ORIGINAL ARTICLE

COVID-19-Associated Neurological Complications in Children

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ABSTRACT

Objectives

Neurological manifestations of Severe Acute Respiratory Syndrome coronavirus-2 have been well documented in adults during and after infection with the virus as well as after vaccination. The incidence of severe neurological symptoms among children is very low. This study aimed to analyze the varied neurological manifestations after COVID-19 infection among children and give a report on a single-center experience with these severe neurological symptoms

Materials & Methods

Case records of patients less than 18 years admitted between July 2021 to December 2022 with neurological manifestations and COVID-19 infection or with elevated COVID-19 antibodies after exclusion of other etiological diagnosis were analyzed.

Results

There were 10 cases in the age range of 1-15 years. All the cases had elevated COVID-19 antibodies with history of contact 2-3 weeks prior except one who was positive for COVID-19 infection. Two cases presented with acute ascending paralysis suggestive of Guillain-Barre syndrome. Four cases presented with features of encephalopathy with clinical presentation fulfilling the criteria of Multisystem inflammatory syndrome in children. One case presented with fever and focal seizures with MRI showing sagittal sinus thrombosis, and one presented with fever and altered sensorium with MRI showing leukoencephalopathy. One child had cerebral mucormycosis without any evidence of immunosuppression. There was one child with features of encephalopathy with active COVID-19 infection.

Conclusion

The varied presentation highlights the central and peripheral nervous system involvement by the virus in the pediatric population. It also emphasizes the need to investigate for COVID-19 in children presenting with these complaints during the pandemic.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was first reported in China in 2019. Since then, multiple studies have been published regarding its epidemiologic aspects, including clinical manifestations and outcomes. Initially thought to have a predominant respiratory involvement, subsequent findings have highlighted the systemic effects of the virus, including on the nervous system.

The neurological manifestations in adults, specifically in the post-acute phase of the infection, have ranged from cerebrovascular stroke, encephalitis, and mood disorders.[1] Among children, only 1% presented with severe neurologic symptoms like encephalopathy, seizures, and meningeal signs, with cases like Guillain-Barre Syndrome (GBS), hemorrhage, cranial nerve palsy, and vision problems being less common[2]. Children presenting with Multi System Inflammatory Syndrome in Children (MIS-C) had a higher probability of neurologic symptoms. [3, 4] There is little available literature on the spectrum of neurological manifestations in the pediatric population from developing countries. This study presents here a single-center experience from a tertiary hospital in Southeast Asia concerning neurological complications in children infected with SARS-CoV-2 infection or with a history of infection in the recent past.

Materials & Methods

The present study analyzed case records of patients less than 18 years old admitted between July 2021 and December 2022 with neurological manifestations and COVID-19 infection or with elevated COVID-19 antibodies after the exclusion of another etiological diagnosis. Details regarding symptoms at admission, neurological examination findings, Electroencephalogram (EEG) and neuroimaging results, final diagnosis, and outcome of all the patients were recorded and analyzed. Written informed consent was obtained from the patients' caregivers.

Results

Ten cases were reported with varied neurological manifestations following infection with SARS-CoV-2. One patient tested positive for SARS-CoV-2 real-time polymerase chain reaction (RT-PCR), while the rest tested negative. However, they all had elevated COVID-19 IgG antibodies. They either had a history of symptoms suggestive of infection with SARS-CoV-2 or had a history of contact with patients infected with the virus 3-6 weeks prior to illness.

Case 1:

An 8-year-old male child presented with a history of weakness of bilateral lower limbs for one week, gradually progressing to involve both upper limbs. On examination, he had normal vitals. Cranial nerve examination was normal, and his power in the proximal and distal groups of muscles in both upper and lower limbs was 4/5 and 3/5, respectively. Deep tendon reflexes (DTRs) were depressed (1+). In view of the acute onset of flaccid paresis of all four limbs, a provisional diagnosis of GBS was made. A nerve conduction study (NCS) showed acute motor axonal polyneuropathy. Cerebrospinal fluid (CSF) analysis was normal. Magnetic resonance imaging (MRI) of the spine was normal. COVID-19 antibodies were significantly elevated, and inflammatory markers were normal (Table 1). The child was given intravenous immunoglobulin (IVIG) infusion of 400 mg/kg/day daily for five days. The child improved

gradually with a modified Rankin Score (mRS) for a neurologic disability of 1 at follow-up after one month.

Case 2:

A 10-year-old male child presented with a history of weakness in both lower limbs for six days, gradually progressing to involve both upper limbs. He gave a history of fever three weeks prior to the onset of weakness. He also had a history of difficulty swallowing solids with a weak cough. On examination, he was alert with a Glasgow coma score (GCS) of 15/15 with mild tachypnea and a weak cough with a single breath count of 10. Neurological examination showed hypotonia with a power of 1/5 in a proximal and distal group of muscles in lower limbs and 2/5 in upper limbs with absent DTRs. In view of impending respiratory muscle paralysis, the child was electively intubated. CSF analysis showed albuminocytological dissociation (Table 1) suggestive of GBS. NCS revealed generalized sensorimotor demyelinating neuropathy with secondary axonal changes. COVID-19 antibodies were positive and inflammatory markers were elevated. He also had neuropathic pain, for which he was treated with gabapentin. He was treated with IVIG, after which he showed significant motor improvement. He was extubated after three days of ventilation and discharged with a mRS of 2.

