



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 symptoms 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.

Keywords

- ▶ pediatric COVID-19 disease
- ▶ neuroimaging in COVID-19
- ▶ acute encephalitis syndrome
- ▶ Guillain-Barré syndrome
- ▶ microhemorrhages
- ▶ leukoencephalopathy

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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 tract but also can involve other major organs such as the heart, liver, kidneys, and brain.²

The aim of our study is to describe neurological and neuroimaging 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.

In total, 19 children met our inclusion criteria.

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 definition^{7,8}).

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-Barré 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 post-contrast 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.

Table 1 Medical details of cases (demographics/symptoms, disease pattern, investigations, imaging, and treatment)

Case No.	Age/sex	Clinical features	Disease pattern	RT-PCR +/- Ab+	Blood investigations ^a	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, 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, inotropes, 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	Normal	No	AEDs, symptomatic	Good
5	4 y, F	Fever, acute gastroenteritis, (focal status epilepticus)	AES	Ab+	Normal	Normal proteins and sugar, pleocytosis (8 cells), high IgG	5 d	Hyperintense signal in bilateral frontal cortex and subcortical white matter, right caudate, putamen, and thalamus—ADEM-like pattern	No	INJ. MPS, AEDs	Good, remote symptomatic Seizures on follow-up
6	6 mo, M	Fever, encephalopathy, seizures	AES	Ab+	High inflammatory markers	High proteins, normal sugar, pleocytosis (40 cells)	3 d	Tiny foci of restricted diffusion in bilateral deep white matter—infarcts	No	Antibiotics, INJ. dexamethasone, AEDs	Good
7	7 y, F	Fever, encephalopathy, seizures	AES	Ab+	High WBC	High proteins, normal sugars, no cells	7 d	Bilateral thalamic restricted diffusion with small necrosis and microhemorrhage Confluent hyperintense signal in bilateral cerebral and cerebellar white matter with restricted diffusion in cerebellum Small foci of restricted diffusion suggestive of acute infarcts in deep cerebral white matter	No	INJ. MPS, AEDs, 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 Bronchoalveolar 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	AFP	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	AFP	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	AFP	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

Table 1 (Continued)

Case No.	Age/sex	Clinical features	Disease pattern	RT-PCR +/- Ab+	Blood investigations ^a	CSF	Onset imaging interval	Imaging	ICU Stay	Treatment	Outcome
13	11 y, M	Difficulty in swallowing, acute flaccid paralysis	AFP	RT-PCR+	Normal	High proteins, normal sugars, no cells	7 d	Ventral root enhancements	Yes	IVIg, supportive care, ventilator support	Still admitted, paraparesis improving
14	9 y, M	Fever, cough acute flaccid paralysis	AFP	RT-PCR+	Normal	High proteins, normal sugars, no cells	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, cerebellum and brainstem. Restricted diffusion in bilateral cerebral 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 transverse and sigmoid sinuses with hemorrhagic infarct in right temporal lobe	Yes, for hypertensive emergency	AEDs, INJ, LMWH, antihypertensives	Good
19	9 y, F	Left focal seizures	Miscellaneous	RT-PCR+	Normal	NA	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, injection methylprednisolone; IVIg, intravenous immunoglobulins; 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.

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

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 (►Fig. 1d-f). Case 9 had additional subtle restricted diffusion in pulvinar of bilateral thalami (►Fig. 1g-i). Case 5 also had T2/FLAIR hyperintensities in cortical and subcortical white matter in bilateral frontal lobes, right basal ganglia, and thalamus suggestive of acute demyelinating encephalomyelitis (ADEM)-like imaging appearance (►Fig. 2a-f).

