Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Pediatric Neurology 136 (2022) 20–27

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

Post-COVID-19 Immune-Mediated Neurological Complications in Children: An Ambispective Study

Lokesh Saini, DM [a, *, 1], Deepthi Krishna, MD [a, 1], Sarbesh Tiwari, DM [b], Jagdish Prasad Goyal, MD [a], Prawin Kumar, MD [a], Daisy Khera, MD [a], Bharat Choudhary, MD [a], Siyaram Didel, MD [a], Ravisekhar Gadepalli, PhD [c], Kuldeep Singh, DM [a]

[a] Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India
[b] Department of Diagnostic and Interventional Radiology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India
[c] Department of Microbiology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

ARTICLE INFO

Article history:
Received 14 December 2021
Accepted 13 June 2022
Available online 6 July 2022

Keywords:
COVID-19
Demyelination
Autoimmune
GBS
Status epilepticus
Multiple sclerosis
Seizures

ABSTRACT

Background: The neurological manifestation following a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is varied, and till now, only a few studies have reported the same.
Methods: We used retrospective data from May to July 2021 and prospective study data from August to September 2021, including that from children aged between one month and 18 years who presented to a tertiary care referral center with the neurological manifestation and had a history of coronavirus disease 2019 (COVID-19) infection or exposure and positive SARS-CoV-2 serology. The neuroradiological manifestations were further categorized as in a predesigned proforma.
Results: Case records of the 18 children who fulfilled the criteria were included in the study; among them, seven (38.8%) were male and 11 (61.1%) were female. Predominant presentation in our study group was status epilepticus (six of 18) and Guillain-Barré syndrome (five of 18). Other manifestations included stroke (two of 18), demyelinating syndromes (three of 18), and autoimmune encephalitis (two of 18). Most of the children had favorable outcomes except for one mortality in our cohort.
Conclusions: Delayed complications following SARS-CoV-2 infection are seen in children. A temporal correlation was noted between the COVID-19 infection and the increasing number of neurological cases after the second wave. Steroids could be beneficial while treating such patients, especially in the presence of high inflammatory markers. Testing for SARS-CoV-2 serology during the pandemic can give a clue to the underlying etiology. Further multicentric studies are required to understand the varied neurological manifestations following SARS-CoV-2 infection in children.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus belongs to the coronavirus family. Aerosols transmit the virus and cause coronavirus disease 2019 (COVID-19) infection.

The first case of COVID-19 was reported in December 2019 in Wuhan, China.[1] Since then, two waves of COIVD-19 infection have occurred. Although a child may appear to be immune or less affected during the acute illness, post-COVID complications like multisystem inflammatory syndrome in children (MIS-C), immune-mediated neurological complications, and other immune-mediated conditions proved to be an ordeal for the treating physician.

SARS-CoV-2 invades via angiotensin-converting enzyme 2 receptor and transmembrane serine protease 2; both the receptors are present in the central nervous system. This invasion triggers a vicious cycle of the proinflammatory and procoagulable cascade. As a result, it causes symptoms either by direct invasion or by inducing vasculitis.[2-4]

Conflict of Interest: None.
Funding: None.
* Communications should be addressed to: Dr. Saini; Department of Pediatrics; All India Institute of Medical Sciences; Jodhpur, Rajasthan, India.
E-mail address: drlokeshsaini@gmail.com (L. Saini).
[1] Both authors share joint first authorship.

https://doi.org/10.1016/j.pediatrneurol.2022.06.010
0887-8994/

However, neurological manifestations in the post-COVID period are attributed to an immune-mediated (cytokine storm) phenomenon similar to MIS-C, in which levels of cytokines such as interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-17, and interferon are found to be elevated.[5] These cytokines cause blood-brain barrier disruption, activate glial cells, and initiate neuroinflammation, leading to manifestations like seizure, fatigue, and encephalopathy.

Furthermore, molecular mimicry between coronavirus with neuronal proteins (such as gangliosides and myelin oligodendrocyte [MOG]) can cause demyelination and manifest as Guillain-Barré syndrome (GBS) and acute disseminated encephalomyelitis (ADEM).[6,7]

The most common post-COVID neurological problems in adults are stroke (ischemic and hemorrhagic) and post-COVID demyelination syndrome, like GBS. These problems are primarily attributed to the prothrombotic state and cytokine storm.[8] However, there is insufficient literature regarding the neurological manifestations in children following SARS-CoV-2 infection; hence this study was conducted to identify the varied spectrum of neurological manifestation following SARS-CoV-2 infection.

