

**NEUROLOGIC MANIFESTATION OF COVID-19 PEDIATRIC PATIENTS
ADMITTED AT THE PHILIPPINE CHILDREN’S MEDICAL CENTER IN THE YEAR
2020: A CASE SERIES¹**

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ABSTRACT

COVID-19 which was first documented in the Philippines in January 2020 had spread alarmingly. Severe acute respiratory symptoms were the most common presentation of this novel coronavirus infection. Reports have described neurologic manifestations of this disease involving the central nervous system as well as the peripheral nervous system. However, studies among the pediatric population are limited. In this paper, we present three pediatric patients who were diagnosed with COVID-19, via RT-PCR, presenting with seizures and behavioral changes. Two of these patients have no concomitant respiratory symptoms while the other one also had Pediatric Community Acquired Pneumonia. These patients were managed as cases of acute viral meningoencephalitis and were given supportive care.

KEYWORDS: Covid-19, Neurologic Manifestations of COVID-19 in children, viral meningoencephalitis

Abbreviations

ACE-2 - Angiotensin-converting enzyme-2, COVID-19 - Coronavirus Disease 19, CNS - Central Nervous System, CSF - Cerebrospinal fluid, CT Scan - Computerized tomography scan, RT-PCR - Reverse Transcription-Polymerase Chain Reaction, SARS-CoV2 - Severe Acute Respiratory Syndrome-Corona Virus 2, ER – Emergency Room

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been declared a worldwide pandemic since March 2020. Also known as the SARS-CoV2, this infectious disease, had been more commonly associated with severe acute respiratory syndrome. Utilizing its mechanisms of entry via the angiotensin-converting enzyme-2 and later, activation of the inflammatory cascade, other non-specific symptoms have also been reported and documented which includes cough, shortness

of breath, fatigue and diarrhea. A number of reports have described neurologic manifestations associated with COVID-19 specifically involving the central and peripheral nervous system. Neurologic symptoms most commonly reported were dizziness, headache, impaired consciousness, ataxia, seizures and acute cerebrovascular disease, owing to the neurotropism of the virus^{2,4}. Most studies on the neurologic manifestations have primarily included adult subjects with limited reports for the pediatric age group. There is also no published report to date in this institution.

OBJECTIVE

To present the neurologic manifestations of three confirmed COVID-19 cases in the pediatric age group admitted in this institution in the year 2020.

Case 1

This is a 1 year and 7-month-old female, previously at par with age who had intermittent fever 2 days prior to admission with no associated respiratory or gastrointestinal symptoms. She developed generalized tonic-clonic seizures on the second day, with a temperature of 38.8°. Seizures were recurrent hence was brought for consult at the ER, where she was noted to be irritable with inconsistent regard and stable vital signs. Neurologic examination showed nuchal rigidity and a bilateral Babinski reflex. Initial laboratory results including a complete blood count, electrolyte determination, urinalysis and chest radiograph. While admitted, she remained febrile until the 3rd hospital day with seizure recurrences until the 5th hospital day. Nasopharyngeal RT-PCR swab results came out positive for SARS-CoV2 on the fifth hospital day. Levetiracetam was started and doses were increased to a total of 50mg/kg/day which offered seizure control.

Lumbar puncture with CSF analysis was performed and showed normal results (Table 1). She was noted to have lost previously met developmental milestones, and was discharged with poor head control and no visual tracking. Improvement was noted at two weeks post discharge follow up, and on the 4th week post discharge, she was again able to walk, talk in phrases and feed self with a spoon. Levetiracetam was continued. An EEG was requested as outpatient basis.

Case 2

This is a 10-year-old male, at par with age, who presented with a sudden onset of high grade fever of 40°C 2 days prior to consult, associated with frontal headache and behavioral changes described as difficulty initiating sleep and disorientation. This was followed by an episode of generalized tonic-clonic seizure, which lasted for less than a minute, after which, he was noted to have no verbal output, regard and no response to name calling, with purposeless fidgeting of clothes. Seizure recurrence of the same semiology prompted consult and subsequent admission at our institution. Examination at the ER showed an agitated patient with stable vital signs, who cannot follow commands with incomprehensible word and eventually