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) (►Fig. 3). Case 1 showed complete resolution on 5-month follow-up scan (►Fig. 3a-d). 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 (►Fig. 3e-g) 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 (►Fig. 4a-g). 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

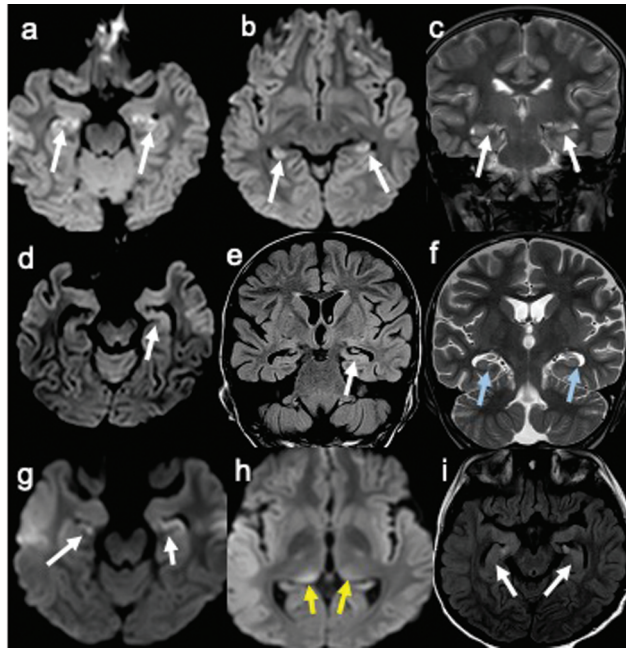


Fig. 1 Hippocampal signal changes: upper row: Axial DWI (a, b) and coronal T2W (c) images in a 10-year-old boy (case 2) showing restricted diffusion in both hippocampi (white arrows) with increased signal on T2W images. Middle row: Axial DWI (d), coronal T2W (e), and FLAIR (f) images in 6-year-old boy (case 3) showing restricted diffusion in left hippocampus (white arrows) with increased signal on FLAIR images. Both hippocampi also show reduced volume with dilated temporal horns (blue arrows). Anti-NMDA antibodies were positive in this child. Lower row: Axial DWI (g, h) and FLAIR (i) images in 10-year-

infarcts; 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 quadriplegia 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 quadriplegia. 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;