Methods

This study collected retrospective data (from May to July 2021) and prospective data (from August to September 2021). The study included all children between the ages of one month and 18 years who presented to the pediatric emergency or outpatient department of a tertiary care center in western India with the neurological manifestation, history of COVID-19 infection, or history of exposure to COVID-19 infection and positive SARS-CoV-2 serology. This study was conducted with the aim of learning the spectrum of post-COVID-19 neurological manifestations in children with a history of COVID-19 infection or a history of exposure to COVID-19.

The study recorded the demographic details, clinical presentation, evidence of SARS-CoV-2 infection, investigations, treatment, and outcome in a predesigned proforma. The neurological manifestations were entered and categorized as status epilepticus, cerebrovascular accident (CVA) (stroke ischemic or hemorrhagic and cerebral venous sinus thrombosis), encephalopathy/encephalitis, demyelinating pathology, peripheral nervous system involvement, neuropsychiatric manifestations, or movement disorder.

The institute Ethics Committee provided ethical approval before data collection began.

Results

Sixty-three patients were admitted with varied neurological manifestations from May to September 2021 in a pediatric ward of a tertiary care center in western Rajasthan. The SARS-CoV-2 serology test was performed on 38 of these patients, and 21 were positive. Among them, three were excluded: one was diagnosed with central nervous system Langerhans cell histiocytosis, one was diagnosed with neuronal brain iron accumulation, and one had concomitant viral hepatitis A with febrile seizures.

Figure 1 displays the flow of patients in the study.

A total of 18 cases were included in the study. The mean age was 7.7 years (four months to 17 years): 11 were female (61.1%), and seven (38.8%) were male (Table 1). None of the patients had pre-existing neurological conditions. However, only one patient had obesity and hypertension as comorbidity. The mean duration of presentation following COVID infection or exposure was 5.7 weeks (three to eight weeks) (Table 2).

Eleven (61.1%) cases had isolated neurological features, and seven (38.8%) also had concomitant systemic features such as fever, hypotension, and shock at presentation. In our study group, six of 18 (33.33%) presented with status epilepticus, and five (27.77%) had peripheral nerve involvement, contributing to almost two-thirds of our study population. Three had demyelinating disorder (multiple sclerosis [MS], ADEM, and longitudinally extensive transverse myelitis), two had a CVA, whereas two presented with features of autoimmune encephalitis (AE).

Nine patients (50%) had elevated inflammatory markers like C-reactive protein, IL-6, or ferritin.

Cerebrospinal fluid (CSF) analysis could be performed in 14 of the 18 patients; among these five (27.77%) had pleocytosis. CSF analysis of five patients who were diagnosed with GBS showed albuminocytologic dissociation. One patient with AE tested positive for the presence of *N-methyl-D-ASPARTATE RECEPTOR* (NMDAR)

