Temporal Correlation Between Neurological and Gastrointestinal Symptoms of SARS-CoV-2

Severe Acute Respiratory Syndrome Coronavirus-2 (SAR-CoV-2) has been shown to invade brain tissue. Based on the evolutionary similarity with SARS-CoV, researchers propose that SARS-CoV-2 can invade the olfactory bulb and gastrointestinal (GI) system through angiotensin-converting enzyme 2. However, how SARS-CoV-2 causes neurological or GI symptoms is not clear. Many suggested intestinal and neural inflammations, caused by viral invasion, as the most likely reason for the GI and neurological symptoms; however, the patients with coronavirus disease 2019 (COVID-19) without neurological or GI symptoms indicate that this is not the case. The gut-brain axis could explain the reason for why some with COVID-19 do not have these symptoms. COVID-19 patients mostly show respiratory distress first, then diarrhea, anorexia, stroke, or loss of consciousness comes into view. Obviously, GI invasion is a mechanical process that begins with oral invasion and, therefore, most probably exists before the brain invasion, as indicated in case reports. However, when the GI tract is invaded, the virus may enter the central nervous system through vascular and lymphatic systems or the vagal nerve. SARS-CoV-2 can infect leukocytes and migrate with them into the brain, or the viral particles can be directly transported across the blood-brain barrier to the brain. Also, more recent research has revealed that SARS-CoV-2 can invade the peripheral lymphatic vessels connecting with the glymphatic system of the brain. The temporal correlation between neurological and gastrointestinal symptoms suggests the lymph vessels around the GI tract, the vascular system, or the gut-brain axis (enteric nervous system) as the most likely entry route for SARS-CoV-2 to the brain.

Key Words: SARS-CoV-2, COVID-19, gut-brain axis, gastrointestinal symptoms, neurological symptoms, anorexia

To the Editors,

With the improvement of scientific methodology, the reductionistic approach ignoring the communication between metabolic systems has lost its appeal, and the functionality (evolutionary) approach marking cofunctioning of metabolic systems in the body has become of age. In line with this routine, herein I discuss gastrointestinal (GI) and neurological symptoms together and highlight the important temporal correlation between them to explain why some patients with COVID-19 have neurologic and GI symptoms and others do not.

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has infected more than 3.19 million people across the globe, and the outbreak of coronavirus infectious disease 2019 (COVID-19) has been the death of 228,000 patients. Unexpectedly, the catastrophic atmosphere of this pandemic increased scientific productivity. Many researchers proposed brilliant views explaining the underlying events of GI symptoms such as nausea, anorexia, vomiting, and diarrhea.[1] However, there is no consensus about the incidence of GI symptoms. Even though early studies reported a low incidence (1%–3.8%), more recent studies suggested a higher rate (11.4%–24.2%). Recently, it has been revealed that with endoscopy, SARS-CoV-2 is present throughout the GI tract.[2] Accumulating evidence posits that GI symptoms are common in COVID-19 infection, and interestingly, even if half of the COVID-19 patients with GI symptoms have the detectable fecal virus, the presence of SARS-CoV-2 in the stool does not correlate with the GI symptoms. Therefore, the diagnostic value of GI symptoms or fecal detection of the virus is still a debated topic. The longer-term studies documenting the GI symptoms will address the precedent about diagnostic and prognostic values of these symptoms for COVID-19.

Almost nothing is known with certainty about how SARS-CoV-2 causes neurological or GI symptoms. Correspondences suggest the intestinal inflammation caused by the invasion of angiotensin-converting enzyme 2 (ACE2) with SARS-CoV-2 as the most likely reason for the GI symptoms, but this is not consistent with the finding that patients with SARS-CoV-2 in their stool do not show abdominal symptoms. Therefore, to shed light on SARS-CoV-2 roles in causing GI symptoms, we should discuss the symptoms with a systemic view. According to the latest information, COVID-19 patients mostly show respiratory distress first; then a second stage of symptoms such as diarrhea, anorexia, stroke, and loss of consciousness comes into view. Apparently, these GI and neurological symptoms show a temporal correlation. Anorexia and nausea may originate from infection of the GI tract or the lateral hypothalamic nuclei.[2, 3] This could explain why SARS-CoV-2 does not cause GI symptoms in some patients who have SARS-CoV-2 in their stool. The neurological symptom incidence rate in COVID-19 patients is 36%,[3] which is as common as the rate of GI symptoms. Perhaps, neurological and GI infections trigger together some of the GI symptoms such as diarrhea, anorexia, and vomiting.

