Neurological and Neuroradiological Patterns with COVID-19 Infection in Children: A Single Institutional Study

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Abstract

Background Varied neurological manifestations in pediatric patients with coronavirus disease 2019 (COVID-19) have been increasingly reported from all across the world in the scientific literature.

Objective We aimed to evaluate pediatric cases with neurological symptoms and neuroimaging findings with COVID-19 infection in our hospital.

Materials and Methods Children from 0 to 12 years with laboratory evidence of COVID-19 infection and acute neurological manifestations within 3 months, who have undergone magnetic resonance imaging (MRI) were included in the study. We categorized them based on neurological findings into four groups: acute encephalitis syndrome (AES), acute flaccid paralysis (AFP), cerebrovascular event/stroke, and miscellaneous consisting of acute seizures without encephalopathy.

Results A total of 19 children with neurological manifestations related to COVID-19 infection were included in the study. AES was the most common neurological syndrome seen in 47.36%, followed by AFP in 26.31% and cardiovascular event/stroke in 21.05%. Seizure was the most common neurological symptom in 62.15%, followed by encephalopathy in 42.10% and AFP in 26.31%. On neuroimaging, pattern observed were immune-mediated cauda equina nerve roots enhancement in 26.31% or acute disseminated encephalitis in 5.26%, small acute infarcts, hippocampal, and bilateral thalamic signal changes seen in 21.05% each, microhemorrhages and leukoencephalopathy in 15.78%, and coinfection in 5.26%.

Conclusion In our study, seizures and encephalopathy were the most common neurological symptoms with COVID-19 infection. Postinfectious immune-mediated cauda equina nerve root enhancement or acute demyelinating encephalomyelitis–like brain imaging, followed by small acute infarcts and hippocampal/thalamic signal changes were most common imaging patterns. We found overlapping neurological and MRI patterns in many children, suggesting that various pathophysiological mechanisms act individually or synergistically.
Introduction

Coronavirus disease 2019 (COVID-19) is a potentially serious infection caused by a novel coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 virus was first reported in Wuhan, China, in December 2019, and in March 2020, the World Health Organization (WHO) officially declared COVID-19 as a global pandemic.¹

The majority of pediatric patients are asymptomatic carriers or suffer from mild-to-moderate respiratory symptoms. As the pandemic progressed, evidence suggested that COVID-19 viral illness not only is limited to the respiratory symptoms. As the pandemic progressed, evidence suggested that COVID-19 viral infection or if alternative diagnosis was considered. The most common COVID-19 manifestations in children were fever, cough, and respiratory distress. Other symptoms included fever, chills, headache, myalgia, and anosmia. The severity of clinical presentation varied widely. Some children experienced severe respiratory symptoms, including hypoxemia, respiratory failure, and multiorgan dysfunction.¹

The aim of our study is to describe neurological and neuromaging findings in children with COVID-19 infection in our tertiary care pediatric hospital.

Methods and Materials

As this was a retrospective study, our institutional review board waived the need for written informed consent and also approved review of patients' imaging studies and medical records. Patient confidentiality was maintained in accordance with HIPAA guidelines.

Inclusion criteria: Children aged 0 to 12 years with laboratory evidence of COVID-19 infection and neurological symptoms who have undergone magnetic resonance imaging (MRI) scans were included in the study. Laboratory evidence of COVID-19 infection included: (1) positive reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal/oropharyngeal mucosa or (2) positive antibodies to COVID-19 infection and acute neurological manifestations within 3 months of COVID-19 infection.³ Medical records and imaging studies were retrospectively evaluated from June 2020 to March 2021.

Exclusion criteria: Patients were excluded if neurological or neuroimaging findings could not be attributed to COVID-19 infection or if alternative diagnosis was confirmed. We categorized the patients into four categories⁴ based on neurological syndromes:

1. Acute encephalitic syndrome (AES): A person of any age at any time of year with an acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/or new onset of seizures (excluding simple febrile seizures) (WHO definition⁵).

2. Acute flaccid paralysis (AFP): A clinical syndrome characterized by rapid onset of weakness, including weakness of the muscles of respiration and swallowing, progressing to maximum severity within several days to weeks (WHO definition⁶).

3. Cerebrovascular event/stroke: Rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin (WHO definition⁷,⁸).

4. Miscellaneous: Acute-onset seizures without encephalopathy.

Routine blood investigations including complete hemogram, liver function test, renal function test, and serum electrolytes were done in all cases. Inflammatory markers such as C-reactive protein, D-dimer, interleukin 6, serum ferritin, fibrinogen, two-dimensional echocardiography (2D-ECHO), nerve conduction velocity (NCV), and electroencephalogram (EEG) were done on case-by-case basis. Neuroimaging of all the patients were reviewed in depth. Only one patient underwent follow-up scan. All these MRI scans were categorized into different patterns as described later. Of 19 patients, 11 patients underwent MRI brain with contrast, 1 patient had MRI brain plain, 2 patients underwent both MRI brain and spine with contrast, and 5 patients suspected of Guillain–Barre syndrome (GBS) had spine contrast scans. Imaging protocol included diffusion-weighted imaging (DWI), susceptibility-weighted imaging (SWI), axial T1-weighted (T1W), T2W, fluid-attenuated inversion recovery (FLAIR), and coronal T2W images in all patients who underwent MRI brain. Additional axial T1W and 3D sagittal postcontrast scans were obtained in children who were injected gadolinium-based contrast. Selected cases also underwent noncontrast MR angiography and MR venography. MRI spine protocol included sagittal and axial T1W, T2W, coronal short tau inversion recovery, and postcontrast fat-suppressed images in all the three planes.