needing restraints. Pertinent neurologic findings included a nuchal rigidity, hyperreflexia on bilateral lower extremities with unsustained clonus and positive Babinski. Initial diagnostic tests showed leukocytosis with segmenter predominance, with normal serum electrolyte, urinalysis and chest radiograph. During the course of admission, he remained highly febrile with temperature reaching 41°C and seizure recurrences. He was started on Levetiracetam at a dose of 20mg/kg which offered seizure control. CSF analysis via lumbar puncture done on the third hospital day showed pleocytosis, all lymphocytes with a slightly low CSF:serum glucose ratio of 49.6% (table 1) and negative cultures. Nasopharyngeal swab of SARS-CoV2 showed a positive result. Neurologic status showed minimal improvement on the 4th hospital day, being able to have spontaneous eye opening but still without regard or verbal output. No seizure recurrences were noted during the rest of admission and he was transferred to a COVID referral institution where a cranial MRI was done, which showed abnormal thalamic intensities and subtle T2/FLAIR hyperintensities in the cortex of the left temporoparietal lobe with gyral enhancement. As of this writing and last

follow up, the patient was noted to be discharged from the said institution ambulatory with good regard, but only had minimal verbal output.

Case 3

The only patient in our series with respiratory symptoms, is a 6 month-old male who presented with a 3-day history of cough and fever reaching up to 38°C associated with recurrent episodes of generalized tonic-clonic seizures, lasting for less than a minute, occurring twice daily at home. This prompted consult at the ER where he was eventually intubated for respiratory distress. A chest radiograph showed bilateral pneumonia. A seizure episode of the same semiology was noted at the ER which lasted for 3 minutes. Intravenous Diazepam at a dose of 0.3mg/kg was given, and he was started on Levetiracetam 20mg/kg/day. Complete blood count and electrolytes determination were all normal but Nasopharyngeal swab for SARS-CoV2 showed a positive result on the 3rd hospital day. While admitted, the patient remained highly febrile and had recurrent episodes of generalized tonic clonic seizures which was poorly controlled despite increased doses of Levetiracetam to 60mg/kg/day. Phenobarbital was then started

orally at a dose of 20mg/kg loading dose and maintained at 5mg/kg/day which offered seizure control. However, maculopapular rashes were noted on the subsequent days, leading to discontinuation of Phenobarbital, while maintaining Levetiracetam. Seizures were still controlled. A Cranial CT Scan was done on the 5th hospital day which showed normal results. CSF analysis on the 7th hospital day did not show CSF pleocytosis but had a low CSF:serum ratio of 48% (table 1). CSF Culture studies were all negative, but blood culture results showed growth of *Acinetobacter baumannii*. Appropriate antibiotics were given and he was extubated on the 9th hospital day. He was discharged with a number of neurologic deficits including poor head control, no visual threat, a left central facial palsy and referential movement of the right extremities. He is still due for follow up and diagnostic workup as of this writing.

DISCUSSION

Coronaviruses are large enveloped single- stranded RNA viruses which causes common colds in humans. There are 7 human pathogenic coronaviruses to date, and this SARS-COV2 is the third strain to have caused a global pandemic. The virus has

79.5% similarity with the previous SARS-CoV, which was already proven to cause central nervous system invasion.²

COVID-19 infection had its peak in the year 2020 when this series was done. In 2020, during the time of this data collection, there were 395 confirmed pediatric patients with the highest percentages found in the 15-18 years age group (DOH, 2020)¹ and as of June 2021, a total of 37 patients were documented to have presented with neurologic manifestations.

Neurologic manifestations

A number of studies have already postulated how neuronal invasion of SARS-CoV2 infection occurs. The virus's spike proteins contain a variable receptor-binding domain (RBD) which allows binding to ACE-2 inhibitors in epithelial cells (Wu et al, 2020) and subsequent entry into the host cells² and subsequent neuronal invasion. Entry to the CNS entry occurs retrograde and anterograde neuronal transport from the peripheral nerves or via the olfactory bulb in the nasal cavity^{2,3} Pathogenesis of the disease may occur from direct injury to the brain, from hypoxic injury secondary to respiratory symptoms and from ACE-2 immunologic and inflammatory responses,

which may lead to infectious encephalopathy, viral encephalitis and cerebrovascular diseases.²

Most neurologic manifestations appear early in the disease within 1-2 days.^{2,4} The most common neurologic symptoms reported in adult patients were impaired consciousness and acute cardiovascular disease. Infections in children have been observed to have a milder clinical course than adults and asymptomatic infections are more common.⁵ Our patients all presented with early onset seizures and impaired consciousness, occurring on the first to second day of illness, prior to the release of a positive COVID PCR result. Only one of our patients also had severe respiratory distress on presentation. Table 1 summarizes the clinical characteristic of these patients.

CSF findings

In patients with SARS-COV-2 CNS infections, complete blood count findings may show leukocytosis with neutrophilic predominance, lower lymphocyte count and thrombocytopenia.⁴ This was not consistently observed in our cases. Previous studies have reported patients with neurologic symptoms and a positive CSF RT-PCR SARS-COV-2

but had negative nasopharyngeal swabs which may describe the neuro-invasive potential of the virus in the absence of pulmonary infection.⁶ In our series, however, no CSF RT-PCR was done as this was not yet available in our setting at the time of the study. However, all of them revealed positive nasopharyngeal swabs. This is one of the limitations of this study.

