

# Neurological Manifestations Associated With SARS-CoV-2 in Children: A Case Series

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## ABSTRACT

Neurological manifestations of COVID-19 may affect both central and peripheral nervous systems. Unlike in adults, in whom majority of severe cases derive from respiratory complications, neurological involvement is one of the main causes of severe COVID-19 in children. This study aimed to detect viral respiratory pathogens, mainly SARS-CoV-2, in nasopharynx and cerebrospinal fluid samples utilizing qRT-PCR (TaqMan) in a pediatric population in Brazil. We evaluated four children with neurological symptoms and laboratory-confirmed SARS-CoV-2 infection: three presenting with meningoencephalitis and one presenting with Guillain-Barré syndrome. All four patients had mild respiratory symptoms. SARS-CoV-2 RNA was identified in two cerebrospinal fluid samples. SARS-CoV-2 involvement should be considered for differential diagnosis in pediatric cases presenting neurological alterations even if symptoms such as headache, anosmia, or dizziness are absent.

**KEYWORDS:** SARS-CoV-2, pediatric, meningoencephalitis, guillain-barré syndrome, cerebrospinal fluid

**TYPE:** Case Series

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## Introduction

Since December of 2019, over 468 million confirmed cases of coronavirus disease 2019 (COVID-19) have been confirmed worldwide, accounting for over 6 million deaths.<sup>1</sup> With over 29 million cases overall and more than 40 thousand hospitalizations in patients under 19 years of age, Brazil is the third leading country in case numbers at the time of writing.<sup>2</sup> Apart from the main respiratory manifestations, there is cumulative evidence that severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has neuroinvasive potential and can be associated with several

neurological conditions such as encephalitis, meningitis, Guillain-Barre, and Miller-Fisher syndrome.<sup>3,4</sup> Studies have shown neurological symptoms in children are prevalent, often being the main manifestation of the infection.<sup>5</sup> Neurological symptoms may appear concomitantly or after the onset of respiratory manifestations. Although, it is not yet determined if such neurological involvement derives directly from the infection, is para-infectious or post-infectious process, SARS-CoV-2 RNA has been detected in cerebrospinal fluid (CSF) of adults and children.<sup>6</sup> However, reports on isolation of SARS-CoV-2 in



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**Table 1.** Characteristics of 4 pediatric patients with COVID-19 disease and neurological manifestations.

CHARACTERISTICS (REFERENCE VALUE)	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4
Age	7 years	9 months	4 years	15 years
Comorbidity	Chronic non-progressive encephalopathy	Global development delay	None	None
Neurological condition	Meningoencephalitis	Meningoencephalitis	Meningoencephalitis	Guillain-Barré syndrome
Nucleated cells				
Total (0-5/ $\mu$ l)	9	124	207	0
Mononuclear (40-80%)	71%	87%	88%	0
Polymorphonuclear (0-6%)	29%	13%	12%	0
Erythrocytes (0/ $\mu$ L)	13.321	0	292	110
Protein (5-40 mg/dL)	125	54	109	163
Glucose (40-80 mg/dL)	63	56	69	57
SARS-CoV-2 in NS (Ct $\leq$ 36)	Not detected	Indeterminate	Detected	Detected
SARS-CoV-2 in CSF (Ct $\leq$ 36)	Detected	Detected	Not detected	Indeterminate
Other respiratory viruses in NS	Rhinoviruses	Rhinoviruses	Not detected	Not detected

CSF: cerebrospinal fluid; NS: nasopharyngeal swab; CNS: central nervous system; PNS: peripheral nervous system; Ct: cycle threshold. Indeterminate: Ct value between 36 and 40.

cerebrospinal fluid (CSF) are inconsistent, exhibiting knowledge gaps of its effects on the central nervous system.<sup>7,8</sup> Additionally, reports regarding neurological complications associated with COVID-19 in the pediatric population are still scarce. Children predominantly present with milder cases and better prognosis than adults.