Results

Demographics: Of the total 19 patients, 12 were male (63.2%) and 7 were female (36.8%). The youngest patient was 1.5 months old, while the oldest was 11 years old. Also, 12/19 (63.15%) patients were RT-PCR positive, while the remaining (7/12; 58.33%) were COVID-19 antibody positive. The details of the cases are summarized in Table 1. Patients were broadly categorized into four categories based on neurological findings.

Acute Encephalitic Syndrome

AES included (9/19, 47.36%) cases with laboratory evidence of cerebrospinal fluid (CSF) pleocytosis or focal or generalized slowing or epileptiform discharges on EEG.

All patients were apparently normal before COVID-19 infection. Of the nine patients, six were RT-PCR positive, while three were COVID-19 antibody positive. All nine patients (cases 1–9) had fever before onset of encephalopathy, which was of varying severity. Eight patients also had seizures. Four of them (cases 1, 2, 5, and 9) had status epilepticus requiring neurointensive care. Case 2 developed refractory status epilepticus with shock and succumbed. Case 3 had abnormal movements with neuropsychiatric manifestations with detection of anti–N-methyl D-aspartate receptor (anti-NMDAR) antibody in CSF. Case 5 had focal seizures with progression to epilepsy partialis continua and left hemiparesis.
| Case No. | Age/sex | Clinical features | Disease pattern | RT-PCR –/ Ab+ | Blood investigations* | CSF | Onset imaging interval | Imaging | ICU Stay | Treatment | Outcome |
|---------|--------|------------------|----------------|------------|---------------------|-----|---------------------|---------|----------|-----------|---------|
| 1       | 1.5 mo, M | Fever, seizures (status epilepticus) | AES | RT-PCR+ | High WBC | High proteins, normal sugar, pleocytosis (100 cells) | 5 d | Tiny foci of restricted diffusion in bilateral thalami, which showed complete resolution on follow-up imaging 5 mo later | Yes, for status epilepticus | INJ. MPS, INJ. LMWH, AEDs, antibiotics, ventilator support | Good |
| 2       | 10 y, M | Fever, seizures (status epilepticus) | AES | RT-PCR+ | Normal | Normal proteins and sugar, pleocytosis (11 cells) | 4 d | Restricted diffusion in bilateral hippocampi | Yes, for status epilepticus, shock | INJ. MPS, LMWH, AEDs, inotropic, ventilator support, antibiotics | Died |
| 3       | 6 y, M | Fever, abnormal movements, behavior, seizures | AES | RT-PCR+ | Normal | Normal proteins and sugar, pleocytosis (9 cells), NMDAR Ab+ | 4 d | Restricted diffusion in left hippocampi, volume loss of both hippocampi | No | IVIG, INJ. MPS, AEDs | Good |
| 4       | 9 y, M | Altered sensorium, seizures | AES | RT-PCR+ | Normal | Normal | 2 d | Hyperintense signal in bilateral frontal cortex and subcortical white matter, right caudate, putamen, and thalamus—ADEMlike pattern | No | INJ. MPS, AEDs | Good |
| 5       | 4 y, F | Fever, acute gastrointestinalitis, (focal status epilepticus) | AES | Ab+ | Normal | Normal proteins and sugar, pleocytosis (8 cells), high IgG | 5 d | Tiny foci of restricted diffusion in bilateral deep white matter—infarcts | No | Antibiotics, INJ. dexamethasone, AEDs | Good |
| 6       | 6 mo, M | Fever, encephalopathy, seizures | AES | Ab+ | High inflammatory markers | Normal proteins and sugar, pleocytosis (40 cells) | 3 d | Bilateral thalamic restricted diffusion with small necrosis and microhemorrhage | No | INJ. MPS, AEDs, supportive care | Good |
| 7       | 7 y, F | Fever, encephalopathy, seizures | AES | Ab+ | High WBC | High proteins, normal sugars, no cells | 7 d | Bilateral thalamic and corona radiata showing restricted diffusion with ring-enhancing lesions on MRI brain. CT chest showed military nodules, Bronchovascular lavage—GeneXpert positive for tuberculosis | No | INJ. MPS, supportive care | Good |
| 8       | 9 y, F | Fever, encephalopathy | AES | RT-PCR+ | High WBC | High proteins, low sugar, no cells | 7 d | Bilateral thalamic and corona radiata showing restricted diffusion with ring-enhancing lesions on MRI brain. CT chest showed military nodules, Bronchovascular lavage—GeneXpert positive for tuberculosis | No | INJ. MPS, supportive care | Good |
| 9       | 10 y, M | Fever, seizures (status epilepticus), encephalopathy | AES | RT-PCR+ | High WBC | Normal proteins and sugars, pleocytosis (17 cells), high IgG | 5 d | Bilateral hippocampal and medial thalamus | Yes, for status epilepticus | INJ. MPS, AEDs, supportive treatment, ventilator support | Residual cognitive deficit on discharge |
| 10      | 5 y, M | Acute flaccid paralysis | APP | Ab+ | High WBC | Normal | 5 d | Ventral root enhancements | Yes | IVIG, supportive ICU care, ventilator support | Lower limb weakness on discharge |
| 11      | 4 y, M | Fever, cold, acute flaccid paralysis | APP | RT-PCR+ | Normal | High proteins, normal sugars, no cells | 10 d | Ventral root enhancements | No | IVIG, supportive care | Good |
| 12      | 3 y, F | Fever, cold, acute flaccid paralysis | APP | RT-PCR+ | Normal | High proteins, normal sugars, no cells | 7 d | Ventral root enhancements | Yes | IVIG, supportive care, noninvasive ventilation | Good, no residual weakness on follow-up |
Leukocytosis and inflammatory markers were raised in four of them and CSF pleocytosis was observed in six cases (cases 1, 2, 3, 5, 6, and 9), while the remaining three had normal CSF findings. CSF immunoglobulin G levels were raised in two of four patients (cases 5 and 9). EEG was done in eight of nine patients, of whom four patients showed generalized slowing suggestive of encephalopathy, while the other four patients had multifocal epileptiform discharges (those who had clinical seizures or status epilepticus). 2D-ECHO was normal in all patients.