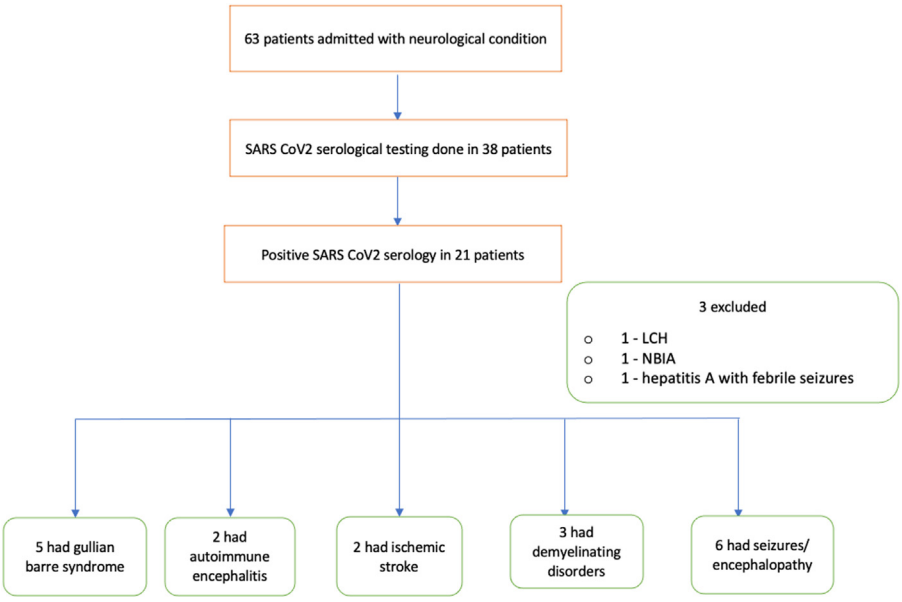

FIGURE 1. Study flow chart. The color version of this figure is available in the online edition. LCH, Langerhans cell histiocytosis; NBIA, neuronal brain iron accumulation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 1.
Clinical and Laboratory Profile of Children With Post-COVID-19 Immune-Mediated Neurological Manifestations (N = 19)

Variables	Seizures (Status Epilepticus) (n = 6)	GBS & Its Variants (n = 5)	CVA (n = 2)	LETM (n = 1)	ADEM (n = 1)	MS (n = 1)	AE (n = 2)
Age, years	0.33-16	3-15	8-12	3	4	14	4
Sex							
Male	3 (50%)	2 (0%)	0	1 (100%)	1 (100%)	0	0
Female	3 (50%)	3 (0%)	2 (100%)	0	0	1 (100%)	2 (100%)
Comorbidity	-	-	-	-	-	Obesity, HTN	-
Clinical features							
Systemic	5 (83.3%)	0	0	1 (100%)	1 (100%)	0	0 (00%)
Seizures	6 (100%)	1 (20%)	0	0	0	0	0
Encephalopathy	4 (67%)	0	0	0	0	0	2 (100%)
CVA	0 (%)	0	2 (100%)	0	0	0	0
Neuropsychiatric	0 (%)	0	0	0	0	0	2 (100%)
Movement disorder	0 (%)	0	0	0	0	0	1 (100%)
PNS involvement	0 (%)	5 (100%)	0	0	0	0	0
Other	0	0	0	0	0	0	0
Demyelination	0	0	0	1	1	1	0
Investigations							
SARS-CoV-2 serology	6 (100%)	5 (100%)	2 (100%)	1 (100%)	1 (100%)	1 (100%)	2 (100%)
Elevated inflammatory markers	3 (50%)	2 (%)	1 (50%)	Not done	1 (100%)	Not done	2 (100%)
CSF pleocytosis >5 cells/Ul		0			1 (100%)	0	0
Other investigations	3/5 (50%)	1 positive Lyme serology	Not done	1 (100%)	Serum MOG positive	OCB positive	1 NMDAR antibody positive
Abnormal neuroimaging	4/5 (80%)	5 (100%)	2 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (50%)
Treatment							
PICU admission	4 (67%)	2 (40%)	0	0	0	0	0
Immunomodulator	2 (33.34%)	5 (100%)	1 (50%)	1 (100%)	1 (100%)	1 (100%)	2 (100%)
IVIG	2	**5**	0	0	0	0	2
MPS	2	1	1	1	1	1	2
PLEX	0	1	0	0	0	0	0
Outcome							
Discharge	5 (83.33%)	5 (100%)	2 (100%)	1 (100%)	1 (100%)	1 (100%)	2 (100%)
Death	1 (16.66%)	0	0	0	0	0	0

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
AE = Autoimmune encephalitis
COVID-19 = Coronavirus disease 2019
CSF = Cerebrospinal fluid
CVA = Cerebrovascular accident
GBS = Guillain-Barré syndrome
HTN = Hypertension
IVIG = Intravenous immunoglobulin
LETM = Longitudinal extensive transverse myelitis
MOG = Myelin oligodendrocyte glycoprotein
MPS = Methylprednisolone
MS = Multiple sclerosis
NMDAR = *N*-methyl-D-aspartate receptor
OCB = Oligoclonal bands
PICU = Pediatric intensive care unit
PLEX = Plasma exchange
PNS = Peripheral nervous system
SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

antibodies, another with ADEM tested positive for MOG antibody, and a third patient with MS had CSF oligoclonal bands.

Neuroimaging could be performed in 17 (94.44%) patients. Among them, two had normal neuroimaging, five had features suggestive of GBS (Fig 2), two (11.76%) had features of ischemic stroke (Fig 2), one child had ADEM (Fig 3), one child had long segment transverse myelitis (Fig 2), one had features of MS (Fig 3), and five (29.4%) had nonspecific findings.