## Material and Methods

This observed four pediatric patients with neurological symptoms caused by mild COVID-19 infection treated at Instituto de Puericultura e Pediatria Martagão Gesteira (IPPMG), a tertiary-care hospital in Rio de Janeiro, Brazil. Nasopharyngeal swabs and CSF samples were collected in sterile tubes or containers and submitted to qRT-PCR for SARS-CoV-2 (CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel and Bio-Manguinhos SARS-CoV-2 Molecular Kit) as well as XGen Multi PR21 Respiratory Panel (Mobius Life Science) and FilmArray<sup>®</sup> Meningitis-Encephalitis (ME) Panel (Bio-Mérieux<sup>™</sup>). Positive (Ct $\leq$ 36) and indeterminate (Ct 36<X<40) PCR results were confirmed via re-extraction and retesting. Characteristics of patients and neurological manifestations are summarized in Table 1.

## Case Descriptions

Patient 1, male, 7-years-old, with a past medical history of chronic non-progressive encephalopathy and epilepsy due to meningoencephalitis sequelae. No history of contact with suspected or confirmed COVID-19 patients. One month prior to admission, the frequency of his seizures increased - beforehand, he would have 3 episodes a week at most, and this

changed to several episodes a day. Upon admission, parents reported coughing for 3 days and sleepiness for the last 2 days - neither symptoms were present previously. No fever or other respiratory symptoms were reported. Neurological examination revealed decreased level of consciousness, in addition to previous abnormalities: axial hypotonia, appendicular hypertonia and hyperreflexia. Laboratory evaluation identified an elevated C-reactive protein (12.6 g/dL) and elevated D-dimer (4999 ng/dL). SARS-CoV-2 RNA was detected only in a CSF sample and rhinovirus (RV) was detected in a nasopharyngeal (NS) sample. No pathogen-specific treatment was performed. The sleepiness complaint improved after 5 days, and seizures subsided after adjusting the anticonvulsant drugs. He was discharged home after 2 weeks without other symptoms. One month after discharge, head MRI was performed and showed petechial hemorrhage in the cerebral parenchyma and bilateral subdural hematoma (data not shown). These findings may be related to SARS-CoV-2 infection, but abusive head trauma is also being investigated.

Patient 2, male, 9-months-old, and past medical history of prematurity (35 weeks) and newborn intraventricular hemorrhage. He was a household contact of a suspected untested COVID-19 patient (his mother). Two days prior to admission, presented with fever, nasal congestion, and vomiting. In addition to previous abnormalities such as mild global muscle hypotonia with hyperreflexia, physical examination revealed a bulging anterior fontanelle, lethargy, irritability. Cranial computed tomography (CT) was normal. Blood count with leukocytosis (20.410 cells/ $\mu$ L), elevated C-reactive protein (32,7 g/dL) and D-dimer (527 ng/dL). SARS-CoV-2 RNA was detected in a CSF sample and indeterminate in a NS,

while RV was detected solely in a NS sample. The patient was treated with antibiotic therapy for 10 days and discharged home without any symptoms.

Patient 3, female, 4-years-old, with an unremarkable past medical history and history of household contact with a suspected untested COVID-19 patient (grandmother). The patient was suffering from abdominal pain and diarrhea for 2 days and developed vomiting, headache, and seizures a few hours before admission. Once admitted in a local emergency room, began treatment with anticonvulsants, ceftriaxone, and acyclovir. Once stabilized, was transferred to an intensive care unit at IPPMG, with normal neurological examination and Cranial CT scan, evolving without seizures. Blood count with leukocytosis (15,590 cells/ $\mu$ L), elevated C-reactive protein (16,1 g/dL). D-dimer was not performed. SARS-CoV-2 was detected in NS and not detected in CSF. Acyclovir treatment was discontinued after negative viral results from CSF. The patient was discharged home after 10 days without any symptoms.

Patient 4, female, 15-years-old, with an unremarkable past medical history. She had no history of contact with suspected or confirmed COVID-19 patients. One week before admission the patient developed otalgia, odynophagia, and anosmia, associated with facial paralysis and difficulty walking and 6 days prior to admission presented with dysarthria. There was no history of fever. Neurologic examination revealed a preserved level of consciousness, dysarthria, normal extrinsic eye movement without diplopia, bilateral peripheral facial paralysis, global areflexia, gait ataxia, and weakness in the abdominal muscles, upper and lower limbs. Cranial CT scan without contrast was unremarkable. Blood count was normal, and C-reactive protein and D-dimer values were within normal range. SARS-CoV-2 was detected in 2 nasopharyngeal samples (collected 7 days apart) and CSF was indeterminate. Guillain-Barré syndrome was suspected and treated with intravenous immunoglobulin 0.4 g/Kg/day for 5 days starting on the eighth day of symptoms. She was discharged 1 week after admission, with resolution of all other symptoms apart from facial paralysis, which subsided after 4 weeks.