On MRI brain imaging of the nine patients, one had normal scan (case 4), while four showed restricted diffusion in either unilateral hippocampus (cases 3 and 5) or bilateral hippocampi (cases 2 and 9) (Fig. 1). In case 3, additionally reduced bilateral hippocampal volume was also noted. Case 9 had additional subtle restricted diffusion in pulvinar of bilateral thalami. Four of the nine patients had restricted diffusion in bilateral thalami, which was either isolated (case 1) or in combination (cases 7, 8, and 9). Case 1 showed complete resolution on 5-month follow-up scan. Case 7, in addition, also showed tiny foci of restricted diffusion suggestive of acute infarcts in bilateral deep white matter and tiny microhemorrhages in bilateral periventricular white matter with RT-PCR+, reverse transcriptase polymerase chain reaction positive; WBC, white blood cell; y, age in years.

| Case No. | Age/sex | Clinical features | Disease pattern | RT-PCR +/- Ab | Blood investigations* | CSF | Onset imaging interval | Imaging | ICU Stay | Treatment | Outcome |
|----------|---------|-------------------|----------------|---------------|----------------------|-----|-----------------------|--------|---------|-----------|---------|
| 13       | 11 y, M | Difficulty in swallowing, acute flaccid paralysis | Cerebrovascular | Ab+ | High WBC, high inflammatory markers | Normal | 7 d | Ventral root enhancements | Yes | IVIG, supportive care, ventilator support | Still admitted, paraparesis improving |
| 14       | 9 y, M  | Fever, cough acute flaccid paralysis | Cerebrovascular | Ab+ | High WBC, high inflammatory markers | Normal | 5 d | Ventral root enhancements | Yes | IVIG, supportive care, ventilator support | Still admitted, paraparesis improving |
| 15       | 6.5 y, M| Fever, pain abdomen, vomiting, focal seizures, hemiparesis | Cerebrovascular | Ab+ | High WBC, high inflammatory markers | Normal | 10 d | Microhemorrhages in cerebral, cerebellar hemispheric white matter and corpus callosum, which is hyperintense on T2W image | Yes, for PIMS | INJ. MPS, IVIG, INJ. tocilizumab, INJ. LMWH, ventilator support, inotropes | Good |
| 16       | 11 y, F | Fever, loose motions, vomiting, hemiparesis | Cerebrovascular | RT-PCR+ | High WBC, high inflammatory markers | NA | 14 d | Small focus of restricted diffusion in left PVWM, microhemorrhages in cerebral subcortical white matter | Yes, for PIMS | INJ. MPS, LMWH, AEDs, antibiotics | Good |
| 17       | 3 y, F  | Fever, acute gastroenteritis, encephalopathy | Cerebrovascular | Ab+ | High WBC | Normal | 7 d | Restricted diffusion with cortical laminar necrosis involving left parieto-occipito-temporal lobe | No | INJ. MPS, IVIG, AEDs | Good |
| 18       | 3.5 y, F| Fever, seizures | Cerebrovascular | Ab+ | High WBC, high inflammatory markers | Normal | 20 d | Deep cerebral venous thrombosis of superior sagittal, right traverse and sigmoid sinuses with hemorrhagic infarct in right temporal lobe | Yes, for hypertensive emergency | AEDs, INJ. LMWH, anti-hypertensives | Good |
| 19       | 9 y, F  | Left focal seizures | Miscellanea | RT-PCR+ | Normal | NA | 3 d | Normal | No | AEDs, symptomatic | Good |

*Inflammatory markers were not performed for all patients, mentioned only for those in which it was abnormal.

**Table 1 (Continued)**

| No. | Age/sex | Clinical features | Disease pattern | RT-PCR +/- Ab | Blood investigations* | CSF | Onset imaging interval | Imaging | ICU Stay | Treatment | Outcome |
|-----|---------|-------------------|----------------|---------------|----------------------|-----|-----------------------|--------|---------|-----------|---------|
| 1   | 16 y, M | Moderate fever, irritability, headache, vomiting | Cerebrovascular | Ab+ | High WBC, high inflammatory markers | Normal | 14 d | Small focus of restricted diffusion in left PVWM, microhemorrhages in cerebral subcortical white matter | Yes, for PIMS | INJ. MPS, LMWH, AEDs, antibiotics | Good |
| 2   | 17 y, M | Acute flaccid paralysis | Cerebrovascular | Ab+ | High WBC, high inflammatory markers | Normal | 14 d | Small focus of restricted diffusion in left PVWM, microhemorrhages in cerebral subcortical white matter | Yes, for PIMS | INJ. MPS, LMWH, AEDs, antibiotics | Good |
| 3   | 18 y, M | Acute flaccid paralysis | Cerebrovascular | Ab+ | High WBC, high inflammatory markers | Normal | 20 d | Deep cerebral venous thrombosis of superior sagittal, right traverse and sigmoid sinuses with hemorrhagic infarct in right temporal lobe | Yes, for hypertensive emergency | AEDs, INJ. LMWH, anti-hypertensives | Good |
| 4   | 19 y, M | Acute flaccid paralysis | Cerebrovascular | Ab+ | High WBC, high inflammatory markers | Normal | 3 d | Normal | No | AEDs, symptomatic | Good |