Case 3:

A 13-year-old boy presented with a history of fever of ten days duration, vomiting for six days, and five episodes of generalized tonic-clonic seizures in the last three days. On admission, his vitals were normal. He had a GCS of 10/15 with hypertonia of all four limbs, brisk DTRs, and bilateral extensor plantar. Investigations revealed thrombocytopenia and leucopenia with raised C-reactive protein (CRP). CSF routine analysis and viral workup were normal. Dengue serology, Widal and Weil Felix tests were negative. Fundoscopy showed Grade 1 papilledema, and MRI brain showed diffuse gyral thickening on FLAIR (Fluid-attenuated inversion recovery) with partially effaced sulci in frontal, temporal, and occipital areas (Figure1). COVID-19 antibodies were significantly elevated with raised

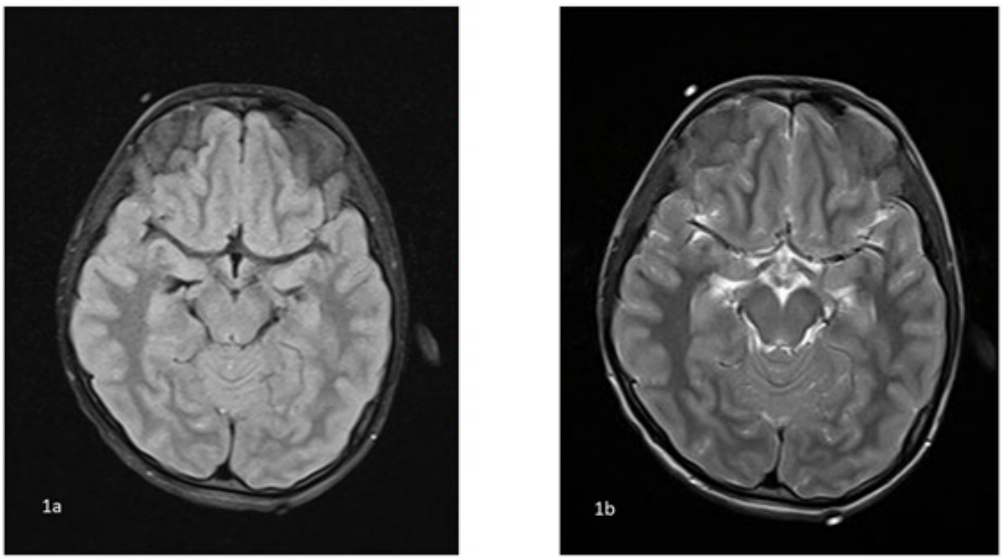

Figure 1. Brain Magnetic Resonance Imaging (MRI) of case 3. Axial FLAIR (Fluid attenuated inversion recovery) (1a) and T2 weighted sequence (1b) showing effacement of sulci with gyral thickening in temporal and occipital lobes

inflammatory markers (Table 1), fulfilling the criteria for MIS-C. 2D Echocardiography was normal. In view of persistent fever with raised inflammatory markers and positive antibodies to