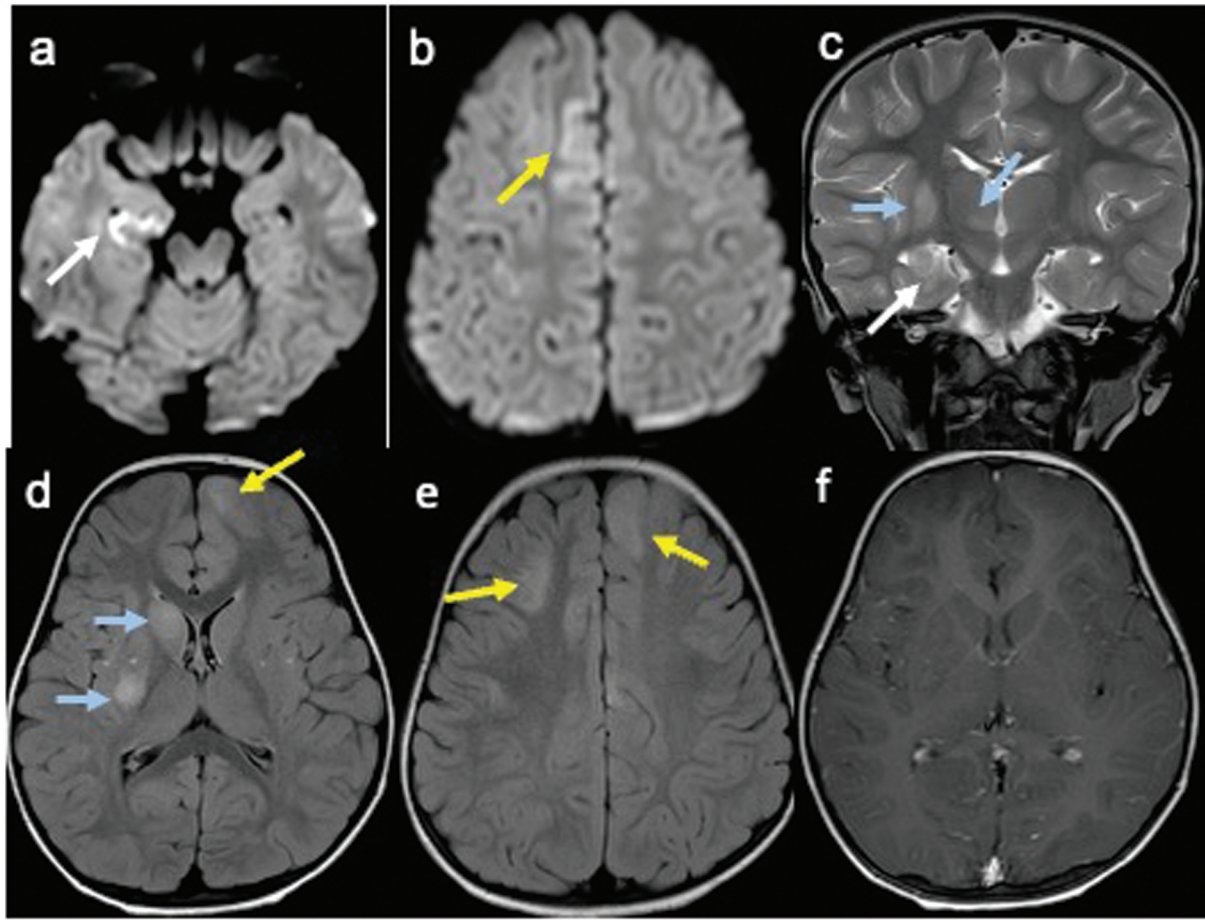


Fig. 2 ADEM-like pattern: axial DWI (a,b), coronal T2W (c), FLAIR (d, e), and T1 postcontrast axial (f) images in a 4-year-old girl (case 5) showing restricted diffusion in right hippocampus (white arrows) and right medial frontal gyrus (yellow arrows) within hyperintensity in cortex and subcortical white matter of bilateral anterior frontal lobes (right > left), right medial frontal gyrus, basal ganglia, thalamus (blue arrows), and hippocampus without postcontrast enhancement.

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.⁹

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.¹⁰ Binding of the virus to ACE-2 receptors incites a massive immune reaction,