Neuroimaging studies

Cranial MRI findings in patients with SARS-COV-2 infection and meningoencephalitis showed diverse findings but hyperintensities along the wall of the inferior horn of the right lateral ventricle in DWI studies, and hyperintense signal changes in the right mesial temporal lobe and hippocampus in FLAIR studies was noted by a study by Murogoshi in 2020.⁶ Cranial CT scan may show symmetric hypoattenuation of the bilateral median thalami with normal basilar and proximal posterior cerebral arteries on CT angiogram.^{6,8} Only Case 2 had an abnormal MRI finding similar to those previously reported cases. Table 2 summarizes our neuroimaging findings

Management

In COVID positive patients who developed seizures, it is reasonable and necessary to start an antiepileptic drug.⁹ According to this study, Levetiracetam is an optimal AED for these patients. Tapering after 6 weeks, then discontinuing after 1-2 weeks is also recommended. Our patients were given appropriate antibiotics as well as Azithromycin and zinc sulfate during their admission. All of our patients were started on Levetiracetam and were maintained on this AED until discharge.

LIMITATIONS OF THE STUDY

Neurodiagnostic procedures were not completed for our patients due to the lack of facilities during the early part of this pandemic. CSF RT-PCR was also not documented for our patients as this test is not available in our institution.

RECOMMENDATIONS

As of this writing, there are no established guidelines for the identification and treatment of COVID-19 CNS infections. Further studies on the neurologic presentation and clinical manifestations of this infection is recommended. A test for CSF

COVID (RT-PCR) which is now readily available will also be beneficial.¹¹

REFERENCES:

1. Yan-Chao L, Wan-Zhu Bai, Tsutomu Hashikawa, the neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients
2. Yeshun Wu, Xiaolin Xu, Zijun Chen, Jiahao Duan, et al. Nervous System Involvement after infection with COVID-19 and Other Coronaviruses. (March 2020) Brain, Behavior and Immunity, <https://doi.org/10.1016/j.bbi.2020.03.031>
3. Xiaoxia Lu et al. SARS-CoV-2 Infection in Children. (April 2020) The New England Journal of Medicine, Volume 382;17; Accessed May 8, 2020
4. Ling M. Huijuan J. Mengdie W. et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China, JAMA Neurology, 2020 Published online: April 10, 2020
5. Li et al. Neuroinvasive potential of SARS-CoV-2 plays a role in the respiratory failure of COVID19 patients. Journal of Medical Virology (Feb 2020)
6. Morugoshi T, Harii N, Goto J, et al. A first case of meningitis and encephalitis associated with SARS-Coronavirus-2. 2020. International Journal of Infectious Disease. Published online: March 25, 2020
7. Asadi-Pooya AA., Leila Simani, Seizures associated with coronavirus infections. Seizure. 2020 Jul; 79:49-52.
8. Pojadji N. MD, Gassan Shashin MD, Noujaim D., MD et. al. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. Radiology. <https://pubs.rsna.org/doi/10.1148/radiol.2020201187> March 31, 2020
9. Oxley et al. Large Vessel Strokes in the young as a Presenting Feature of COVID-19. The New England Journal of Medicine, 2020 Published online: April 29, 2020
10. Dugue R. Cay-Martinez K. Thakur K et al. Neurologic Manifestations in an Infant with COVID-19. (2020) Neurology Accessed April 24, 2020
11. 2020. McIntosh K. Coronavirus disease 2019 (COVID-19).. Available at <https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19>

Table 1. CSF Findings of cases

	CASE 1	CASE 2	CASE 3
Color	Colorless	Colorless	Colorless
Transparency	Clear	Clear	Clear
RBC	3 (100% crenated)	3 (70% crenated)	None
WBC	0	7 (100% lymphocytes)	None
Protein (g/L)	0.1	0.1	0.3
Sugar (mmol/L)	3.87	3.5	2.77
Ratio	57%	49.6%	48%
Culture	Negative	Negative	Negative
HSV 1 and 2	Not done	Negative	Negative
Jap B	Not done	Negative	Negative

Table 2. Neuroimaging Findings of Patients

	Case 1	Case 2	Case 3
Cranial CT scan			Normal
Cranial MRI		Abnormal thalamic intensities and subtle T2/FLAIR hyperintensities in the cortex of the left temporoparietal lobe with gyral enhancement	