Table 1. Demographic characteristics and investigation findings of the cases

Case no	Age (in yrs), gender	Investigations	Electrophysiologic findings	Neuroimaging findings	Diagnosis
1	8, male	COVID-19 antibodies- 236 units/mL, CSF analysis- normal	NCS -bilateral motor axonal polyneuropathy	MRI spine - Normal	GBS
2	10, male	COVID-19 antibodies- 405units/ml CSF cell count - 2 lymphocytes, protein - 979 mg/dl (Albuminocytological dissociation), LDH 215U/L, d-Dimer 1.83mcg/mL.	NCV -generalized sensorimotor demyelinating neuropathy with secondary axonal changes	Not done	GBS
3	13, male	COVID -19 antibodies- 207 units/mL CSF analysis- normal	EEG (recovery period)- normal	MRI brain- Diffuse gyral thickening in temporal and occipital lobes CT brain- areas of hypodensities in subcortical white matter	MIS-C with encephalopathy
4	3, female	COVID-19 antibodies-905 units/mL Inflammatory markers-LDH 288units/l, CRP-34mg/dL, ferritin-118ng/ml, D dimer >8mcg/mL. ECHO- Dilated coronaries with Myocarditis		MRI brain-Extensive bilateral cerebral subcortical white matter hyperintensities extending to striatal and corpus callosal white matter tract with punctate focus of diffusion restriction in the body of corpus callosum	MIS-C with encephalopathy
5	1, female	COVID-19 antibodies-787units/ml, CSF- 122cells/cumm, 89% lymphocytes, LDH-324IU/ml, Ferritin- 181.5 ng/ml, D- dimer-3.69mcg/ml	EEG- background slowing with frontotemporal beta waves	MRI brain -Bilateral hyperintensities in the basal ganglia, caudate and midbrain with left temporal lobe enhancement	MIS-C with encephalopathy
6	10, female	COVID-19 antibodies-290 units/ml, CSF analysis- normal Ferritin- 335ng/ml, LDH- 771U/L	EEG- Grade 2 encephalopathy,	MRI brain (day1) - Thin pachymeningeal enhancement in bilateral frontal and parietal regions MRI brain with contrast(day10) - thrombosis of superior sagittal sinus and its tributaries MRI (3 months)- complete resolution of thrombus.	Cerebral venous sinus thrombosis
7	2, male	COVID-19 antibodies- 440 units/mL Inflammatory markers-LDH-641U/L, Ferritin -82 ng/mL, d Dimer 3.72mcg/mL. CSF- normal	EEG- normal	MRI brain: Hyperintensity of the deep white matter of bilateral temporal, frontal lobes and periventricular white matter and splenium of corpus callosum (Figure 5). MR spectroscopy-lactate peak	Leukoencephalopathy
8	6, female	COVID antibodies- 391.7U/ml CSF- cell count-705 with 60%neutrophils , protein-23.8mg/dl, glucose-41mg/dl	EEG- bihemispheric background slowing with continuous left hemispheric spike and slow-wave discharges	CT brain- hypodense lesion in right parietal lobe MRI brain - multiple bilateral cerebral and solitary left cerebellar white matter tumefactive lesions.	Cerebral mucormycosis
9	15, female	Ferritin >1000ng/ml. ECHO- left ventricular dysfunction,	EEG showed intermittent left frontocentral sharp	MRI- Acute corpus callosal infarcts. Bilateral symmetrical	MIS-C with encephalopathy

Continued Table 1.

		LDH-618U/L,	wave discharges with bi frontal slow wave	T2/ FLAIR hyperintensities in capsule ganglionic regions with subtle diffuse gyral hyperintensity in both cerebral hemispheres MR venogram- normal	
10	14, male	COVID RT PCR-positive , Platelet count -99,000/mm^3 NLR- 7.3, CRP-17.71mg/l, LDH - 498U/L, ferritin >1000 ng /ml , interleukin-6 levels - 67.74 pg/ml, plasma d-dimer level - 3.38 mcg/ml , procalcitonin -1.41ng/ml		CT brain- normal	COVID-19 with encephalopathy

GBS- Guillain Barre Syndrome, MIS-C- Multisystem inflammatory syndrome in children

SARS-CoV-2, after excluding other infectious causes, a diagnosis of MIS-C with encephalopathy was considered and was given IVIG as per protocol. Pulse doses of methylprednisolone and aspirin were started. The child was electively intubated after four days, given worsening GCS and recurrent seizure episodes. The child's sensorium improved gradually, and he was extubated after four days. EEG done during the recovery period was normal. He was discharged on a tapering dose of steroids with an mRS of 4.

Case 4:

A 3-year-old female child presented with fever and vomiting of three days duration and altered sensorium of 1-day duration. On examination, she had a GCS of 8/15 and hypotension, requiring inotropic support and mechanical ventilation. Investigations revealed pancytopenia with elevated inflammatory markers and positive COVID-19 antibodies (Table 1). The echocardiogram showed dilated coronaries and features of myocarditis. MRI showed extensive bilateral cerebral subcortical white matter hyperintensities extending to striatal and corpus callosal white matter (Figure 2). A diagnosis of MIS-C with encephalopathy and myocarditis was considered as it satisfied the MIS-C criteria. The child was treated with IVIG and aspirin. On day 5 of admission, the child had seizures and was started on antiepileptics. A gradual improvement was observed in consciousness by day 7, and she was weaned off the ventilator. She had regression of speech with motor sequelae in the form of unsteady gait and hypotonia in her lower limbs during her stay. At discharge, she had ataxia and speech impairment with mRS of 4. On follow-up after three months, she was able to walk without assistance but continued to have expressive language impairment.

Case 5:

A 1-year-old female child presented with fever of five days and seizures and paucity of limb movements of 1-day duration on examination had low GCS of 7/15, generalized hypotonia, and brisk DTRs. The child required ventilator support for low GCS for ten days and inotropic support for hypotension. EEG showed background slowing with frontotemporal beta waves. MRI brain showed hyperintensity in bilateral basal ganglia and midbrain in T2 and FLAIR sequences with diffusion restriction in the corresponding areas (Figure 3). CSF analysis showed lymphocytic pleocytosis and was negative for herpes simplex and Japanese encephalitis virus.