Abbreviations: Ab+, antibody positive; AEDs, antiepileptic drugs; AES, acute encephalitis syndrome; AFP, acute flaccid paralysis; CSF, cerebrospinal fluid; CT, computed tomography; F, female; ICU, intensive care unit; IgG, immunoglobulin G; INJ. MPS, injection methylprednisolone; IVIG, intravenous immunoglobulin; LMWH, low-molecular-weight heparin; M, male; mo, age in months; NMDAR, N-methyl D-aspartate receptor; PIMS, pediatric inflammatory multisystem syndrome; PVWM, periventricular white matter; RT-PCR+, reverse transcriptase polymerase chain reaction positive; WBC, white blood cell; y, age in years.

Four of the nine patients had restricted diffusion in bilateral thalami, which was either isolated (case 1) or in combination (cases 7, 8, and 9). Case 1 showed complete resolution on 5-month follow-up scan. Case 7, in addition, also showed tiny foci of restricted diffusion suggestive of acute infarcts in bilateral deep white matter and tiny microhemorrhages in bilateral periventricular white matter with leukoencephalopathy changes involving both cerebral and cerebellar hemispheres. Case 8 also showed confluent restricted diffusion in bilateral cerebral deep white matter suggestive of acute leukoencephalopathy along with few small ring-enhancing lesions with mild perilesional edema suggestive of tuberculomas. High-resolution computed tomography (HRCT) thorax findings were consistent with diagnosis of tuberculosis. Eight out of nine patients underwent contrast imaging, and no enhancement abnormality was detected in seven patients except for case 8 with tuberculomas.

Case 6 showed restricted diffusion in bilateral periventricular and deep white matter and insular cortex and left frontal and parieto-occipital region suggestive of acute
Infants; however, it was included in AES category based on symptoms and CSF findings (Fig. 5f–i).

Seven of the nine patients required methylprednisolone injection, two were given intravenous immunoglobulins (IVIG) along with steroids, and one was given only symptomatic treatment for seizures and antibiotics. Out of nine patients, one (case 2) expired, while others improved during the hospital stay with no residual deficit on follow-up.

**Acute Flaccid Paralysis**

It included 5 out of 19 cases (26.31%; cases 10–14) out of which 1 case (case 10) was antibody positive, while the remaining 4 were RT-PCR positive. Case 10 had a history of gastrointestinal infection preceding the paralysis and rapidly progressive quadriparesis with respiratory and autonomic involvement requiring intensive care. Case 11 was a paraparetic variant without respiratory, sensory, or autonomic involvement. Three cases had respiratory symptoms prior to the onset of AFP. Case 14 was pharyngobulbar variant of GBS who later progressed to quadriparesis. Except for case 11, the remaining four cases needed intensive care unit (ICU) for respiratory support. NCV tests of all patients were consistent with GBS. CSF showed albuminocytological dissociation in four out of five patients. MRI spine of all patients revealed ventral cauda equina nerve root enhancement in lumbar spine consistent with the diagnosis of GBS (Fig. 6a–d). All patients were treated with IVIG along with supportive and symptomatic management including physiotherapy. Case 10 required 2 months of hospital stay, while two patients (cases 11 and 12) improved and was discharged after 10 days without residual weakness and two patients (cases 13 and 14) were still in hospital at the time of writing this manuscript.

**Cerebrovascular Cause**

Of the 19 patients, 4 patients (21.05%) were included in this category (cases 15–18). Three of the four patients (cases 15, 16, and 18) had normal development, while case 17 was a case of developmental delay to begin with. All four of them presented with febrile illness. Three of them presented with acute gastroenteritis along with fever. Only one patient (case 18) had presented with seizure and severe hypertension requiring multiple antihypertensives. Cerebrovascular symptoms were observed in the median of 12 days (range: 7–30). Two patients (cases 15 and 16) had leukocytosis and increase in serum inflammatory markers such as serum ferritin, fibrinogen, D-dimer, and interleukin 6, suggestive of multisystem inflammatory syndrome in children (MIS-C) requiring intensive care and also developed hemiparesis and focal seizures during the second week of illness. 2D-ECHO of these two patients showed left ventricular dysfunction. MRI showed multiple microhemorrhages in cerebral subcortical white matter as well as in corpus callosum. Case 15 had more extensive microhemorrhages also involving brainstem and cerebellar hemispheres along with restricted diffusion in centrum semiovale and corona radiata with acute leukoencephalopathy changes (Fig. 7d–g). In addition to microhemorrhages, small focal restricted diffusion was seen in the left posterior periventricular white matter in case 16 (Fig. 5a–e and Fig. 7a–c). CSF examination was done in three patients (cases 15, 17, and 18), which was normal. Case 17 developed hemiparesis after 30 days of onset of fever, and MRI showed restricted diffusion involving left parieto-occipito-temporal region with laminar cortical necrosis (appearing hyperintense on T1W images) (Fig. 5j–m). Case 18, who had hypertensive emergency, showed extensive venous sinus thrombosis involving superior sagittal, right transverse and sigmoid sinuses, proximal left transverse sinus, and cortical veins along with venous hemorrhagic infarct in right temporal lobe (Fig. 8a–e). Three of the four patients (case 15, 16, and 18) required low-molecular-weight heparin, IV methylprednisolone, and IVIG. One patient (case 15) required injection tocilizumab. All patients were doing good on follow-up with no residual deficit.

