

Is SARS-CoV-2 a neurotropic virus and a potential facilitator of CNS infection for other pathogens?

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The epidemic of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in December 2019, and it has currently resulted in the loss of more 100,000 human lives in the US. [1] This unprecedented SARS-CoV-2 epidemic is likely one of the largest worldwide crises in the last 100 years. SARS-CoV-2 was originally reported to be a respiratory virus however it seems plausible that like other coronaviruses, the gastrointestinal tract and the olfactory bulb are ports of entry for SARS-CoV-2. In fact, smelling abnormalities have been the clinical presentation in some cases with coronavirus disease 2019 (COVID-19). [2] Furthermore, CNS symptoms have been reported in about one third of patients with COVID-19 [3] and SARS-CoV-2 have been isolated from CSF in patients with CNS symptoms. [4,5]

A patient with neurologic symptoms at the time of the COVID-19 epidemic.

Patross et al. reported a male patient with 2 days of confusion, headache, and fever with the final diagnosis of presumptive meningitis. [6] Blood cultures grew *S. pneumoniae*. Subsequently, the throat swab COVID-19 PCR test was reported positive. Interestingly, the patient did not have respiratory or gastrointestinal symptoms. The patient improved clinically on appropriate antibiotic treatment and was discharged home to continue the treatment. It was not clear whether this patient had olfactory or gustatory abnormalities, as these are difficult to evaluate in a confused patient. The MRI showed findings that were highly suggestive for ventriculitis supporting the diagnosis of acute brain injury and very likely meningitis. This case is unique to explore the association of SARS-CoV-2 and CNS infections and the tropism of SARS-CoV-2 to CNS. Furthermore, SARS-CoV-2 might facilitate the invasion of other pathogens into the CNS. Because the cerebrospinal fluid exam was not done in this patient, the etiology of the CNS symptoms was not confirmed. The etiologies of the CNS symptoms could be due to either SARS-CoV-2 or *S. pneumoniae*, both pathogens or metabolic abnormalities. The lack of CSF exam in a patient with presumptive meningitis during the time of COVID-19 is a diagnostic limitation. This practice of not doing a CSF exam is acceptable if the risk of infection for the physician is substantial. An additional observation is that the fact that this patient with fever and CNS complaints did not receive a SARS-CoV-2 test upon initial presentation. This illustrates the suboptimal awareness of SARS-CoV-2 causing CNS infection.

Characterization of the neurological findings in patients with COVID-19.

CNS symptoms have been reported in 36.4% of 214 patients with COVID-19. [3] When comparing patients with severe COVID-19 versus those without severe COVID-19, the impaired consciousness was reported in 14.8% vs. 2.4% and cerebrovascular accidents in 5.7% vs. 0.8% respectively. [3] Interestingly, fever, cough, sore throat and diarrhea were less common among patients without severe illness. [3] Oxley et al. reported large-vessel strokes as a presenting feature of COVID-19 in patients with ages 33 and 49 years with no or mild comorbidities. [7] In addition, neurological signs were found in 84% from a series of 58 patients with severe SARS-CoV-2. [8] In this series, fever was present in only 16% of patients. However, corticospinal tract signs were present in 76% of the patients.

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The brain MRI revealed leptomeningeal enhancement in 62%, perfusion abnormalities in 100% and ischemic CVA in 23% of the patients. However, the SARS-CoV-2 PCR was negative in the cerebrospinal fluid in 7 out of 7 patients. Overall, patients with neurological symptoms were more severely ill but reported fever, respiratory and gastrointestinal symptoms less often.

Pathogenesis of CNS symptoms in patients with COVID-19.

The findings of more neurological symptoms among patients with severe COVID-19 could be due to the inflammatory and thrombotic complications. There appear to be a correlation among the severity of the COVID-19, increasing findings of neurological symptoms, high levels of C-reactive protein (CRP) and D-dimer. [9,10] CRP was 3.94-fold times and D-dimer 2.25-fold times higher in patients with severe COVID-19 than those with non-severe COVID-19. High CRP levels is triggered by IL-6 that may reflect the ongoing cytokine release syndrome (CRS) leading to organ injury including neurological symptoms. The angiotensin converting enzyme-2 (ACE-2) is found in many cells and organs including the CNS. ACE converts angiotensin-I into angiotensin-II; which through the angiotensin type-1 receptor (AT-1R) triggers vasoconstriction, inflammation, thrombosis and activation of microglial cells plus neuroinflammation. [11] On the other hand, ACE-2 converts angiotensin II into angiotensin 1-7 which binds to angiotensin type 2 receptor (AT-2R) triggering vasodilation and less thrombosis. Thus, ACE-2 is a master regulator of the renin-angiotensin system (RAS) by converting angiotensin I and angiotensin II to 1-9 and 1-7 respectively. ACE-2 is the receptor of SARS-CoV-2. Upon the virus binding to the ACE-2, the counter regulation activity of the ACE-2 over RAS is lost.

The olfactory bulb is a potential port of entry for SARS-CoV-2 and *S. pneumoniae* for the case under discussion with presumptive meningitis. The fact this patient did not have respiratory symptoms and the chest CT did not show lung abnormalities makes it tempting to consider the possibility that the olfactory bulb as the port of entry for both pathogens. Nasal epithelial cells display the highest expression of the SARS-CoV-2 receptor, the ACE-2, in the respiratory tract. [12] Furthermore, the olfactory bulb has been reported to be the port of entry for bacteria, fungi and protozoa. In 1937, Rake G. showed that pneumococci instilled intranasally in mice pass through the mucosal surfaces to the peripheral blood within 2 minutes. [13] A test with Prussian blue showed that pigment went through the olfactory cells, lymphatics and blood vessels, perineural sheaths and then to the subarachnoid space and pia mater over the olfactory bulb. These findings were confirmed by others, such as Ginkel et al. [14]

Conclusion

The case reported by Patross et al. with neurological symptoms and MRI findings consistent with CNS injury could be due to *S. pneumococcus* and SARS-CoV-2 infection. [6] Regardless of the lack of confirmation of the etiology of this case, it illustrates very well the challenges to deliver optimal care of patients at the time of COVID-19 epidemic. Physicians are concerned about their own safety in doing a lumbar puncture in a patient with presumptive COVID-19. This practice of not doing a CSF exam on a patient in the time of COVID-19 deserves a good analysis. It is very important that physician protects his/her own health. Secondly, physicians are not expected to spread the infection. Finally, the fact that this patient with fever and CNS complaints did not receive a SARS-CoV-2 test upon initial presentation illustrate well the suboptimal awareness of SARS-CoV-2 causing CNS infection. More studies are needed to evaluate the mechanisms causing CNS symptoms in patients with COVID-19 including in those with *S. pneumoniae* bacteremia. New guidelines should include SARS-CoV-2 tests in patients with neurological symptoms and fever.

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