Of the 18 patients, six (33.33%) required pediatric intensive care unit admission, and all these six required mechanical ventilation, whereas four of six (66.66%) required ionotropic support.

In our study, 13 patients (72.22%) were treated with immunomodulatory drugs like methylprednisolone pulse therapy followed by oral steroids. Nine patients (50%) were given intravenous immunoglobulin (IVIG), one child required plasmapheresis, and six (33.3%) patients received more than one type of immunomodulatory therapy. Methylprednisolone pulse therapy was added to those with elevated inflammatory markers and showed little or no improvement after receiving first-line immunotherapy.

Patients were assessed at the time of discharge and three-month postdischarge for the neurological outcome; 12 (66.66%) children had normal to mild disability as assessed by modified Rankin scale (mRS) (score of 0 to 1), three (16.66%) had an mRS score of 2 to 3, severe disability was seen in two (11.11%) patients (score 4), and one patient died (mRS 6) because of cerebral edema with bilateral uncal herniation secondary to uncontrolled status epilepticus.

Of the five GBS cases in our cohort, only one child had a severe disability whose disease course was complicated by reversible cerebral vasoconstriction syndrome and the remaining four children with GBS had a normal neurological outcome.

TABLE 2.
Characteristics, Clinical Course, and Outcome of Patients With Post-COVID Neurological Manifestations

Variables	Case 1	Case 2	Case 3	Case 4	Case 5
Age (year)	4	17	3	10	10
Gender	F	M	F	M	F
Diagnosis	GBS (classical)	GBS (classical)	Descending variant of GBS	Miller Fischer variant	Descending variant of GBS
Comorbidity	No	No	No	No	No
COVID infection/ exposure (weeks)	4	6	5	7	8
Presenting complaints	Weakness and paresthesia of lower limbs	Weakness of both lower limbs	Weakness of both upper limbs	H/o wobbling gait and h/o headache	Difficulty in sitting and weakness of both upper limbs
Respiratory involvement	Yes	No	No	No	Yes
Investigation					
Inflammatory markers	Normal	High	Normal	Normal	High (IL-6 >55,000)
CSF analysis	Albuminocytologic dissociation	Albuminocytologic dissociation	Albuminocytologic dissociation	Albuminocytologic dissociation	Albuminocytologic dissociation
Other	-	-	-	-	-
Treatment					
IVIG	Yes	Yes	Yes	Yes	Yes
Steroids	No	Yes	No	No	Yes
PLEX	Yes	No	No	No	No
Complications	Autonomic dysfunction SIADH RCVS	Nil	Nil	Nil	Nil
mRS					
At admission	5	3	3	4	5
@3 months	4	0	0	0	0

	Case 6	Case 7	Case 8	Case 9	Case 10
Age (year)	12	8	4	3	14
Gender	F	F	M	M	F
Diagnosis	FCA	FCA	ADEM	LETM	MS
Comorbidity	No	No	No	NO	Obesity
COVID infection/exposure (weeks)	5	4	8	6	8
Presenting complaints	Paucity of movements of right upper limb	Paucity of movements of right upper and lower limbs	Fever for 15 days Irritability	Fever	Blurring of vision
Respiratory involvement	No	No	No	No	No
Investigation					
Inflammatory markers	Normal	High	High	Normal	Normal
CSF analysis	Not done	Not done	Pleocytosis	Pleocytosis	Not done
Other	-	-	MOG antibody positive	-	CSF OCB positive
Treatment					
IVIG	No	No	No	No	No
Steroids	No	Yes	Yes	Yes	Yes
PLEX	No	No	No	No	No
Complications	No	No	No	No	No
mRS					
At admission	3	4	4	3	2
@3 months	0	0	0	0	0

	Case 11	Case 12	Case 13	Case 14	Case 15
Age (year)	4	4	16	5 yr	0.8
Gender	F	F	M	F	F
Diagnosis	AE	AE	Status epilepticus	Status epilepticus	Status epilepticus
Comorbidity	No	No	Nil	Nil	Nil
COVID infection/exposure (weeks)	8	7	4	6	4
Presenting complaints	Altered sensorium for past 1 month Abnormal movements for past 20 days	Altered sensorium for 1 weeks Seizures twice in past 1 week	Seizures	Seizures	Seizures
Respiratory involvement	No	No	Yes	No	No
Investigation					
Inflammatory markers	High	High	Normal	Normal	High
CSF analysis	Normal	Normal	Pleocytosis	Not done	Normal
Other	NMDAR antibody positive	NMDAR antibody negative	-	-	
Treatment					
IVIG	Yes	Yes	No	No	No
Steroids	Yes	Yes	No	No	No
PLEX	No	No	No	No	No
Complications	No	No	Nil	No	No
mRS					
At admission	5	5	5	2	2
@3 months	3	2	0	0	0