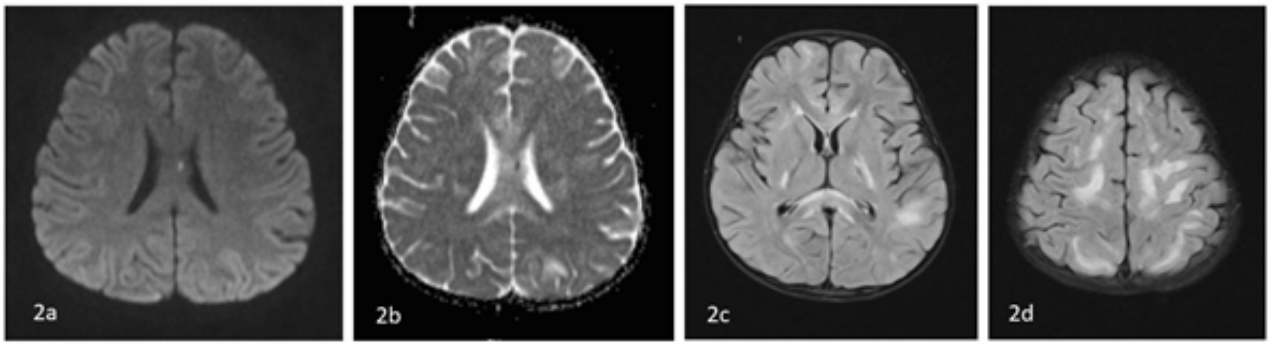

Figure 2. Brain Magnetic Resonance Imaging (MRI) of case 4. Axial DWI (2a) and corresponding ADC (2b) image shows tiny focus of diffusion restriction in the corpus callosum. Axial FLAIR (Fluid attenuated inversion recovery) images (2c,2 d) show hyperintensity in bilateral internal capsule, corpus callosum and subcortical white matter

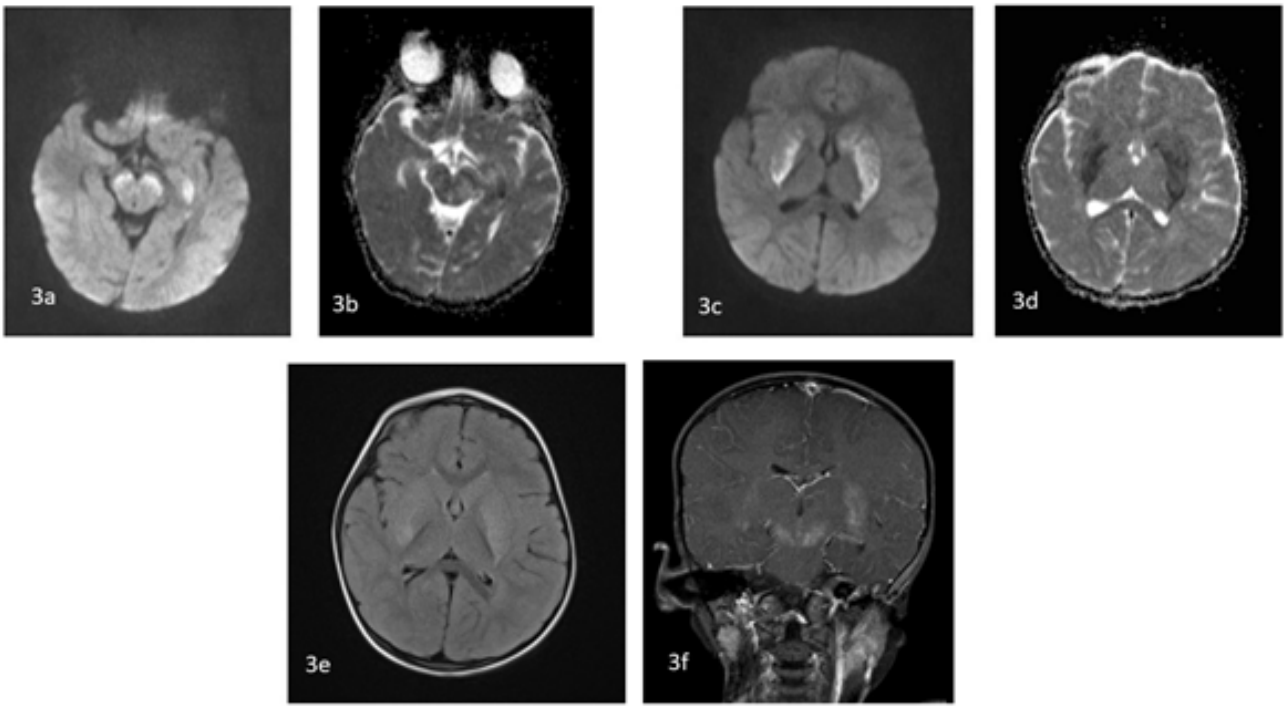

Figure 3. Brain Magnetic Resonance Imaging (MRI) of case 5. Axial DWI (3a, 3c) and corresponding ADC (3b, 3d) image show diffusion restriction in the substantia nigra, left temporal lobe and bilateral basal ganglia. Axial FLAIR (Fluid attenuated inversion recovery) image (3e) shows hyperintensity in bilateral basal ganglia. T1 weighted axial image post gadolinium contrast shows enhancement in bilateral basal ganglia and substantia nigra

COVID-19 (Table 1) antibodies were positive for thrombocytosis and raised inflammatory markers satisfying the MIS-C criteria, and she was treated with IVIG and aspirin. She was discharged with an mRS of 5 with residual sequelae of spasticity and language regression.

