinical evidence of the involvement of multiple organs, including the central nervous system (CNS). In this context, we hypothesized that both oligosymptomatic and symptomatic patients present an imbalance in the microbiota-gut (immune system) and nervous system axis, worsening the clinical picture. The brain constantly receives a direct and indirect influence from the intestine, more specifically from the immune system and intestinal microbiota. The presence of SARS-CoV-2 in the intestine and CNS, can contribute to both neurological disorders and gut immune system imbalance, events potentialized by an intestinal microbiota dysbiosis, aggravating the patient's condition and causing more prolonged harmful effects.

Introduction

The novel Coronavirus 2019 (COVID-19) pandemic, which had the first diagnosed case in Wuhan (China), has different clinical manifestations, ranging from asymptomatic to severe or critical conditions [1]. Worldwide data confirms a higher incidence in elderly patients. For these patients, severe cases cause acute and lethal pneumonia, developing the severe acute respiratory syndrome (SARS). This later is not confined to the respiratory tract, as demonstrated by clinical evidence of the involvement of multiple organs [2]. Based on experimental research, *in vitro* studies, laboratory analyses from patient's samples, comparative analyses between the SARS and the Middle East respiratory syndrome (MERS) infection, and computational modeling studies, the course of the disease is still being understood and there are gaps regarding the understanding concerning the evolution, pathogenesis and, mainly, therapeutic strategies [3].

One of these gaps concerns the relationship between SARS-CoV-2 and the nervous system, especially with the brain-gut-microbiota axis. It is now known that a neuro-invasive and neurovirulence profile was demonstrated, in a great number of case reports, in other Coronavirus belonging to the same genetic grouping (*Beta* Coronavirus), such as the SARS-CoV-1 and the MERS-CoV [4–6]. During the SARS pandemic of 2002–2003, patients presented neurological complications and in brain tissue specimens' autopsies, SARS-CoV-1 was detected mainly in the cytoplasm of neurons and associated tissue inflammation [7]. It is probable that brain invasion by SARS-CoV-1 occurs via an olfactory route, and is associated with neuronal death as demonstrated in experimental models using mice transgenic for human ACE2 (Angiotensin-converting enzyme). Unlike SARS-CoV (type 1 and 2), MERS-CoV uses a distinct receptor in the cell surface to get access to cytoplasm, named dipeptidyl peptidase 4 receptor (DPP-4), broadly expressed throughout the body on the epithelia, vascular endothelia, and on the brain [7]. It is important to note that in many patients with MERS-CoV infection, was related to neurological complications were observed, ranging from mild to severe clinical manifestations [8,9]. Since they share genetic, structural, and clinical aspects of the disease, it is likely that many similar mechanisms may apply to SARS-CoV-2. In this respect, an increase in scientific publications suggesting the possibility that the SARS-CoV-2 may affect the central nervous system (CNS) has been observed, with symptoms starting after hospitalization, including headache, disturbed consciousness, and paresthesia as the most frequent of them [10–12]. It is not known by which pathway the virus accesses the CNS, and it is speculated that it is through retrograde transport through the olfactory nerve and blood pathways infecting endothelial cells or leukocytes [5,13].

In addition to the possible direct impacts of the tropism of the virus to the CNS, the homeostatic relationship on the microbiota-intestine and nervous system axis, due to the presence of SARS-CoV-2 in the intestine, can contribute to both neurological disorders and gut immune system imbalance. Since the brain-gut microbiota-immune axis presents bidirectional communication, and microbiota is important for the maintenance of immunological homeostasis and Th17/Treg dynamic balance, which suppress pro-inflammatory responses throughout the body [14], an intestinal dysbiosis induced by SARS-CoV-2 may favor a cerebral CNS vulnerability to different injury-causing agents, including the coronavirus itself.