(continued on next page)

TABLE 2. (*continued*)

	Case 16	Case 17	Case 18
Age (year)	0.3	1.5	0.5
Gender	M	M	M
Diagnosis	Status epilepticus	Status epilepticus	Status epilepticus
Comorbidity	Nil	Nil	Nil
COVID infection/exposure (weeks)	5	3	4
Presenting complaints	Seizures	Seizures	Seizures
Respiratory involvement	Yes (ventilated for 1 week)	Yes	No
Investigation			
Inflammatory markers	High	High	Normal
CSF analysis	Pleocytosis	Pleocytosis	Normal
Treatment			
IVIG	Yes	Yes	No
Steroids	Yes	Yes	No
PLEX	No	No	No
Complications	Nil	Nil	Nil
mRS			
At admission	5	5	3
@3 months	4	6 (Death)	2

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
AE = Autoimmune encephalitis
COVID = Coronavirus
CSF = Cerebrospinal fluid
CVA = Cerebrovascular accident
F = Female
FCA = Focal cerebral arteriopathy
GBS = Guillain-Barré syndrome
h/o = History of
HTN = Hypertension
IL-6 = Interleukin 6
IVIG = Intravenous immunoglobulin
LETM = Longitudinal extensive transverse myelitis,
M = Male
MOG = Myelin oligodendrocyte glycoprotein
MPS = Methylprednisolone
mRS = Modified Rankin scale
MS = Multiple sclerosis
NMDAR = *N*-methyl-D-aspartate receptor
OCB = Oligoclonal bands
PLEX = Plasma exchange
PNS = Peripheral nervous system
RCVS = Reversible cerebral vasoconstriction syndrome
SAIDH = Syndrome of inappropriate antidiuretic hormone secretion

Children with demyelinating disorders and arteriopathy had a normal neurological outcome at three months' follow-up with no residual weakness. Those with AE had an mRS score of 2 to 3, i.e., moderate disability, and they are still under follow-up for their treatment protocol.

Among those presenting with status epilepticus, three children had good neurological outcomes, one had moderate disability, one had severe disability, and one died due to herniation following prolonged status resulting in diffuse cerebral edema.

Discussion

In the COVID-19 pandemic, initial literature showed that the children were less affected and asymptomatic or had milder symptoms than adults. However, there were increasing reports of children presenting with Kawasaki-like disease or MIS-C. Similarly, the number of adults infected with COVID-19 presenting with neurological manifestation increased. Hence, this study focused on determining the spectrum of neurological manifestations in children with a history of COVID-19 infection or exposure to COVID-19.

In our study, many children presented with postinfectious immune-mediated conditions involving the brain, spinal cord, nerves, and nerve roots like GBS, including descending variant of GBS in one; AE; CVA; demyelinating conditions; and seizures.

Pathology

The pathology behind the post-COVID neurological manifestations is similar to other postinfectious immune-mediated neurological disorders.

Molecular mimicry: Epitopes on microorganisms share similarities with the host antigens causing immune intolerance. In susceptible hosts, this can activate lymphocytes, which self-react with the host antigens causing the breakdown of immune tolerance leading to varied manifestations.[9,10]

In infection with a virulent organism, lymphocytes get activated via antigen-independent mechanisms. This inflammatory cascade may stimulate autoreactive immune cells and cause autoimmunity.[11,12]

Moreover, inflammation can disrupt the blood-brain barrier giving access to the nervous system.[13]

Guillain-Barré syndrome (GBS)

The coronavirus spike protein binds to the receptors on respiratory epithelial cells and interacts with glycoproteins and gangliosides. Antibodies against ganglioside- monosialic acid 1 (GM1) and ganglioside D1a (GD1a) have been reported in patients with