The initiator factor underlying this gut-brain response is most likely viral inflammation in the GI tract.[4] Human gut flora harbor approximately 10^3 to 10^4 microorganisms. A shift in the most abundant genera of gut flora may trigger some pathologies such as inflammatory bowel disease and

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neurodegenerative diseases. More recently, Effenberger et al[4] found a relation between intestinal inflammation (determined by fecal calprotectin) and the occurrence of fecal SARS-CoV-2 RNA in hospitalized patients with COVID-19. Proinflammatory mediators in the GI tract can reach up to the brain via the vascular or lymphatic system. Also, it has been indicated that virus-welded intestinal inflammation can affect cognitive functions through the vagal nerve (Fig. 1). Together, I suggest that the connection between gut and brain can explain the temporal correlation between these two systems' symptoms, and viral infection of lateral hypothalamic nuclei, which has neural and hormonal links with the GI tract,[5] could be the reason that some patients with COVID-19 in their stool do not have GI symptoms. Also, the gut-brain axis could provide an alternative entry route for SARS-CoV-2 to the brain.

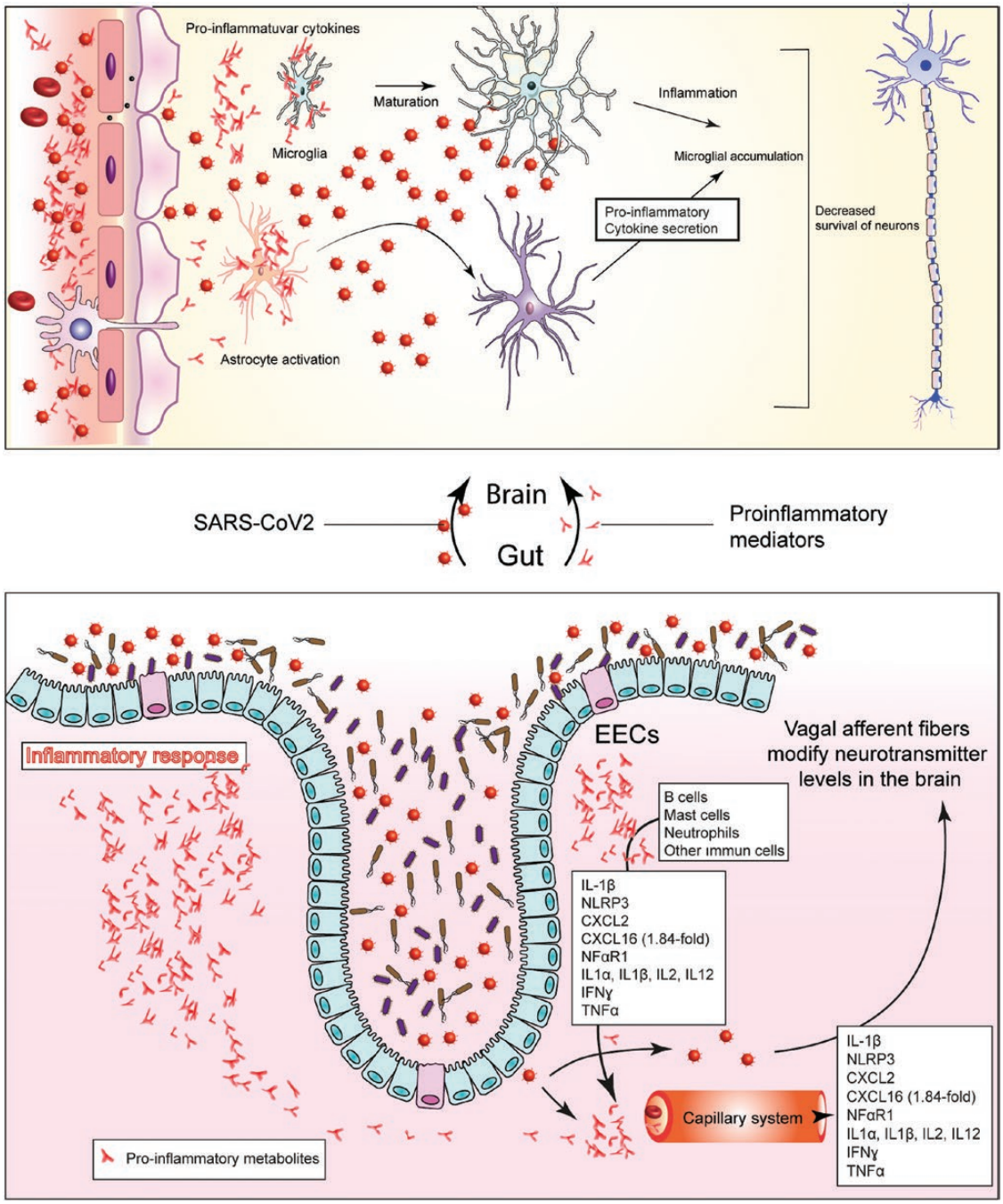

FIGURE 1. Overview of the interactions between the gastrointestinal tract and the brain.

Precise documentation of GI symptoms and neurological signs (eg, meningeal signs, decreased consciousness) with neurological, electrophysiological (eg, EEG), and postmortem investigations of brain tissue of patients with COVID-19 with GI symptoms can clarify how and whether this virus plays a role in causing gastrointestinal and neurological manifestations.

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Conflicts of interest: The author declares that there is no conflict of interest in this letter.

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