**Miscellaneous**

It included 1 out of 19 cases (0.05%)—case 19. The previously healthy child presented with unprovoked left focal seizure with normal sensorium and examination. Her basic blood investigations were normal and CSF analysis was not done. Brain imaging was also normal and was given symptomatic treatment, and she is doing well on follow-up with no further seizures.

Based on neuroimaging findings, the cases were categorized into normal study (2/19; 10.52%), hippocampal signal changes (4/19; 21.04%) (Fig. 1), ADEM-like pattern (1/19; 5.26%) (Fig. 2), bilateral thalamic signal changes (4/19;...
21.04%) (Fig. 3), coinfection (1/19; 5.26%) (Fig. 4), infarcts (4/19; 21.04%) (Fig. 5), GBS (5/19; 23.31%) (Fig. 6), leukoencephalopathy (3/19; 15.7%), microhemorrhages (3/19; 15.7%) (Fig. 7), and venous thrombosis (1/19; 5.26%) (Fig. 8). Hippocampal changes included restricted diffusion in bilateral hippocampi with/without T2/FLAIR signal changes and/or volume loss. ADEM-like pattern included cases having multifocal asymmetrical cortical/subcortical lesions, white matter and deep gray nuclei involvement. Thalamic signal changes included restricted diffusion suggestive of cytotoxic edema with/without necrotic areas/hemorrhages. We observed small infarcts in four of our cases without any large vessel occlusion stroke. Leukoencephalopathy was considered when white matter involvement was confluent, bilaterally symmetrical, with/without restricted diffusion or microhemorrhages and postcontrast enhancement. Microhemorrhages were seen as foci of small hemorrhages (<5 mm). The results of MRI findings are summarized in Table 2.

Discussion

Pathophysiology: The cellular and molecular basis of SARS-CoV-2 neurotropism, neuroinvasiveness, and neurovirulence are poorly understood. Neurological involvement in COVID-19 might be associated with at least four potential mechanisms: (1) a direct neurotropic or neuroinvasive effect of SARS-CoV-2 (e.g., anosmia, encephalitis); (2) systemic hyperinflammatory responses triggered by the virus (e.g., encephalopathy); (3) microangiopathic and prothrombotic effect of the viral infection on the central nervous system (CNS) or peripheral nervous system (PNS) vasculature (e.g., strokes, encephalopathy); (4) an immune-mediated parainfectious or postinfectious effect in response to the viral infection (e.g., acute inflammatory demyelinating polyradiculopathy, acute disseminated encephalomyelitis). It is important to consider the mechanisms associated with neurological manifestations of COVID-19, with an aim toward developing therapeutic options. These mechanisms might act separately or synergistically in a particular patient leading to diverse but overlapping clinical and neuroimaging findings.

Explaining SARS-CoV-2 virus at cellular level: The SARS-CoV-2 virus utilizes the angiotensin-converting enzyme type 2 (ACE-2) receptor for entry into the host cell. These receptors are highly expressed in the brain, explaining the neuroinvasiveness of SARS-CoV-2 virus. Binding of the virus to ACE-2 receptors incites a massive immune reaction,
consisting of a hyperinflammatory response hallmarked by excessive cytokine release, termed cytokine storm. Other potential routes for virus to enter the CNS are through hematogenous spread or via disruption of the blood–brain barrier (BBB).

Coagulopathies: Available evidence strongly suggests that COVID-19 illness is known to cause coagulopathy. In addition to hypercoagulable states, SARS-CoV-2 causes damage to endothelial cells, which leads to systemic arterial and venous microvascular and macrovascular complications.

Neurologic Manifestations
The neurological complications of SARS-CoV-2 have similarities to those described in the other coronavirus epidemics, specifically severe acute respiratory syndrome (SARS) in 2003. Even in the recent pandemic, we observed a similar pattern of neurological involvement.

In COVID-19, both the CNS and PNS are affected with myriad of neurological presentations in adults and children. In a multicentric study in the United States, 22% (356/1,695) of children and adolescent hospitalized for COVID-19 infection had neurological manifestations, whereas in an Italian study only 3% (5/168) of children had neurological manifestation of seizure.

We grouped our cases into four subcategories for simplification of clinical symptomatology. We observed seizure as the most common neurological symptom in our cohort (12/19; 63.15%), of whom 8 had it as a presenting symptom (AES group) and 4 developed during the course of the illness (3 from cerebrovascular group and 1 isolated seizure). Encephalopathy was the second most common neurological symptom (8/19; 42.10%). Among these 12 patients, we observed 4 patients presenting with fever and status epilepticus, of whom 1 had focal status epilepticus.

A systematic review of COVID-19 and status epilepticus suggested status epilepticus as a presenting symptom in many case series and studies in adults. Of 47 patients studied, 13 patients recovered, while 10 died and the rest has residual dyscognitive symptoms on follow-up. In our cohort, one patient died and the remaining three patients recovered well.

A French study on neurological complications in ICU adult patients found 13/58 (22%) presented with encephalopathic features. Brain MRI showed that 8/13 patients displayed leptomeningeal enhancement on postcontrast T1-weighted images, which was not seen in any of our patient.

We observed CSF abnormalities in 12/17 patients, out of which 6 presented with AES, 4 with AFP, 2 in cerebrovascular group. CSF COVID-19 RT-PCR could not be assessed on any of them due to laboratory constraints.