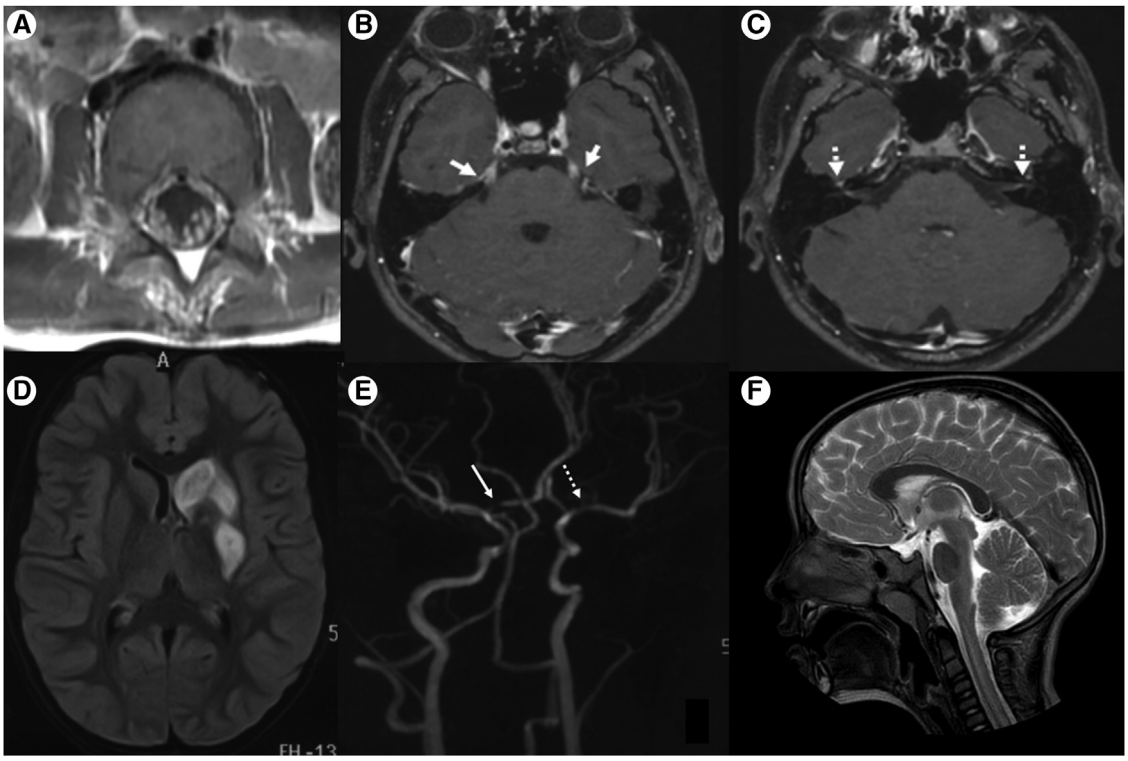

FIGURE 2. The postcontrast axial (A) images of the lumbar spine shows enhancement of the cauda equina nerve roots. The axial postcontrast T1 images of the brain (B, C) show enhancement of bilateral fifth and seventh to eighth cranial nerves depited by arrows. Correlating with the clinical details, the imaging features are consistent with Guillain-Barré syndrome. The axial fluid-attenuated inversion recovery (D) image shows a subacute infarct involving the left caudate nucleus and the putamen. The time-of-flight magnetic resonance angiogram (E) shows focal narrowing of the A1 segment of the right anterior cerebral artery (arrow) and the proximal M1 segment of the left middle cerebral artery (dashed arrow). Sagittal T2 sagittal image (F) showing long segment demyelination extending from cervicomedullary junction to C6 vertebra.

GBS following SARS-CoV-2 infection, suggesting molecular mimicry as the underlying mechanism.[6,14,15]

Five of 18 children were diagnosed with GBS in the current study. One had Miller Fisher variant of GBS, one had a descending variant of GBS, and three children had bilateral symmetric ascending lower limb weakness. All had magnetic resonance imaging (MRI) features of nerve root enhancement; two of five had cranial nerve root enhancement. Of the five children, one was also positive for Lyme serology. All five patients were treated with IVIG therapy as per protocol, and two of them also required plasmapheresis and IVIG. Of these five children, two required pediatric intensive care unit admission and one had a stormy course complicated by autonomic dysfunction causing posterior reversible encephalopathy syndrome, syndrome of inappropriate antidiuretic hormone secretion, and reversible cerebral vasoconstriction syndrome. Two children who had raised inflammatory markers were initially treated with IVIG as per protocol. However, because of persistent weakness, they were also treated with steroids (after two weeks of IVIG), following which a significant improvement was noted.

