



Central Nervous System Infections Associated with the SARS-CoV-2 Virus

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Abstract

Neurological manifestations in addition to the typical clinical symptoms of COVID-19, have been reported around the world. A case series of clinical suspect of SARS-CoV-2 infection in the central nervous system (n=8) were analyzed. Cerebral Spinal Fluid (CSF) and nasopharyngeal swab were analyzed by RT-PCR. Our results showed SARS-CoV-2 in five CSF samples and three patients testing positive for COVID-19 also on nasopharyngeal swab. The patients showed different clinical manifestations, including <95% saturation, fever, cough, dyspnea and abdominal pain. The findings of this study alert to the existence of nonspecific symptoms associated with central nervous system infection caused by SARS-CoV-2.

Keywords: SARS-CoV-2; COVID-19; Cerebrospinal fluid; RT-PCR

Short Communication

In December 2019, cases of severe acute respiratory syndrome emerged and were after associated with SARS-CoV-2. Since then, reports have described neurological manifestations in addition to the typical clinical symptoms of COVID-19. This virus can spread from the respiratory system to the central nervous system, using transneuronal and hematogenous mechanisms. Although not all COVID-19 patient test positive for the virus in the cerebrospinal fluid exam, the appearance of neurological symptoms associated with SARS-CoV-2 infection reveals the importance of understanding the neurologic manifestations and capacity for neural invasion associated with the pathogen. These aspects are relevant for correct diagnosis and treatment and for the potential development of vaccines [1].

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Hospitalized patients with COVID-19, especially those with severe disease, can display neurological disorders as shown by Mao et al. [2], such as acute cerebrovascular disease in up to 5.7%, impaired consciousness in 14.8%, and skeletal muscle injury in 19.3% of cases. Nonetheless, COVID-19 seems to be associated with a wide spectrum of neurological manifestations including meningoencephalitis [3-5], encephalomyelitis [6], Guillain-Barré Syndrome [7], and perfusion abnormalities in brain magnetic resonance imaging [4]. This study highlights the evidence of SARS-CoV-2 infection with a focus on neurological involvement and laboratorial diagnosis, based in a case series.

We describe cases of clinical suspect of SARS-CoV-2 infection in the central nervous system. The patients (n=8) were admitted in a Brazilian public hospital. Cerebral Spinal Fluid (CSF) and nasopharyngeal swab were obtained for laboratorial tests. The samples were analyzed by RT-PCR using technical protocol based on the Center of Disease Control.

Ours results showed SARS-CoV-2 in five CSF samples. Of the total, 3 patients also presented positive test for COVID-19 in nasopharyngeal swab. The patients showed different patterns of clinical manifestations, including <95% saturation, fever, cough, dyspnea and abdominal pain (Table 1).

Laboratorial analysis of 3 CSF samples by RT-PCR did not demonstrate the presence of the virus. Of the 8 patients evaluated, 6 were newborns, 3 of them were children of mothers with COVID-19 during the pregnancy (Table 1).

This study describes cases of COVID-19 with clinical presentation and positive RT-PCR testing for SARS-CoV-2 in CSF. To our knowledge, this presentation of COVID-19 is little reported so far and is important to consider as an atypical manifestation of the viral infection. Our findings reinforce data obtained by Huang et al. (2020) [8] that RT-PCR of SARS-CoV-2 in CSF can be

Table 1: Epidemiological, laboratorial and clinical aspects in suspect patients of central nervous system by SARS-CoV-2.

Patients	Age (years)	Symptoms days	Hospitalization sector	CSF +	Nasopharyngeal swab +	<95% saturation	Fever	Cough	Dyspnea	Abdominal pain	Others
1	Newborn	1	Neonatology ITU								- Prematurity - Mother tested positive for COVID-19 during pregnancy -Non-invasive ventilatory support
2	Newborn	5	Neonatology ITU								-Invasive ventilatory support
3	Newborn	2	Neonatology ITU								-Invasive ventilatory support -Mother tested positive for COVID-19 during pregnancy -interstitial infiltrate by x-ray
4	20	17	Ward								-Vomit - Pregnant
5	Newborn	16	Neonatology ITU								
6	Newborn	7	Neonatology ITU								-Invasive ventilatory support
7	Newborn	1	Neonatology ITU								-Diarrhea - Prematurity - Mother tested positive for COVID-19 during pregnancy -Mother in sepsis treatment
8	7	7	Pediatric ITU								

Footnote: Blank columns means no symptoms or negative lab test; Black columns means presence of symptoms or positive laboratory test; ITU: Intensive Treatment Unit; CSF: Cerebral spinal fluid.

considered as a detection modality for cases of COVID-19 affecting the central nervous system.

