

Potential neurological symptoms of COVID-19

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Dear Editor,

The coronavirus disease 2019 (COVID-19) outbreak in Wuhan, China has spread rapidly, with confirmed cases currently appearing in multiple countries. Although many details, such as the source of the virus and its ability to spread between individuals, remain unknown, an increasing number of cases have been confirmed to have been caused by human-to-human transmission.^{1,2} The primary symptoms of COVID-19 include fever, dry cough, and fatigue.² However, some physicians in affected areas have found that some patients diagnosed with COVID-19 have not shown typical respiratory symptoms, such as fever and coughing, at the time of diagnosis; rather, some infected patients have exhibited only neurological symptoms as the initial symptoms, such as the following: (1) headache, languidness, unstable walking, and malaise, which may be due to non-specific manifestations caused by COVID-19 (the proportion of non-specific manifestations as the first symptoms needs to be further explored); (2) cerebral hemorrhage; (3) cerebral infarction; and (4) other neurological diseases. In a recent study of 214 patients with COVID-19, 78 (36.4%) patients had neurological manifestations, such as headache, dizziness, acute cerebrovascular diseases, and impaired consciousness.³ Of these 214 patients, 40 (18.7%) patients required intensive care unit (ICU) interventions for their severe neurological involvement.³ Currently, although there have been many cases of patients with COVID-19 complicated by cerebral hemorrhages, relevant studies on this association are lacking. Hence, the physiological relationship between COVID-19 and the incidence of cerebral hemorrhage remains unclear. Based on several lines of evidence, we hypothesize that COVID-19 may involve cranial hemorrhage. First, recent studies have shown that this novel severe acute respiratory syndrome (SARS) coronavirus, SARS-CoV-2, invades human respiratory

epithelial cells mediated by its S-proteins and angiotensin-converting enzyme 2 (ACE2) receptors on human cell surfaces,⁴ as ACE2 is required for SARS-CoV-2 to infect cells.^{5,6} ACE2 signaling lowers blood pressure. Since the expression of ACE2 is reduced in patients with hypertension, the ability of ACE2 to lower blood pressure is concomitantly reduced in these patients. Following SARS-CoV-2 infection, the expression and function of ACE2 proteins are reduced. Since the expression of ACE2 in patients with hypertension is already low, SARS-CoV-2 infection is more likely to induce cerebral hemorrhage in such patients. As a second line of evidence suggesting that SARS-CoV-2 infection may induce cerebral hemorrhage, patients with COVID-19 often suffer from coagulopathy and prolonged prothrombin time,^{7,8} both of which are also contributing factors to secondary cerebral hemorrhage. In contrast, no cases of secondary cerebral infarctions have been reported in patients with COVID-19. However, COVID-19 may cause an increase in D-dimers,⁷ which lead easily to thrombotic vascular events. Previous studies have reported cases of secondary cerebral infarction in SARS. Hence, we speculate that COVID-19 also has the potential to induce cerebral venous and/or arterial infarctions. Finally, few studies have reported any cases of neurological damage associated with COVID-19. However, a previous study has shown that RNA sequences of the novel human-infectious coronavirus, HCoV-OC43, were detected in the cerebrospinal fluid of a 15-year-old child with acute demyelinating encephalomyelitis.⁹ SARS-CoV has also been detected in the sera and cerebrospinal fluids of two patients with persistent epilepsy and SARS.¹⁰ A recent report firstly shows that SARS-CoV-2 can also attack and damage the nervous system, with detection of SARS-CoV-2 RNA in the cerebrospinal fluid.¹¹ With the outbreak of COVID-19, we should be vigilant for the presence of neurological symptoms similar to those reported

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for infections by these previous human infectious coronaviruses.

Due to a lack of clear and specific clinical symptoms in the patients mentioned above, diagnosis of COVID-19 is especially challenging, which may lead to missed or erroneous diagnoses that may increase the chance of transmitting the infection. In addition, due to the absence of fever and respiratory symptoms, such patients with COVID-19 may ignore or be unaware of their illness. Since infected patients are contagious during the incubation period, these patients with atypical presentations represent an important hidden source of the spread of the virus. Therefore, medical staff should inquire about the medical history of each patient in more detail. For such atypical cases, timely routine blood tests, respiratory-tract pathogen tests, and chest computed tomographies should be conducted. Furthermore, protective measures should be taken to avoid the risk of exposure to medical staff and other patients.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethic statement

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