The most important diagnostic tool in these patients was neuroimaging, which showed abnormalities in 17/19 patients.
patients (89.47%). Various neuroimaging patterns in our patients with COVID-19 infection were as follows:

- Hippocampal signal changes: Four patients showed restricted diffusion in hippocampus, of whom three (cases 2, 5, and 9) presented with status epilepticus. Case 5, in addition to restricted diffusion in hippocampus, also showed involvement of cerebral cortex, white matter, and deep gray matter nuclei suggestive of ADEM-like pattern, and 1/19 (case 9) had additional restricted diffusion in pulvinar of bilateral thalami. MRI signal changes after seizures have been described to involve ipsilateral or bilateral hippocampus, thalamus, and cerebral cortex.\(^1\)

Hippocampal signal changes have been described with COVID-19 infection in literature in adults in relation to encephalitis.\(^3,20\) Moriguchi et al described a case of meningoencephalitis with MRI signal changes in hippocampus and mesial temporal lobe with hippocampal atrophy and they could isolate SARS-CoV-2 RNA in the CSF but not in nasopharyngeal swab.\(^20\)

- Changes in hippocampi in our patients are most likely to be status epilepticus. Of the 19 patients, 1 (case 3) additionally showed loss of hippocampal volume and had CSF anti-NMDAR antibody positive. Immune-mediated encephalitis is known to occur with any viral infection including COVID-19 infection.\(^3,21\)

- ADEM-like pattern: In our cohort, 1/19 (5.26%) patients (case 5) had MRI brain findings of ADEM-like pattern. This was reported to be most common pattern in a study by Lindan et al.\(^3\)

- Bilateral thalamic signal changes: 4/19 (21.04%) patients (cases 1, 7, 8, and 9) showed either isolated restricted diffusion in bilateral thalami (case 1) or in combination with other findings (cases 7, 8, and 9). This finding of cytotoxic edema in thalami completely reversed on follow-up imaging at 5 months in 1 patient (case 1), which is similar to a case described by Abel et al.\(^22\) COVID-19–associated acute necrotizing encephalopathy is known in children and has characteristic bilateral thalamic hemorrhagic lesions seen in two of our patients. It has also been observed in other viral infections including influenza and is related to cytokine storm with resultant break in BBB without direct viral invasion or parainfectious demyelination.\(^23,24\)

- Leukoencephalopathy: 3/19 cases (cases 7, 8, and 15) showed the pattern of confluent symmetrical diffuse white matter signal changes with involvement of deep and periventricular white matter with/without restricted diffusion without postcontrast enhancement. This pattern is similar to that described by Lang et al who postulated that it could be sequelae to COVID-19–related hypoxemia. COVID-19–related leukoencephalopathy has also been described by Rapalino et al\(^25,26\) characterized by confluent symmetrical supratentorial and middle cerebellar peduncular white matter changes with reduced diffusivity occurring in setting of cytokine storm syndrome. None of our cases showed changes in middle...
The changes are multifactorial and additionally are due to viral endothelial injury, cytokine storm cascade changes with secondary coagulopathy, and thrombotic microangiopathy.

- Acute infarcts (case 6, 7, 16, and 17): 4/19 cases showed small foci of acute infarcts in deep and periventricular white matter not associated with microhemorrhage, with 1 patient showing laminar cortical necrosis involving parieto-occipital lobe. MR angiography was normal in all these patients. None of our patients showed major arterial infarct, which was reported to be the most common neuroimaging findings by Ladopoulos et al. Acute cerebrovascular event is more likely associated with severe COVID-19 infection in older patients and with pre-existing comorbidities. The exact data of incidence of stroke in COVID-19 outbreak is not known in pediatric population. Cerebrovascular manifestations in COVID-19 suggest an underlying microangiopathic process.

- Microhemorrhages: We found 3/19 patients having microhemorrhages. Two of these had pediatric inflammatory multisystem syndrome (PIMS) (cases 15 and 16) with stormy clinical course but ultimately recovered fully without any residual deficit unlike adults who have been reported to have increased mortality and poor functional outcome. Both the patients with PIMS had tiny punctate juxtacortical microhemorrhages in...
cerebral hemispheres as well as splenium of corpus callosum. One patient also had microhemorrhages in periventricular location. Similar microhemorrhages have been described with COVID-19 infection, likely due to thrombotic microangiopathy.\(^{26,27}\) Varga et al explained direct viral infection of the endothelial cell and diffuse endothelial inflammation in multiple organ systems in COVID-19.\(^{31}\)

- **Venous thrombosis:** Involvement of deep, superficial veins as well as sinuses has been described with equal frequency.\(^{28}\) Our only case showed involvement of both cortical and superficial venous sinus thrombosis with hemorrhagic venous infarct.\(^{32}\)

- **GBS:** AFP developed after a median of 1 week of COVID-19 symptoms (range: 4–10 days). The temporal relationship between respiratory or gastrointestinal symptoms and onset of AFP was strongly suggestive of postinfectious immune-mediated process.\(^{33}\) We observed five cases of GBS that presented with classic neurologic signs, symptoms, nerve conduction studies, CSF, and neuroimaging similar to multiple case reports of GBS and its variants in children with COVID-19.\(^{3,4}\)

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**Fig. 7** Microhemorrhages with leukoencephalopathy: upper row: SWI (a, b) and FLAIR (c) images in an 11-year-old girl with MIS-C (case 16) showing microhemorrhages (white arrows) in subcortical white matter of bilateral parieto-occipital regions and splenium of corpus callosum without FLAIR signal changes. Middle row: SWI (d, e), DWI (f), and coronal T2W (g) images showing diffuse microhemorrhages (white arrows) in bilateral cerebral and cerebellar hemispheres, corpus callosum, and brainstem in a 6.5-year-old boy with MIS-C (case 15) with restricted diffusion in bilateral cerebral hemispheric white matter and corpus callosum, which is hyperintense on T2W image (yellow arrows). Lower row: axial SWI (h, i), FLAIR (j, k), and DWI (l) images in a 7-year-old girl (case 7) showing periventricular location of microhemorrhages with confluent hyperintense signal in bilateral cerebral and cerebellar white matter with restricted diffusion in cerebellum (blue arrows).