Case 6:

A 10-year-old girl presented with fever for one week and multiple episodes of left focal seizures with secondary generalization and altered sensorium for two days. She had no history of seizures. On examination, vitals were normal, and the child had a GCS of 10/15. Neurologic examination was unremarkable, and no meningeal signs existed. EEG showed diffuse theta slowing. MRI brain

showed thin pachymeningeal enhancement in bilateral frontal and parietal regions (Figure 4a and b). CSF cell count and biochemistry were normal, and PCR analysis for the Japanese Encephalitis virus, Herpes Simplex virus, and fungal culture were negative. Serum aquaporin-4 antibodies and myelin oligodendrocyte glycoprotein (MOG) IgG antibodies were negative. In view of persistent seizures, disorientation, irrelevant speech, and emotional lability, an MRI brain was repeated, showing a filling defect in the superior sagittal sinus suggestive of thrombosis of the superior sagittal sinus and its tributaries (Figure 4d). Repeat EEG showed focal epileptiform discharges. Echocardiogram was normal. Workup for other causes of cerebral venous thrombosis was negative, including antinuclear antibody, antiphospholipid antibody, and serum homocysteine level was normal. COVID-19 antibodies were significantly elevated with raised inflammatory markers (Table 1). The child was started on antiepileptics along with steroids and anticoagulants. The child improved gradually and was discharged on anticonvulsants and anticoagulants with mRS of 1. On follow-up, a repeat MRI showed complete resolution of the thrombus after three months, and anticoagulants were stopped. However, the child continues to be on antiepileptic drugs in view of persistent seizures.

Case 7:

A 2-year-old male child with no significant perinatal history and isolated speech delay came with complaints of fever for five days and multiple episodes of posturing for one day. On examination, the child was drowsy with a GCS of 10/15 had decerebrate posturing with brisk reflexes and extensor plantar reflex. Initial investigations revealed mild anemia and elevated CRP. The workup for infective etiology (dengue, typhoid, malaria) was negative. CSF analysis showed normal cytology and biochemistry. CSF PCR for HSV was negative, and serum MOG antibodies were negative. EEG showed diffuse theta slowing of the background MRI brain showed hyperintensities involving the deep white matter of bilateral temporal, frontal lobes and periventricular white matter and splenium of corpus callosum suggestive of leukoencephalopathy on T2 and FLAIR images along with hyperintense signal in the right

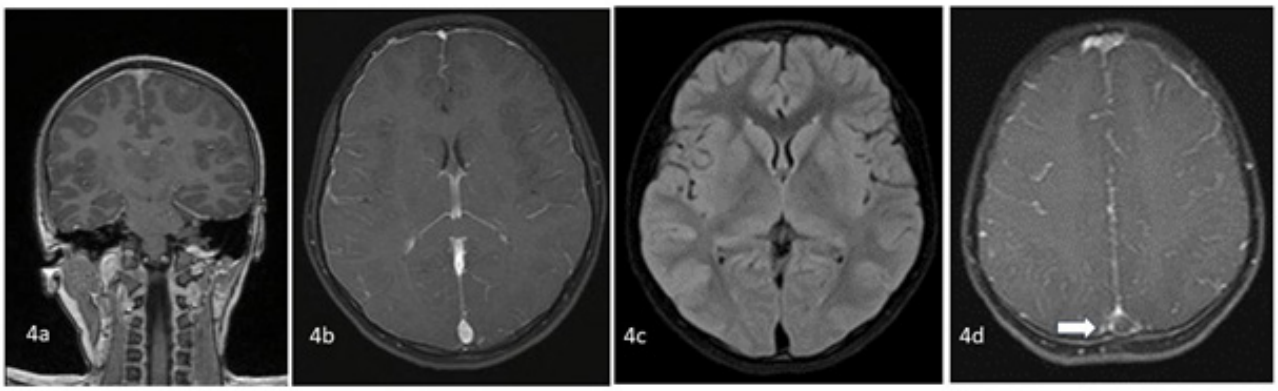

Figure 4. Brain MRI of case 6. T1 weighted coronal (4a) and axial image (4b) with contrast revealing the pachymeningeal enhancement. Axial FLAIR image (4c) demonstrating the gyral edema with effacement of sulci. Repeat MRI brain T1 weighted contrast axial image (4d) showing a filling defect (arrow) in superior sagittal sinus

thalamus (Figure 5). These lesions showed diffusion restriction. The child was treated with intravenous steroids and anticoagulants. During the course, the child had intermittent episodes of dystonia and was treated with trihexyphenidyl. Cardiac evaluation was normal. Tandem mass spectrometry done to rule out inborn error of metabolism was normal. MR spectroscopy showed a lactate peak, arterial blood gas showed elevated lactate levels, and hence, a diagnosis of leukodystrophy due to possible mitochondrial etiology was made, and the mitochondrial cocktail was started. The ophthalmologic evaluation done was normal. Geneticist opinion was taken, and whole exome sequencing and mitochondrial genome sequencing were sent, with negative reports. COVID-19 antibody titers were raised (Table 1). Inflammatory markers were elevated; hence, the possibility of MIS-C was finally considered after ruling out other infectious, immune-mediated, and genetic causes. The child improved gradually with no recurrence of seizures and resolution of the dystonia and was discharged with an mRS of 4. He has been on physiotherapy, antiseizure medications, trihexyphenidyl, and baclofen. At follow-up after six months, he has cognitive improvement with recovery of the language functions; he has residual spasticity in all four limbs and can walk independently with orthotic support.