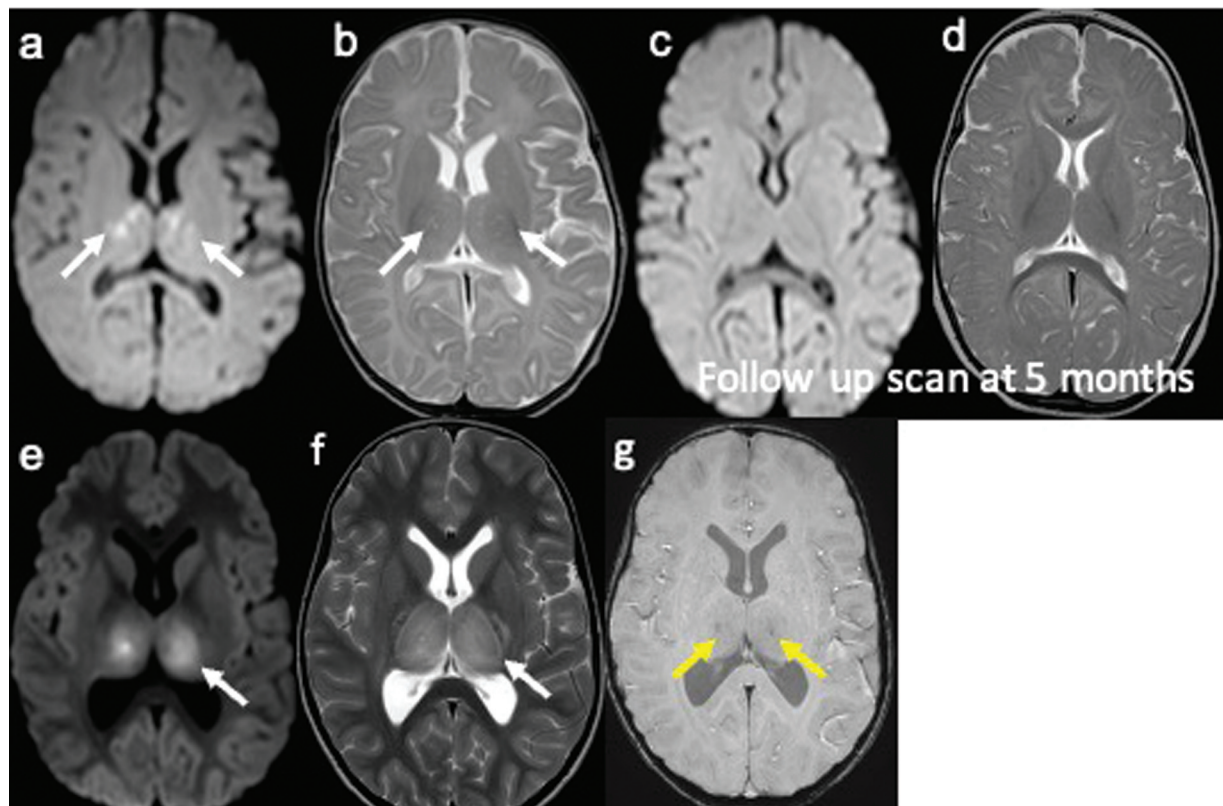


Fig. 3 Thalamic signal changes: upper row: axial DWI (a) and T2W (b) images in a 1.5-month-old child (case 1) showing tiny foci of restricted diffusion, which appear hyperintense on T2W images (white arrows) without any hemorrhage or perilesional edema. These completely reversed on follow-up imaging after 5 months (c, d). Lower row: axial DWI (e), T2W (f), and SWI (g) images in a 7-year-old girl (case 7) showing symmetrical restricted diffusion in bilateral thalami with edematous changes on T2W image (white arrow and small microhemorrhage in left thalamus and necrosis on right side (yellow arrow).

consisting of a hyperinflammatory response hallmarked by excessive cytokine release, termed *cytokine storm*.¹¹ Other potential routes for virus to enter the CNS are through hematogenous spread or via disruption of the blood–brain barrier (BBB).¹²

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.¹³

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 2003.¹⁴ 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,¹⁵ whereas in an Italian study only 3% (5/168) of children had neurological manifestation of seizure.¹⁶

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 dycognitive symptoms on follow-up.¹⁷ 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.¹⁸ 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