Curtis et al. reported a case of an eight-year-old boy presenting with progressive ascending paralysis with areflexia, with MRI and nerve conduction studies suggestive of GBS during acute COVID-19 infection.[16]

Abu-Rumeileh et al. conducted a systematic review regarding the GBS spectrum associated with COVID-19 infection; they included 73 patients with ages ranging from 11 years to 94 years. Their review concluded that classic sensorimotor form and acute inflammatory demyelinating polyneuropathy cases were higher. However, other variants of GBS like Miller Fisher syndrome, pure motor form, bilateral (B/L) facial palsy with paresthesia, polyneuritis cranialis, and paraparetic variant were also reported.[17]

NMDAR encephalitis (AE)

A four-year-old female presented with neuropsychiatric manifestations followed by encephalopathy and movement disorder (orofacial dyskinesia, choreoathetoid movements, and characteristic pelvic thrust) following a viral prodrome (fever with cough and coryza). CSF was positive for NMDAR encephalitis, hence confirming the diagnosis of AE. Also, she had positive titers for SARS-CoV-2 serology (indicative of COVID-19 infection as the plausible triggering factor in this case).

Similarly, multiple case reports have been published presenting AE following COVID-19 infection, both in children and adults.[18,19]

Cerebrovascular accidents (CVAs)

Two children presented with the sudden onset of right-sided hemiparesis in our series. Weakness was maximal at the onset and improved gradually over the next few days in both of them. Neuroimaging in both the children revealed ischemic stroke, and vessel wall imaging of one child showed inflammatory focal cerebral arteriopathy involving the A1 segment of the anterior cerebral artery on the right and M1 segment of the middle cerebral artery on the left. The patient was treated with steroids and aspirin. The vessel wall imaging of the other child was normal, and the child received only aspirin.

Appavu et al. reported two similar cases of eight- and 16-year-old patients presenting with arteritis three to four weeks following acute COVID-19 infection.[20]