Case 8:

A 6-year-old female child was admitted with a fever of one week duration, focal seizures, and left hemiparesis. MRI brain revealed multiple hyperintense lesions in bilateral cerebral

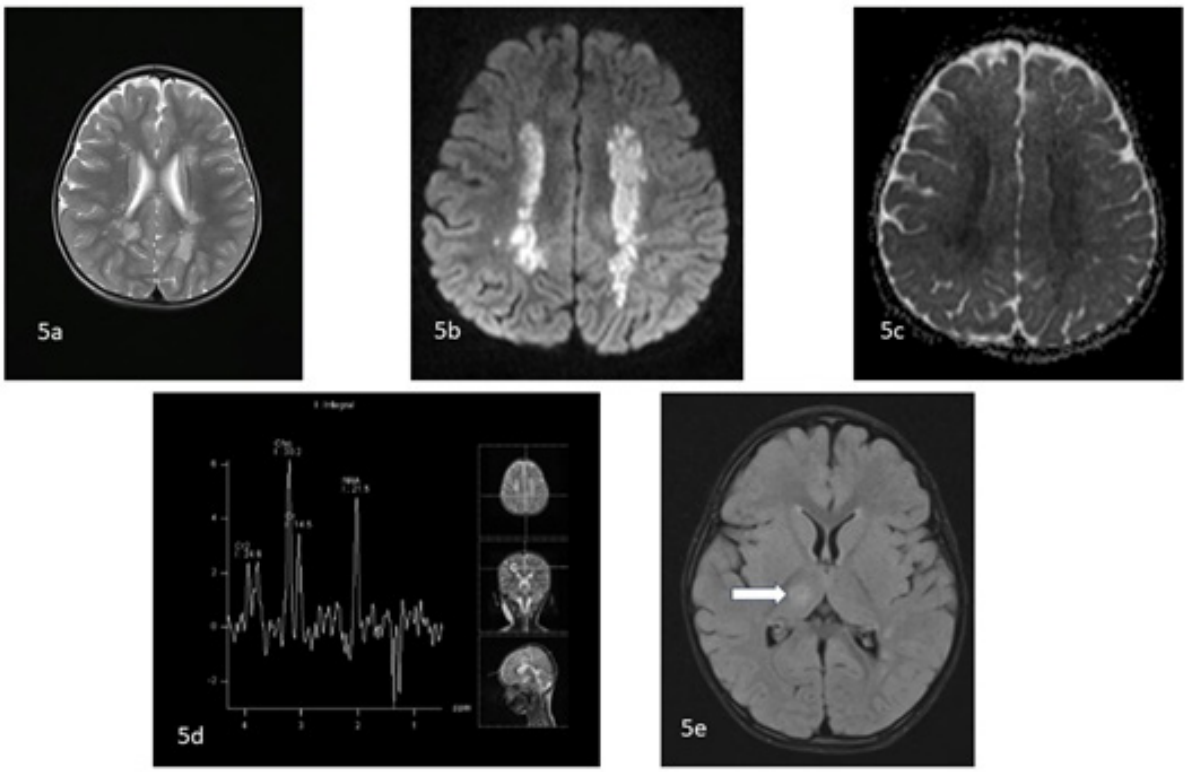

Figure 5. Brain MRI of case 7. T2 weighted axial image (5a) shows hyperintensity in periventricular white matter. Diffusion weighted image (DWI)(5b) and corresponding ADC (apparent diffusion coefficient) sequence (5c) show diffusion restriction in the white matter in centrum semiovale with reversal. MRS (magnetic resonance spectrometry) (5d) shows lactate peak. Axial FLAIR sequence (5e) shows right thalamic hyperintensity

hemispheres and a single large ring-enhancing lesion in the right peritrigonal region on contrast, indicating a cerebral abscess. A stereotactic brain biopsy, done to identify the causative organism, was diagnostic of necrotizing fungal abscess. Workup for immunodeficiency was negative. This child had no predisposing cause for developing a fungal cerebral abscess on detailed investigations. However, the COVID-19 antibody titers were found to be elevated (Table 1) with a history of recent respiratory infection. Whole body PET CT revealed fungal infection in the kidneys and lungs. The child was treated with antifungals and antiepileptic medications for a prolonged duration of one year and recovered completely. Details of the case have been published [5].