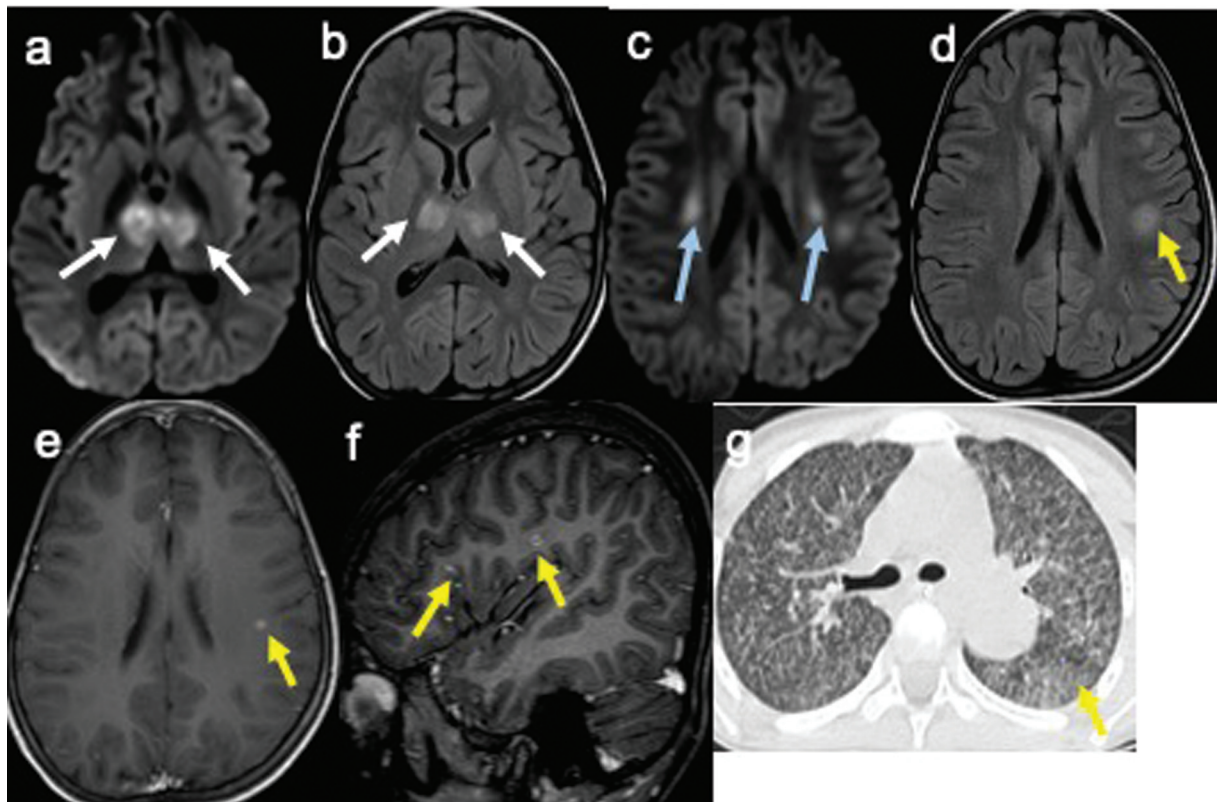


Fig. 4 Coinfection: upper row: axial DWI (a, c), FLAIR (b, d), and postcontrast (e, f) brain images showing symmetrical restricted diffusion in bilateral thalami with FLAIR hyperintense signal (white arrows) in a 9-year-old girl (case 8). Restricted diffusion in bilateral corona radiata (blue arrows) not appreciated on FLAIR images and small ring-enhancing lesions in left parietal, right perisylvian regions (yellow arrows). HRCT scan of thorax (g) showing miliary pattern of tuberculosis (yellow arrows).

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.¹⁹ 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

