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Commentary

The neuro-invasive potential of severe acute respiratory syndrome coronavirus 2; A threat of viral latency.

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Abstract

Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2) induced coronavirus disease (COVID-19) presents with several neurological manifestations just like other Beta Corona Virus (βCoV) family members. SARS-CoV-2 affects the central nervous system (CNS) in many ways eliciting various neurological disorders generally from headaches, ataxia, mental confusion to severe respiratory distress, and eventually death. The different portals of access of SARS-CoV-2 into the CNS, i.e., hematogenous and neuronal retrograde motion, increase the incidence of neurological manifestations and poor disease prognosis. A new idea regarding neuro-invasion of SARS-CoV-2, i.e., its potential of latency and possible later reactivation and complications, has been presented. This aims to direct the attention towards research to determine the impact range of latency and reactivation of SARS-CoV-2. Keeping in view, these aspects finding SARS-Cov-2 in cerebrospinal fluid (CSF) by reverse transcriptase-polymerase chain reaction (RT-PCR) and complete CSF examination should be employed.

Keywords

COVID-19, Neuro-Invasion, Latency, Cerebrospinal Fluid.

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The neurological manifestations are quite common in severe acute respiratory syndrome-CoronaVirus-2 (SARS-CoV-2) induced COVID-19 disease, which was declared as a global pandemic in December 2019[1]. Neuro-invasion has also been reported commonly in most of the members of the βCoV family, i.e., including SARS-CoV[2], Middle East Respiratory Syndrome (MERS)-CoV[3], HCoV-229E[4], Human coronavirus (HCoV)-OC43[4], and porcine hemagglutinating encephalomyelitis coronavirus (HEV)[5].

With increasing experience and information regarding SARS-CoV-2 and its growing clinical presentation, the literature review has shown increasing neurological symptoms of COVID-19 patients[6]. A study reported that 36.4% of cases present with neurological manifestations caused by COVID-19 disease[6]. COVID-19 patients were observed to show symptoms of encephalitis, including sudden olfactory and gustatory instability (10–70%), headache (13%), attention deficit (8–15%), giddiness (17%), neuralgia (2%), audiovisual hallucinations, mental confusion, post-intensive care dysexecutive ailments (36%), tonic-clonic epileptic seizures (1%), motor ataxia (1%), abrupt neurological deficits including respiratory depression (3%) or signs of the pyramidal tract (67%)[7].

Two portals of entry have been documented in literature, mainly opted by SARS-CoV-2 for invasion in the CNS[8]. One is hematogenous, and the other is via the retrograde neuronal route. Angiotensin-converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP4) receptor is the main culprit of hematogenous spread[9]. The SARS-CoV-2 virus binds to the ACE-2 receptor, with its viral spike protein to penetrate the cell, which amply appears in the endothelium of capillaries of the cerebral tissue[9]. This may initiate an immune response in the brain by infecting blood leucocytes, e.g., macrophages and monocytes. Then the virus is transported to the nervous system by crossing the blood-brain barrier[10]. Although ACE-2 receptors in CNS are not as much as in the pulmonary system, they still hold an important position while discussing the neuro-invasive capacity of SARS-CoV-2[11].

The olfactory nerve fibers connect the nasal epithelium with the olfactory bulb and are responsible for access of SARS-CoV-2 to CNS. Most of the respiratory viruses are known to gain access to CNS through this route, thus infecting the CNS, and these patients are presented with neurological manifestations[12]. Similarly, SARS-CoV-2 penetrates the nervous system by invading the same route of the olfactory nerve, just like other respiratory viruses[13]. A study on transgenic mice had also documented that SARS-CoV-2 when was given intranasally to the mice, the virus entered in CNS of the mice through retrograde neuronal invasion via the olfactory nerve[14].

CSF examination of COVID-19 diseased patients presenting with neurological manifestations can aid in recognizing SARS-CoV-2 virus presence, evaluation of disease severity, and prognosis[15]. The existence of SARS-CoV-2 is detected in CSF using the reverse transcription-polymerase chain reaction (RT-PCR) method similarly as it is detected in nasopharyngeal swab[16]. The SARS-Cov-2 virus in CSF fluid is documented in cases of encephalitis, one in China and the other in Japan[16]. So, the PCR-based detection of SARS-CoV-2 in CSF should be widely employed as a diagnostic investigation of neurological invasion. The inflammatory response of CSF can be evaluated by doing a complete CSF examination, i.e., proteins, cell count, glucose, lactate dehydrogenase, and sodium levels[17].

Many patients have a latent lesion in the olfactory nerve as they permanently suffer from anosmia even after recovery from SARS-CoV infection[18]. SARS-CoV-2 had the same pathogenicity as SARS-CoV could implicate a very important and threatening aspect of neuro-invasion[19]. An important suggestion for future research is that SARS-CoV-2 could be hypothesized to exist as the latent virus in the spinal fluid of the previously recovered or asymptomatic COVID-19 infected patients and later its revival and reactivation. A similar reactivation of SARS-CoV-2 15-17 days after the PCR for the previous infection came out to be

negative has been reported in Korea[20]. This later reactivation could be deadly as it may cause life-threatening complications. So, this is the need of the hour to extend research regarding the neuro-invasion and the latency of the SARS-CoV-2 virus. The larger scope of the research should aim to contain the impact range of late complications of SARS-CoV-2 to develop a feasible response plan to avoid prospect destruction to humanity.

Conclusion

Reverse transcriptase-polymerase chain reaction (RT-PCR) of cerebrospinal fluid (CSF) should be employed for early detection of neuro-invasion of SARS-CoV-2 and prevention of development of a complication.

Conflicts of Interest

The authors have declared that no competing interests exist.

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