## Discussion

Here we report 4 patients with COVID-19 presenting mild respiratory symptoms and varying neurological manifestations in a pediatric hospital in Brazil. Several reports have been published regarding SARS-CoV-2 infection and neurological manifestations since the onset of the COVID-19 pandemic, with few focusing on children. However, the detection of viral RNA in CSF is not consistent throughout these reports.<sup>7,8</sup> In our case series 2 patients had detectable SARS-CoV-2 RNA in CSF, a third had indeterminate results. Interestingly, 1 did not have detectable viral load in a nasopharyngeal sample. This could be due to sampling in the latter stages of infection, with lower viral load, yielding false negative results.

Some patients with COVID-19 may initially present with nonspecific neurological symptoms including headache and dizziness while others develop more specific neurological complications. There are reports of meningoencephalitis, encephalopathy, cerebrovascular disease and intracranial hemorrhage,<sup>9-11</sup> olfactory and gustatory disorders, and few with Guillain-Barré syndrome in adult patients.<sup>12</sup> In pediatric patients, 2 previous studies with children who tested positive for COVID-19 in Wuhan, China, reported no neurological symptoms.<sup>13,14</sup>

The CSF characteristics were compatible with meningoencephalitis with varied clinical presentations in 3 cases and 1 Guillain-Barré. According to literature, critically ill patients have greater risk of developing serious neurologic manifestations,<sup>3,7</sup> however our 4 patients had mild respiratory symptoms and only 1 required intensive care.

Several hypotheses have been suggested to explain COVID-19 related neurological manifestations, a main 1 being direct viral effects utilizing the angiotensin-converting enzyme 2 receptor (ACE2) and/or transmembrane serine protease 2 (TMPRSS2).<sup>4</sup> Indeed, SARS-CoV-2 proteins were detected in 53% of the brains in a post-mortem case series.<sup>8</sup> Another possible mechanism is through transsynaptic transfer via peripheral nerve terminals, as seen with other coronaviruses. A para-infectious or post-infectious process in the form of hyperinflammation caused by the “cytokine storm”; damages to the blood-brain barrier (BBB) caused by endothelial injuries or even hypoxic-ischemic injuries. The detection of viral RNA in CSF demonstrates the ability to cross the BBB and the observance of elevated D-dimer in 2 cases where viral DNA was detected suggests endothelial lesion supporting the hematogenous route of dissemination.

Additionally, rhinoviruses (RV) were detected in the respiratory tract and not detected in CSF of the 2 patients that had SARS-CoV-2 RNA detected in CSF. Although rare, RV infection has been associated with neurological disease, and a 27% coinfection rate of SARS-CoV-2 and RV was recently reported.<sup>15</sup> However, further investigations on RV implications in neurological syndromes are still needed.

The detection of SARS-CoV-2 in CSF of 2 children is intriguing, especially considering the fast recovery and absence of sequelae. Their first symptoms varied between an increase in the frequency of epileptic seizures, in the case of patients with previous comorbidity, and a decrease in the level of consciousness. These cases were initially a cause for concern, given the overall unfamiliarity with the evolution of the disease and the complications that could ensue.


It is important to mention that the result of the brain MRI of Patient 1, which was performed 1 month after discharge, showed petechial hemorrhage in the cerebral parenchyma and bilateral subdural hematoma. This finding should always be evaluated in children who are victims of abuse, but this patient did not present other characteristics, such as retinal hemorrhage

and fracture of long bones and skull, which makes abuse an unlikely cause.

The main limitations of the present study were the inability to perform antibody, cytokine expression analysis and imaging tests on all patients as well as the lack of paired whole blood samples.

In conclusion, this article presents a case series with 4 COVID-19 patients, under 16 years of age, with meningo-encephalitis and Guillain-Barré syndrome with good outcomes and distinct viral detection patterns. While it has not yet been proven, these cases strengthen a possible involvement of SARS-CoV-2 in the nervous system in children, which at the time are not fully understood. Although further studies are required to elucidate SARS-CoV-2 involvement in the central nervous system, it should be suspected as a differential diagnosis, especially in children and patients with neurological comorbidities, who may have communication difficulties and do not report symptoms such as headache, anosmia or dizziness.