**Fig. 8** Venous sinus thrombosis: axial FLAIR (a, b), SWI (c), and MIP 3D venography (d, e) images in a 3.5-year-old girl with hypertensive emergency (case 18) showing thrombosis of superior sagittal sinus and cortical veins, right transverse, sigmoid sinuses, and medial half of left transverse sinus (white arrows) with hemorrhagic venous infarct (blue arrows) in the right temporal lobe. Note markedly dilated left vein of Labbé (yellow arrows).
Table 2 MRI patterns observed in our cohort

| Normal | Hippocampal changes | Thalamic changes | ADEM-like pattern | Infarcts | Leukoencephalopathy | Microhemorrhages | Venous thrombosis | Coinfection | GBS |
|--------|---------------------|------------------|-------------------|----------|---------------------|-----------------|------------------|-------------|-----|
| Case 1 | +                   |                  |                   |          |                     |                 |                  |             |     |
| Case 2 | +                   |                  |                   |          |                     |                 |                  |             |     |
| Case 3 | + (& volume loss)   |                  |                   |          |                     |                 |                  |             |     |
| Case 4 | +                   |                  |                   |          |                     |                 |                  |             |     |
| Case 5 | +                   | +                | +                 | +        |                     |                 |                  |             |     |
| Case 6 |                    |                  |                   |          |                     |                 |                  |             |     |
| Case 7 | +                   | +                | +                 | +        |                     | +               |                  |             |     |
| Case 8 |                    | +                | +                 | +        |                     |                 | +(TB)            |             |     |
| Case 9 | +                   |                  |                   |          |                     |                 |                  |             |     |
| Case 10|                    |                  |                   |          |                     |                 |                  | +           |     |
| Case 11|                    |                  |                   |          |                     |                 |                  | +           |     |
| Case 12|                    |                  |                   |          |                     |                 |                  | +           |     |
| Case 13|                    |                  |                   |          |                     |                 |                  | +           |     |
| Case 14|                    |                  |                   |          |                     |                 |                  |             |     |
| Case 15|                    | +                | +                 |          |                     |                 |                  |             |     |
| Case 16|                    | +                | +                 |          |                     |                 |                  |             |     |
| Case 17|                    |                  |                   |          |                     |                 |                  |             |     |
| Case 18|                    |                  |                   |          |                     |                 |                  |             |     |
| Case 19|                    | +                |                  |          |                     |                 |                  |             |     |

Abbreviations: ADEM, acute demyelinating encephalomyelitis; GBS, Guillain–Barré syndrome.
• Coinfection: We had one child (case 8) with COVID-19 infection along with pulmonary and neutrotuberculosis. Such coinfections have been reported previously, and these occurred in severely ill patients.3,15,34 Our patient is currently on antitubercular therapy and plausible explanation for this is that COVID-19 infection impedes host immune response and, in endemic countries, infections such as tuberculosis unfold.

Partial or complete loss of smell (anosmia) and taste (ageusia) are the most common peripheral nervous system neurological symptoms, with anosmia being the first manifestation of COVID-19 disease.9 We were unable to elicit this history in our patient cohort due to young age, and most had altered sensorium. However, none of the children showed MRI findings of signal changes or enhancement of olfactory nerves/tracts. Reversible splenial lesions have also been described in a pediatric case series of children with MIS-C; however, we did not observe those neuroimaging findings in our cohort.35

Outcome: Most children did well with COVID-19 disease and were either normal or had some mild residual neurological deficits at last follow-up. One child with AES died due to status epilepticus and shock. Low mortality in children was served by many other authors.16,36

Limitations
The limitations of this study include the small sample size and retrospective nature of the study. Imaging was dictated by need of time and so not all patients underwent contrast brain imaging; hence, leptomeningeal enhancement as well as neuritis may be missed. Certain symptoms that were common in adults such as anoma, ageusia, myalgia, and neuropathic pain could not be studied due to younger age or altered mentation. Long-term follow-up and repeat neuroimaging were not done and hence neurological sequelae to COVID-19 infection could not be elicited.

Conclusion
In our study, seizures and encephalopathy were the most common neurological symptoms with COVID-19 infection in pediatric cases. Postinfectious immune-mediated cauda equina nerve root enhancement or ADEM-like brain imaging, small acute infarcts, and hippocampal/thalamic signal changes were most common imaging patterns. We found overlapping neurological and MRI patterns in many children, suggesting that various pathophysiological mechanisms act individually or synergistically. Further studies are required to confirm our observation and evaluate the mechanism of disease in these distinct syndromes.

Availability of Data and Material
Retrospectively collected from medical record office.

Ethics Approval
Approval taken from our hospital internal ethics committee (IEC). Conflicts of Interest
None declared.

Author Contributions
Sanjich Rastogi, Foram Gala, and Shilpa Kulkarni have equally contributed to this manuscript.