We demonstrate that patients with COVID-19 displaying distinct neurological disorders have extremely low levels of SARS-CoV-2 in CSF, according high CT (cycle threshold) value of the samples, indicating that viral clearance precede the neurological involvement. It is important to emphasize that the RT-PCR for SARS-CoV-2 detection in CSF has not been validated yet. Besides that, undetectable results in some CSF samples of patients could be false negative. This finding points to the need for the development of more sensitive molecular tests and the investigation of other neurotropic pathogens to exclude neuroinfection.

Considering the sole report of a severe case of meningoencephalitis with detectable SARS-CoV-2 RNA in CSF [5], likely presenting a low viral load since just one of two RT-qPCR assays turned positive at a cycle CT of 37, we can assume that whether SARS-CoV-2 is detectable in CSF, it may depend on disease severity, the time of sample collection or the sensitivity of the molecular test used. On the other hand, herpes simplex viruses 1 and 2, varicella zoster virus, and enterovirus are responsible for the greatest number of CNS infection in immunocompetent hosts [9]. Therefore, CSF investigation of COVID-19 patients presenting with GBS or CNS manifestations to exclude concurrent neuroinfection with other neurotropic viruses should be encouraged [4,8].

It was not possible to perform the next generation sequencing in the positive samples, to determine the genetic variant responsible for the infection, because this methodology requires a high viral load,

consequently, a low Ct value. Based on the SARS-CoV-2 genomic surveillance network in Brazil, during the period in which the present study samples were collected, the variant of concern that predominated was Gamma (P.1), with an occurrence of 85% in the month of March 2021, 93.8% in April and 95.5% in May. It may be reasonable to infer that the variant responsible for the CNS manifestations was Gamma by the circulation scenario at the time [10].

Few cases of encephalitis/meningitis with positive RT-PCR assays of the CSF have been described [1-8]. This can be attributed to several reasons: The RT-PCR assay of CSF may yield negative results when performed early; the method has limited sensitivity associated with false negative tests in CSF; and low viral load in the CSF [1].

Cases of SARS-CoV-2 infection with invasion of the nervous system are being described with the emergence of the new pandemic due to the infectious disease COVID-19. Patients with COVID-19 may present initially neurological symptoms or experience neurological complications during hospitalization. The diagnosis of neuro-COVID-19 can be challenging. Since SARS-CoV-2 has neuroinvasive and neurotropic properties, early recognition can help initiate treatment and isolation early, to prevent clinical worsening and spread of the virus and the underreporting of neurological cases associated with COVID-19 [1].

Recent observations suggested possible neurological complications of COVID-19, including the first report of suspected viral encephalitis. We report a case of a 29-year-old male with on nasopharyngeal testing- confirmed SARS-CoV-2 infection with severe respiratory symptoms, followed by clinical and radiological

signs of encephalitis. Magnetic resonance imaging of the brain showed an asymmetric FLAIR-hyperintensity of the left medial temporal cortex associated with mild gyral expansion. Lumbar puncture was normal and PCR for SARS-CoV-2 on CSF were negative. Clinicians treating SARS-CoV-2 infected patients should be aware of possible neurological complications, like encephalitis. The diagnosis of SARS-CoV-2 encephalitis is difficult as the laboratory analysis of the CSF may not be altered [9,11]

Clinicians treating SARS-CoV-2 infected patients should be aware of possible neurological complications. In case of suspected meningoencephalitis, additional exams should be performed such as brain MRI scan, long-term EEG monitoring, and lumbar puncture. However, the absence of a typical CSF profile of viral meningitis/encephalitis as well as the negative PCR for SARS-CoV-2 in CSF, makes diagnosing encephalitis linked to SARS-CoV-2 less obvious [9,12].

One of the study limitations was the lack of follow-up of diagnosed patients. This follow-up was not possible because the diagnosis was performed as a service to the municipal health authorities, therefore, there were no personnel and financial resources available for this purpose.

Conclusion

The findings of this study alert to the existence of nonspecific symptoms associated with central nervous system infection caused by SARS-CoV-2. This raises the need for laboratory examination to detect this virus in CSF samples and subsequent early and assertive treatment. Further studies are important to elucidate mechanisms of pathogenesis, protocols of clinical management, and laboratory practices of SARS-CoV-2 neurological manifestations.

Contributors

A.B. Ferreira-Machado, A.S.A. Watanabe, V.L. Silva, C.G. Diniz and V.C. Dias contributed to the study conception, data analysis and interpretation and writing. All authors approved the final version to be published.

Compliance with Ethical Standards

This study involving human participants and was approved by the Ethics Committee of the Federal University of Juiz de Fora (protocol #4.743.435).

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