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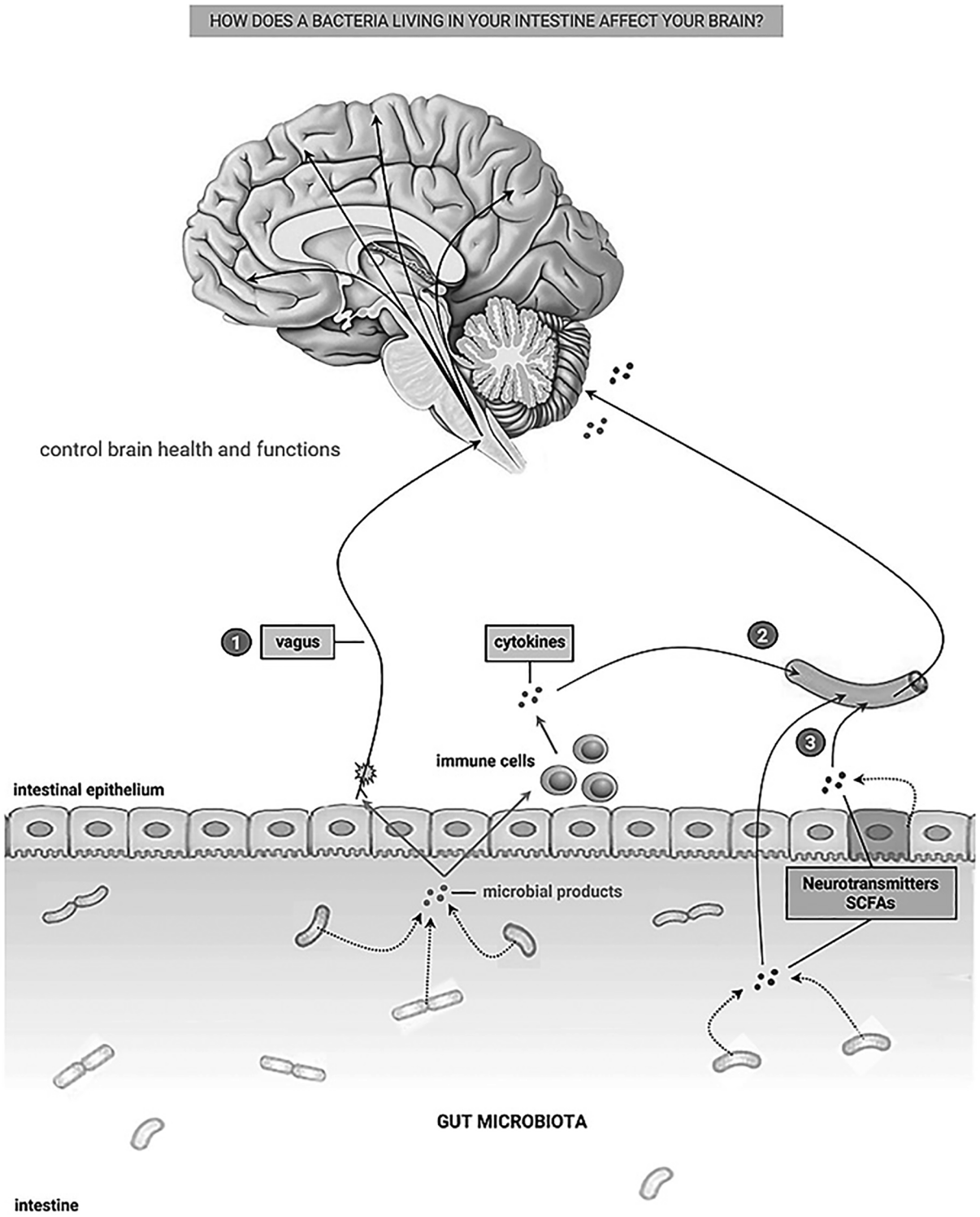

Fig. 1. Communication pathways between the gut - brain. (1) through vagal afferent neurons, (2) through cytokines of the immune system, (3) through microbial products themselves and intestinal epithelial cells. SCFAs (Short-chain fatty acids). Figure is modified from Cryan, JF and Dinan, TG. Nat Rev Neurosci. 2012;13(10):701-712.

Hypothesis

Since SARS-CoV-2 has been observed in feces of patients, adding to the fact that there is evidence of intestinal disorders in 30% of the infected [15], we hypothesize that both oligosymptomatic and symptomatic patients present an imbalance in the microbiota-gut (immune system) and nervous system axis. This results in immediate consequences for symptomatic patients, mainly with regards to the regulation of the inflammatory phase of COVID-19, as well as in oligosymptomatic ones. These changes may have a late repercussion on immunological phenomena, which is crucial to the homeostasis of the body.