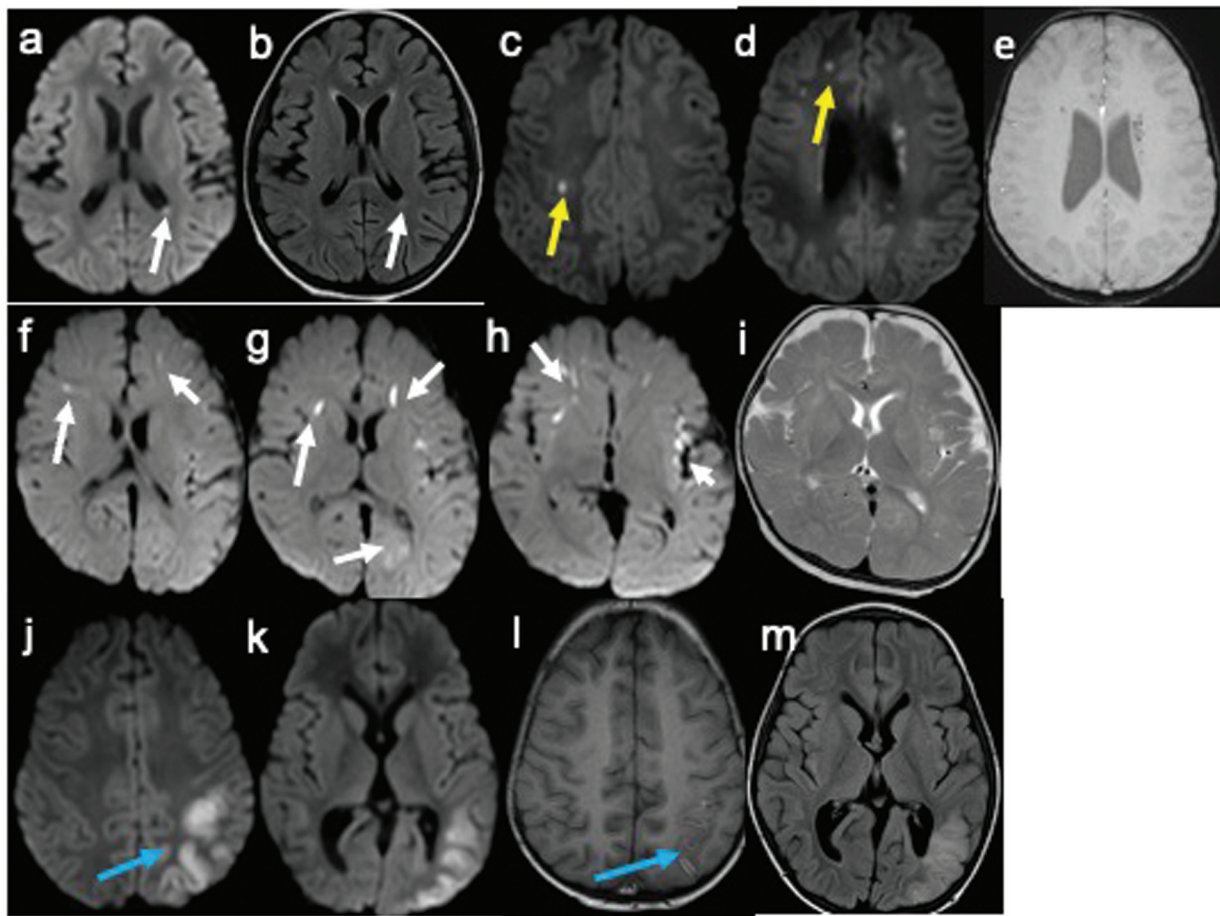


Fig. 5 Infarcts: upper row: axial DWI and FLAIR (a, b) image in an 11-year-old girl with MIS-C (case 16) showing small focus of restricted diffusion in left periventricular white matter (white arrows). Axial DWI (c, d) and SWI (e) images in a 7-year-old girl (case 7) showing tiny infarcts (yellow arrows) with microhemorrhages. Middle row: axial DWI (f–h) images in a 6-month-old boy (case 11) showing multiple foci of restricted diffusion in bilateral frontal periventricular and deep white matter, left insular cortex, and left medial occipital lobe (white arrows), which appears slightly hyperintense on T2W image (i). Axial DWI (j, k), T1W, and FLAIR images (l, m) show restricted diffusion involving left parieto-occipito-temporal region with laminar cortical necrosis and swelling (blue arrows) in a 3-year-old girl (case 17).

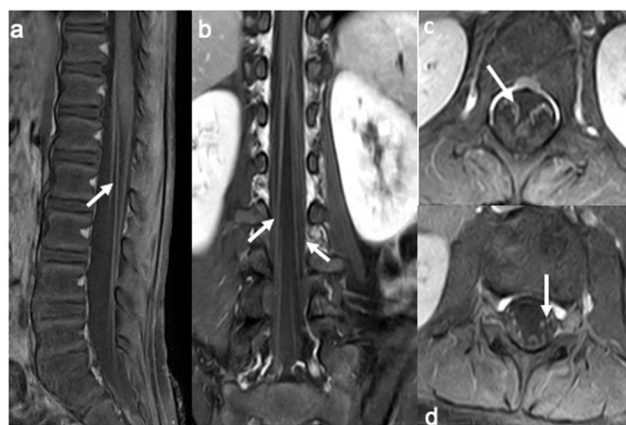


Fig. 6 Guillain-Barré syndrome: sagittal (a), coronal (b), and axial postcontrast T1 fat-saturated (c, d) images in a 5-year-old with acute flaccid paralysis (case 10) showing enhancement of ventral nerve roots (white arrows).

cerebellar peduncle. These changes are multifactorial and additionally are due to viral endothelial injury, cytokine storm cascade changes with secondary coagulopathy, and thrombotic microangiopathy.²⁷

- 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.²⁸ Acute cerebrovascular event is more likely associated with severe COVID-19 infection in older patients and with pre-existing comorbidities.²⁹ 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.^{29,30} Both the patients with PIMS had tiny punctate juxtacortical microhemorrhages in