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### Abbreviations

ACE2: angiotensin-converting enzyme 2; BBB: blood-brain barrier; CNS: central nervous system; COVID-19: Coronavirus disease 2019; CSF: cerebrospinal fluid; CT: Computed Tomography; Ct: Cycle threshold; IPPMG: Martagão Gesteira Childcare and Pediatrics Institute; MRI: Magnetic Resonance Imaging; NS: Nasopharyngeal swab; PBS: Phosphate-Buffered Saline; PNS: peripheral nervous system; RNA: Ribonucleic acid; RT-PCR: Reverse Transcription Polymerase Chain Reaction; RV: Rhinovirus; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2

### REFERENCES

1. World Health Organization. Weekly epidemiological update on COVID-19 - 22 March 2022. 2021. <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19-22-march-2022>. <https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19-22-march-2022>. accessed 25 March 2022.
2. Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Boletim Epidemiológico Especial 102: Doença pelo Coronavírus COVID-19. Semana Epidemiológica 8 (20/2 a 26/2/2022). *Bol Epidemiol.* 2022;102:35.; v.
3. Alquisiras-Burgos I, Peralta-Arrieta I, Alonso-Palomares LA, et al. Neurological Complications Associated with the Blood-Brain Barrier Damage Induced by the Inflammatory Response During SARS-CoV-2 Infection. *Mol Neurobiol.* 2020;58:1-16. doi:10.1007/s12035-020-02134-7.
4. Lin J, Asfour A, Sewell T, et al. Neurological issues in children with COVID-19. *Neurosci Lett.* 2021;743:135567. doi:10.1016/j.neulet.2020.135567.
5. LaRovere KL, Riggs BJ, Poussaint TY, et al. Neurologic Involvement in Children and Adolescents Hospitalized in the United States for COVID-19 or Multisystem Inflammatory Syndrome. *JAMA Neurol. Published online March.* 2021;05:536. doi:10.1001/jamaneurol.2021.0504.
6. Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. *JAMA Neurol.* 2020;77(11):1440-1445. doi:10.1001/jamaneurol.2020.2687.
7. Benameur K, Agarwal A, Auld SC, et al. Encephalopathy and Encephalitis Associated with Cerebrospinal Fluid Cytokine Alterations and Coronavirus Disease, Atlanta, Georgia, USA, 2020. *Emerg Infect Dis.* 2020;26(9):2016-2021. DOI: 10.3201/eid2609.202122.
8. Matschke J, Lütgehetmann M, Hagel C, et al. *The Lancet Neurology*; 2020. S1474442220303082 DOI: 10.1016/S1474-4422(20)30308-2. Neuropathology of patients with COVID-19 in Germany: A post-mortem case series.
9. Abbas R, El Naamani K, Sweid A, et al. Intracranial Hemorrhage in Patients with Coronavirus Disease 2019 (COVID-19): A Case Series. *World Neurosurg.* 2021; 154:e473-e480. doi:10.1016/j.wneu.2021.07.067.
10. Nawabi J, Morotti A, Wildgruber M, et al. Clinical and Imaging Characteristics in Patients with SARS-CoV-2 Infection and Acute Intracranial Hemorrhage. *J Clin Med.* 2020;9:2543. doi:10.3390/jcm9082543.
11. Altschul DJ, Unda SR, de La Garza Ramos R, et al. Hemorrhagic presentations of COVID-19: Risk factors for mortality. *Clin Neurol Neurosurg.* 2020;198:106112. doi:10.1016/j.clineuro.2020.106112.
12. Paybast S, Gorji R, Mavandadi S. Guillain-Barré Syndrome as a Neurological Complication of Novel COVID-19 Infection. *Neurol.* 2020;25(4):101-103. doi:10.1097/nrl.0000000000000291.
13. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. *N Engl J Med.* 2020;382:1663-1665. DOI: 10.1056/NEJMc2005073.
14. Dong Y, Mo X, Hu Y, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. *Pediatrics.* 2020;145:e20200702. doi:10.1542/peds.2020-0702.
15. Uddin SMI, Englund JA, Kuypers JY, et al. Burden and Risk Factors for Coronavirus Infections in Infants in Rural Nepal. *Clin Infect Dis.* 2018;67(10):1507-1514. DOI: 10.1093/cid/ciy317.