Case 9:

A 15-year-old girl presented with a fever of four days and left hemiparesis with altered sensorium of 1-day duration. She had petechial rash and icterus with tender hepatomegaly and a GCS of 10/15. Investigations revealed thrombocytopenia with hyperbilirubinemia and normal liver enzymes. Infective workup for dengue fever, enteric fever, rickettsial fever, and viral hepatitis markers was negative. She had an episode of prolonged convulsion in the hospital on the first day and was started on antiseizure medications phenytoin and levetiracetam. She was ventilated in view of low GCS and required inotropes for treating hypotension. EEG showed intermittent left frontocentral sharp wave discharges with a bifrontal slow wave. MRI brain showed acute corpus callosal infarcts with symmetrical T2/FLAIR hyperintensities in capsuloganglionic regions with subtle diffuse gyral hyperintensity in both cerebral hemispheres. MR venogram was normal (Figure 9). Further investigations showed raised inflammatory markers (Table 1). The echocardiogram showed moderate left ventricular dysfunction, satisfying the MIS-C criteria. A diagnosis of MIS-C with encephalopathy was made, and she was treated with IVIG, after which she was extubated on day 8. A repeat MRI on day 10 showed infarcts in the corpus callosum and posterior limb. Her hemiparesis improved after two weeks of admission, and she was discharged with an mRS of 2. She has no residual deficit at follow-up after one year.

Case 10:

A 14-year-old male child presented with fever, headache, and abdominal pain of three days

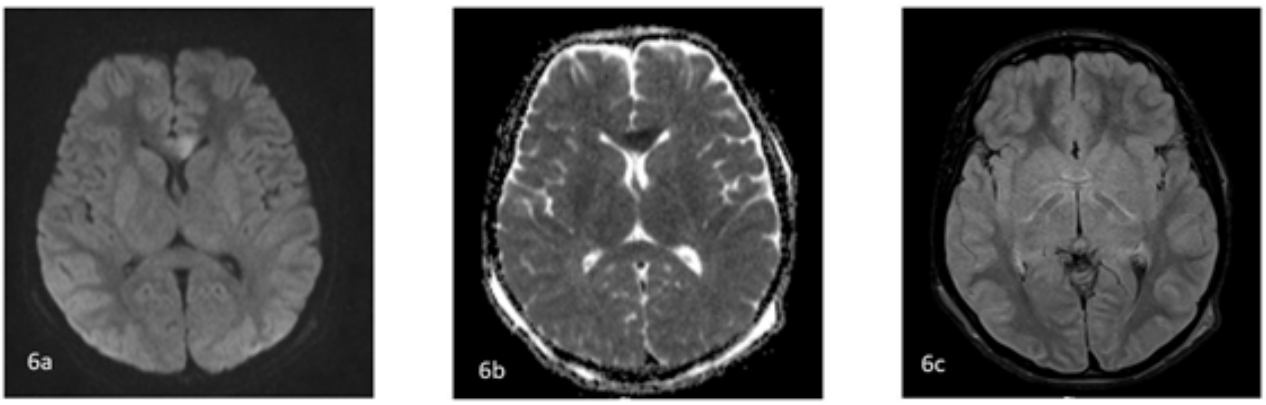

Figure 6. Brain Magnetic Resonance Imaging (MRI) of case 9. Axial DWI (6a) and corresponding ADC (6b) image show diffusion restriction in the genu of the corpus callosum. Axial FLAIR (Fluid attenuated inversion recovery) image (6c) shows bilateral symmetrical hyperintensities in capsule ganglionic regions with subtle diffuse gyral hyperintensity in both cerebral hemispheres

duration and altered sensorium since morning on the day of admission. On examination, he was febrile, irritable, and agitated, with a GCS of 11/15. He had a petechial rash all over his body. His DTRs were brisk with extensor plantar response. A provisional diagnosis of acute febrile encephalopathy, probably secondary to dengue infection, was made.

His initial blood investigations showed thrombocytopenia, negative serology for Dengue virus, high neutrophil-lymphocyte ratio, and elevated inflammatory markers (Table 1). His electrolytes and liver function tests were normal. Considering the presentation during the pandemic, his nasopharyngeal swab was sent for COVID-19 RT-PCR, which was positive. CT brain and CSF analysis were normal. He was treated for severe COVID-19 infection with encephalopathy with intravenous remdesivir for five days. His sensorium gradually improved, the thrombocytopenia resolved, and he was discharged with mRS of 2.

Discussion

Although SARS CoV-2 is a virus causing predominantly respiratory manifestations, its affection for the nervous system has been widely documented in children, as well as adults. The neurological symptoms have been protean, raising varied postulations and explaining the mechanism of neurotropism. The most popular of the theories is the entry of the virus through the ACE receptor present in the respiratory, as well as in the glial cells of the central nervous system and spinal neurons. The virus could also possibly enter peripherally through the nerves and have a retrograde entry into the central nervous system. The other postulated mechanism is immune-mediated damage. This study describes the varied neurological manifestations in the post-COVID-19 phase with both peripheral and central nervous system involvement.