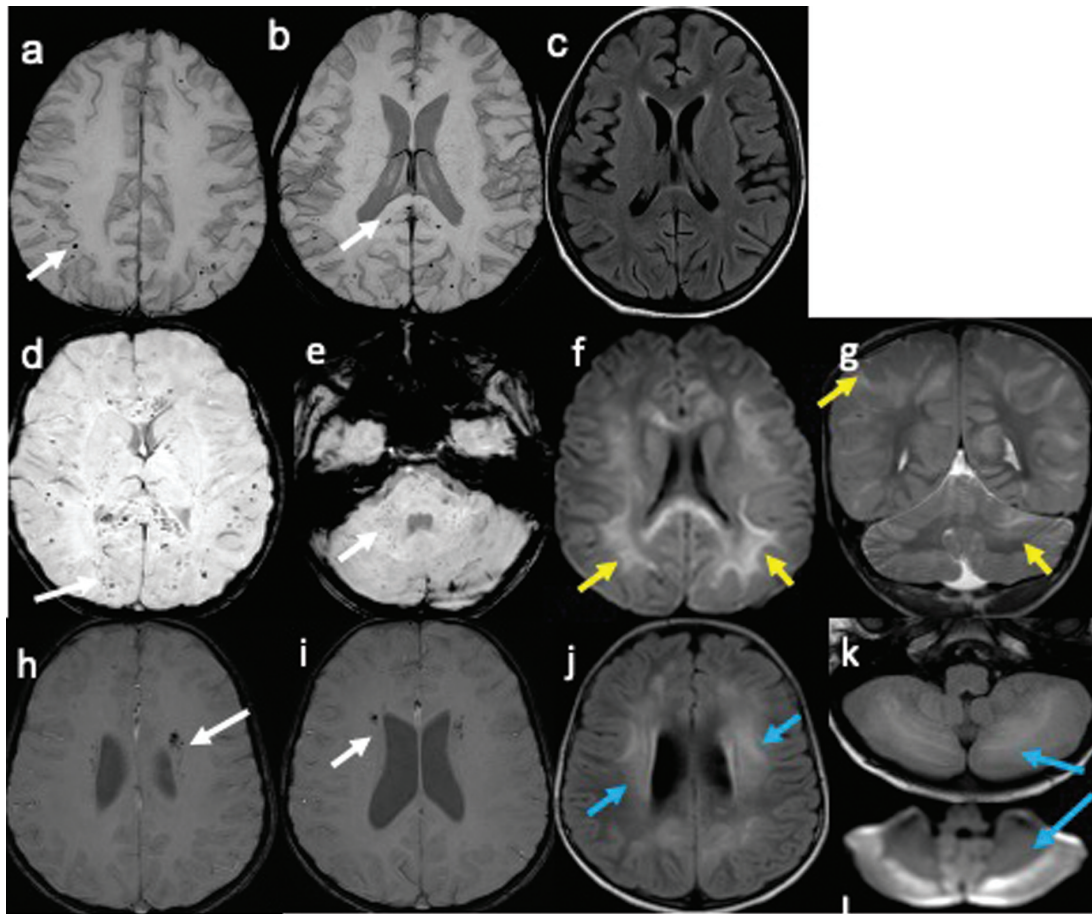


Fig. 7 Microhemorrhages with leukoencephalopathy: upper row: SWI (a, b) and FLAIR (c) images in an 11-year-old girl with MIS-C (case 16) showing microhemorrhages (white arrows) in subcortical white matter of bilateral parieto-occipital regions and splenium of corpus callosum without FLAIR signal changes. 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).

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}

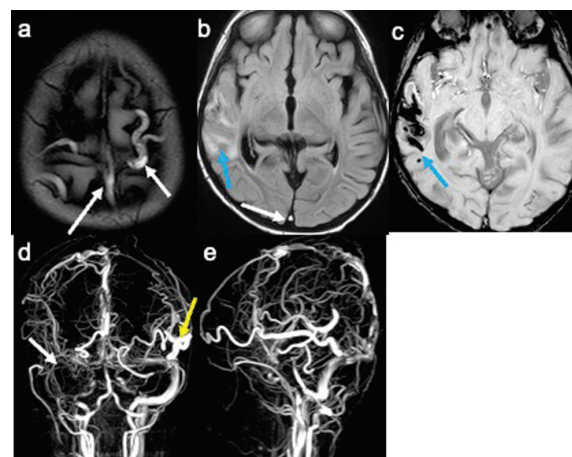


Fig. 8 Venous sinus thrombosis: axial FLAIR (a, b), SWI (c), and MIP 3D venography (d, e) images in a 3.5-year-old girl with hypertensive emergency (case 18) showing thrombosis of superior sagittal sinus and cortical veins, right transverse, sigmoid sinuses, and medial half of left transverse sinus (white 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		+								
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 neurotuberculosis. 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 anomia, 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

Sanchi Rastogi, Foram Gala, and Shilpa Kulkarni have equally contributed to this manuscript.

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

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