Rationale and discussion

Microorganisms in the gut influence immune system function and health brain

Over 95% of the body's entire microbiome (about 100 trillion)

resides in the intestine. In turn, the intestine is the largest human immune organ, in continuous contact with the diversity of bacterial products. This microbiome is crucially fundamental for the maturation and maintenance of immunophysiology. The intestinal microbiota is responsible for aiding digestion, synthesizing vitamins, degrading toxins, and forms the microbiome-gut axis. It provides two-way communication (Fig. 1) through cytokine, immunological, hormonal, and neuronal signals [16–18]. Several studies show that the brain constantly receives a direct and indirect influence from the intestine, more specifically from the intestinal microbiota, which modulates neural functions, regulates its health, and reverses disease processes [19–21]. Bravo and coauthors [19] showed that the administration of *L. rhamnosus* was able to reduce stress and anxiety/depression behaviors in rodents, whereas in vagotomized animals these benefic effects were not observed. Demyelinating diseases could be modulated by the action of anti-inflammatory cytokines produced by regulatory T lymphocytes (Treg) induced by microbial products of *B. fragilis* [20,22]. Antigen-presenting cells (APCs) in Peyer's patches in the intestine, present a distinct phenotype and play a crucial role in the generation of Treg cells, contributing to maintaining the immune tolerance in the intestine, and several studies show the contribution of the gut microbiota and its products in regulating the development of APCs [23]. Currently, there are no studies that establish the relationship between the presence of SARS-CoV-2 and alterations in immune tolerance mediated by local APCs and Treg cells.

In all likelihood, the intestine acts as a secondary site for novel coronavirus tropism and infection through the communication among mucosal tissues. The entrance in the respiratory mucosa and the lack of control in this environment could favor the virus spread to other mucous tissues. However, it is also possible that the intestine represents a primary site of infection through the mouth. The presence of SARS-CoV-2 in the intestinal lumen and its entry into the body through the intestinal epithelial cells which express ACE2 entrance receptor [24,25], may affect the homeostasis of the microbiota-mucosal immune system's relationship, with repercussions to the CNS, once neuroinflammatory and functional consequence after brain injury are affected by the gut microbiota homeostasis [26]. The real impact of SARS-CoV-2 on the gut microbiota with consequent dysbiosis remains to be defined, but it has become evident that COVID-19 patients with gastrointestinal symptoms such as diarrhea, nausea, vomiting, and abdominal pain had more severe disease. Still, some of them presented microbial dysbiosis with decreased levels of *Lactobacillus* and *Bifidobacterium* [27]. After invading the gut, the virus can reach the CNS through the circulatory pathway or the vagal nerve [28]. Neurological consequences may initially be subjective, such as the above-mentioned headache, disturbed consciousness, and paresthesia [10], but there may be more severe symptoms (such as depressed level of consciousness, seizure, and stroke) with the course of infection [29] and the inflammatory process, as glial cells and neurons have been reported to express ACE-2 receptors, which intermediates the entry of the virus into cells.

Another key point is related to immunological phenomena that occurs in the intestine. This contributes to the generation of fundamental regulatory activities for the modulation of local and systemic inflammatory immune responses. It is known that the generation and maintenance of this mucosal immunity are stimulated and maintained by the acquisition of a complex microbiota, with which symbiotic relationships are established [30].

A breakdown of this dynamic relationship results in chronic inflammatory disorders, including autoimmunity, allergies, and metabolic syndromes and compromises the control of exacerbated immune responses in many diseases [30]. It is known that COVID-19 presents a biphasic course, initially viremic and then uncontrolled inflammation. Therefore, we hypothesize that greater severity of pathogenesis is related to an immune dysregulation added to SARS-CoV-2 gut infection. Therefore, a mucosa proinflammatory response instead of an immune regulation, associated with microbial dysbiosis, may affect the CNS.

Conclusion

In conclusion, it is reasonable to consider this worsening of the clinical picture when the new coronavirus reaches the intestine. This may also cause more severe neurological impairment. Furthermore, the control of the inflammatory process will be even more difficult due to changes in the immune regulation in the intestinal mucosa microenvironment. To the best of our knowledge, there is no publication specifically exploring this hypothesis, but there are data and independent results that support this theory.

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.

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