Conceptualization: Foram Gala, Sanjich Rastogi; methodology: Shilpa Kulkarni; formal analysis and investigation: Sanjich Rastogi, Foram Gala; writing—original draft preparation: Sanjich Rastogi, Foram Gala; writing—review and editing: Shilpa Kulkarni, Vrushabh Gavali; funding acquisition: none; resources: Sanjich Rastogi, Foram Gala, Shilpa Kulkarni, Vrushabh Gavali; supervision: Shilpa Kulkarni, Vrushabh Gavali.

References
1 Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020;20(05): 533–534
2 Koralnik IJ, Tyler KL. COVID-19: a global threat to the nervous system. Ann Neurol 2020;88(01):1–11
3 Lindan CE, Mankad K, Ram D, et al; ASPNR PECOBIG Collaborator Group. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. Lancet Child Adolesc Health 2021;5(03):167–177
4 Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain 2020;143(10):3104–3120
5 Guidelines for Surveillance of Acute Encephalitis Syndrome (With Special Reference To Japanese Encephalitis) NVBDCP. 2006. Accessed April 19, 2022 at: http://www.nvbdcp.gov.in/Doc/AES%20guidelines.pdf
6 World Health Organization. Dept of Vaccines and Biologicals. Logistics Management. Geneva: World Health Organization; 2001
7 Hatano S. Experience from a multicentre stroke register: a preliminary report. Bull World Health Organ 1976;54(05):541–553
8 World Health Organization. WHO: International Classification of Diseases. 1965 revision, 15. Geneva: WHO; 1965
9 Garg RK. Spectrum of neurological manifestations in COVID-19: a review. Neurol India 2020;68(03):560–572
10 Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(02):271–280.e8
11 Kompuraj D, Selvakumar GP, Ahmed ME, et al. COVID-19, mast cells, cytokine storm, psychological stress, and neuroinflammation. Neuroscientist 2020;26(5–6):402–414
12 Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood–brain barrier. Nat Med 2013;19(12):1584–1596
13 Pons S, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. Crit Care 2020;24(01):353
14 Umapathi T, Kor AC, Venketasubramanian N, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). J Neurol 2004;251(10):1227–1231
15 LaRovere KL, Riggs BJ, Poussaint TY, et al. Overcoming COVID-19 Investigators. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol 2021;78(05):536–547
16 Garazzino S, Montagnani C, Donà D, et al. Italian SITIP-SIP Pediatric Infection Study Group Italian SITIP-SIP SARS-CoV-2 paediatric infection study group. Multicentre Italian study of SARS-CoV-2 infection in children and adolescents, preliminary data as at 10 April 2020. Euro Surveill 2020;25(18);200600
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17 Dono F, Nucera B, Lanzone J, et al. Status epilepticus and COVID-19: A systematic review. Epilepsy Behav 2021;118:107887
18 Helms J, Kremer S, Merdji H, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 2020;382(23):2268–2270
19 Kim SE, Lee BI, Shin KJ, et al. Characteristics of seizure-induced signal changes on MRI in patients with first seizures. Seizure 2017;48:62–68
20 Moriguchi T, Harri N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-CoV-2. Int J Infect Dis 2020;94:55–58
21 El Beltagi AH, Vattoth S, Abdelhady M, et al. Spectrum of neuroimaging findings in COVID-19. Br J Radiol 2021;94(1117):20200812
22 Abel D, Shen MY, Abid Z, et al. Encephalopathy and bilateral thalamic lesions in a child with MIS-C associated with COVID-19. Neurology 2020;95(16):745–748
23 Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features. Radiology 2020;296(02):E119–E120
24 Rossi A. Imaging of acute disseminated encephalomyelitis. Neurol Imaging Clin N Am 2008;18(01):149–161, ix
25 Lang M, Buch K, Li MD, et al. Leukoencephalopathy associated with severe COVID-19 infection: sequela of hypoxemia? AJNR Am J Neuroradiol 2020;41(09):1641–1645
26 Rapalino O, Pourvaziri A, Maher M, et al. Clinical, imaging, and lab correlates of severe COVID-19 leukoencephalopathy. AJNR Am J Neuroradiol 2021;42(04):632–638
27 Radmanesh A, Derman A, Lui YW, et al. COVID-19-associated diffuse leukoencephalopathy and microhemorrhages. Radiology 2020;297(01):E223–E227
28 Ladopoulos T, Zand R, Shahjouei S, et al. COVID-19: neuroimaging features of a pandemic. J Neuroimaging 2021;31(02):228–243
29 Fitsiori A, Pugin D, Thieffry C, Lalive P, Vargas MI. COVID-19 is associated with an unusual pattern of brain microbleeds in critically ill patients. J Neuroimaging 2020;30(05):593–597
30 Agarwal S, Jain R, Dogra S, et al. Cerebral microbleeds and leukoencephalopathy in critically ill patients with COVID-19. Stroke 2020;51(09):2649–2655
31 Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020;395(10234):1417–1418
32 Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020;18(05):1023–1026
33 Alkan O, Yildirim T, Tokmak N, Tan M. Spinal MRI findings of guillain–barre syndrome. J Radiol Case Rep 2009;3(03):25–28
34 Pezzini A, Padovani A. Lifting the mask on neurological manifestations of COVID-19. Nat Rev Neurol 2020;16(11):636–644
35 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
36 Lu X, Zhang L, Du H, et al; Chinese Pediatric Novel Coronavirus Study Team. SARS-CoV-2 infection in children. N Engl J Med 2020;382(17):1663–1665