Concerning peripheral nervous system involvement, we had two cases of GBS. GBS is a post-infectious polyneuropathy seen following viral infections. Cases of GBS have also been documented with newer viruses like Zikavirus.[6,7] During the present pandemic, cases of GBS in adults have been reported during the post-infectious or para-infectiousperiod,[8,9] as well as post-vaccination.[10] Similarly, few reported cases exist in children during the acute phase [11] of infection and the post-infectious period.[12] The cases of GBS in our center presented in the post-infection phase as demonstrated by the presence of antibodies against coronavirus. Both the cases presented with the typical ascending paralysis with areflexia, and the CSF analysis demonstrated albuminocytological dissociation in one of them. The NCS in one case showed acute motor axonal neuropathy and demyelinating motor sensory polyneuropathy in the other. An Egyptian study reported demyelination in all of the 14 children who presented with polyneuropathy.[13] Another review of 35 children with GBS after COVID-19 reported acute motor axonal neuropathy (AMAN), acute inflammatory demyelinating polyneuropathy (AIDP), Miller Fisher syndrome (MFS), MFS with posterior reversible encephalopathy syndrome (PRES), inexcitable as the different variants[14]. GBS, as a post-infectious complication, could be explained by the production of antibodies to the surface glycoprotein of the virus, which could also affect certain similar components of the peripheral nerves due to molecular mimicry.[15]

The rest of the eight cases involved the central nervous system. We had three cases with

encephalopathy fulfilling the MIS-C criteria. Neurological manifestations in MIS-C can range from muscle weakness and headache to encephalopathy, brainstem, and cerebellar signs.[16] Olivotto et al.[17] found that MIS-C can present with rapid onset encephalopathy, with EEG studies showing diffuse slowing with periodic posterior complexes. Neuroimaging found signal changes in the splenium of the corpus callosum.[16] The MRI in our cases involved the occipital and temporal lobe and corpus callosum. One of the possible explanations for the encephalopathy could be immune-mediated neuronal damage due to the cytokine storm seen with MISC. The release of IL-6 could further aggravate this neuronal damage.[18] CSF studies showed lymphocytic pleocytosis in one case but was normal in another, as reported in other case reports.[15, 19] The corpus callosum has a high density of cytokine and glutamate receptors, making it vulnerable to the cytokine storm[20]. The callosal dysfunction, in turn, enables T cells to cross the blood-brain barrier and cause inflammation and edema[21.] This probably explains the corpus callosum's involvement in many cases. One of the patients presented with focal weakness and, on MRI, was found to have cerebral venous sinus thrombosis. Cerebral venous sinus thrombosis has been reported after COVID-19 infection in adults.[22] One of the proposed mechanisms of hypercoagulability could be the cytokine storm and the virus-induced damage to the endothelial cells.[23] Infection with the virus can cause a predisposition to development of neutrophil extracellular traps, which could also contribute to thrombosis[24].

We had one case with MRI showing leucoencephalopathy. There are case reports in adults with leucoencephalopathy and microhemorrhages on neuroimaging.[25 ,26] This was attributed to hypoxemia encountered during the acute phase of COVID-19 infection. However, one reported adult case existed with leucoencephalopathy without hypoxia. The authors have proposed that the penetration of the blood-brain barrier by the virus with a resultant inflammatory response is the likely mechanism of pathogenesis [27]. Without any history of hypoxia and with elevated inflammatory markers, the immunological mechanism probably seems to be the cause in our case, too.

The pandemic saw an increase in the cases of mucormycosis among adults, specifically those with diabetes mellitus or those on corticosteroid therapy[28]. Mucor mycosis in children is rare and generally presents as rhino-orbito-cerebral mucormycosis among those who are the immunocompromised. However, our case presented with cerebral mucormycosis without evidence of immunosuppression and involvement of the paranasal sinuses and orbit.

One case was diagnosed with encephalopathy during the active COVID-19 infection. A meta-analysis done by Panda et al.[2] found that in 41 pediatric cases presenting with definite neurological complications, encephalopathy was the commonest seen in 25 cases, seizures were seen in 12, and meningeal signs were observed in 17. CSF for SARS-Cov-2 had been negative in most cases in children and adults, as was seen in our case.

These manifestations in the post-COVID-19 phase, as evidenced by COVID-19 antibodies and the remarkable improvement with IVIG and steroids, strongly suggest an immunological mechanism. This report is among the first few to document such varied neurological complications in a single center of a developing country. This is also the first to report leucoencephalopathy

in a child post-COVID-19. Besides, this report highlights that these immune-mediated sequelae can involve the central and peripheral nervous systems.

In Conclusion

In this study, children presented with GBS, encephalopathy, cerebral venous thrombosis, cerebral mucor mycosis, and leukoencephalopathy following COVID-19 infection. COVID-19 infection should be considered a possibility while treating such cases, primarily during the pandemic.

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Authors' Contribution

Sangeetha S and Divya N - conceptualisaton of the study, data collection and drafting the manuscript, Divya N- interpretation of MRI, Sunil Kumar BM, Somashekar AR, Chandrika R- critical revision of manuscript. All authors approved the final manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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