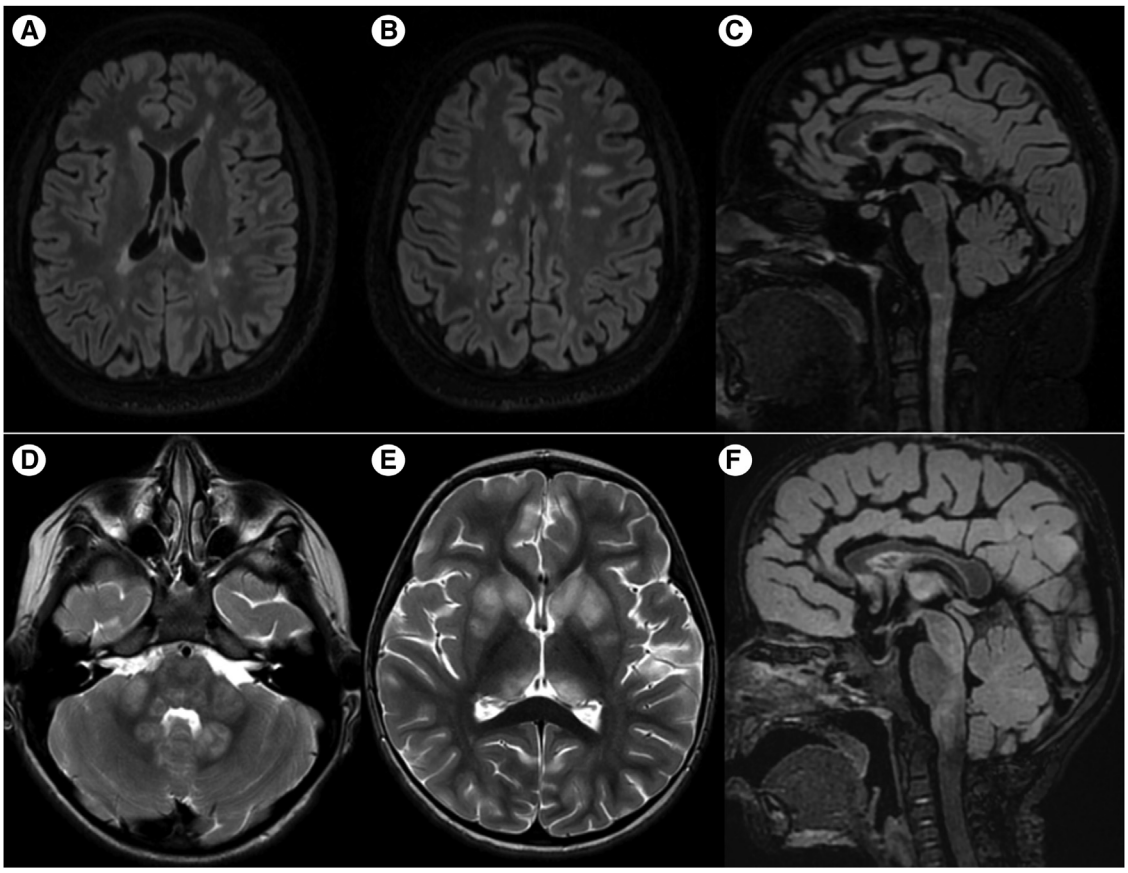

FIGURE 3. The axial fluid-attenuated inversion recovery (FLAIR) images (A, B) shows multiple oval-shaped periventricular and deep white matter lesion in perivenular distribution. The sagittal FLAIR image (C) shows multiple small demyelinating plaques at the undersurface of the corpus callosum, producing the ependymal "dot and dash" sign. Similar lesions are also noted at the upper cervical cord. The axial T2-weighted images (D & E) show fluffy hyperintense lesions at pons, bilateral middle cerebellar peduncles, dentate nucleus, bilateral striatum, and posteromedial thalami. The sagittal FLAIR image (F) shows the involvement of the brainstem (midbrain, dorsal pons, and medulla).

Status epilepticus

Six of 18 children presented with status epilepticus to our emergency room in our study. Of the six children, one child improved and was discharged on the same day; one child had encephalitis. One child (10 months old) had atypical febrile seizures with few features of MIS-C but not fulfilling the criteria for MIS-C. Three children had associated encephalopathy.

Among the six, only two children required immunomodulatory therapy (both IVIG and steroids). One child continued to have seizures even after immunomodulatory therapy (super-refractory status epilepticus). Five of them were discharged, and one child succumbed because of cerebral edema (secondary to hypoxia), resulting in herniation.[21]

Demyelination disorders

Longitudinally extensive transverse myelitis

One child was diagnosed with long segment transverse myelitis extending from the cervicomedullary junction to C7 following COVID-19 infection. He was treated with methylprednisolone pulse therapy.

MOG ADEM

One of the interesting cases in our study group was a child presenting with prolonged fever and irritability and no other neurological manifestations, with history of COVID-19 infection in family members. Initially, he was evaluated as having pyrexia of unknown origin. However, none of the investigations were contributory. Later an MRI was performed; to our surprise, the MRI showed multifocal patchy T2/fluid-attenuated inversion recovery hyperintensities suggesting ADEM, and the child later also tested positive for MOG antibodies. This child behaved similarly to the cohort reported by Udani et al.[22]

McLendon et al. reported a case of ADEM in a 17-month-old child who presented with irritability, weakness, and gait disturbance with MRI showing diffuse patchy T2 hyperintensities.[23]

Multiple sclerosis (MS)

One child presented with a blurring of vision and numbness over the dorsum of the left foot. She had a history of COVID-19 infection one month before the symptom onset. Neuroimaging showed lesions typical of MS, and she was treated with methyl prednisolone pulse therapy and started on interferon.

Conclusion

In our study, steroids were given to all those children who had raised inflammatory markers. However, others were managed as per protocol, like IVIG in patients with GBS.

As viruses are involved in immune-mediated neurological conditions' pathogenesis, testing for prevalent infection can give essential clues to the underlying etiology.

There was a significant temporal association between the COVID-19 pandemic and increased cases of immune-mediated neurological diseases. It prompted the authors to look for evidence of COVID-19 infections in such patients. Hence, it can be hypothesized that SARS-CoV-2 infection triggers an autoimmune phenomenon, leading to variable neurological manifestations. The increased numbers at our centers, especially the clustering of these cases following our country's peak of COVID waves, made us strongly believe in this possible association.

Although we could not test all children for various possible antibodies because of financial constraints, clinicoradiologically, most of our children had underlying post-COVID-19 immune-mediated etiologies like GBSMOG-associated demyelination, NMO, MS, Miller Fisher syndrome, etc.

Thus, we conclude that, during a pandemic, testing for the prevalent infection, as well as syndrome-specific antibodies such as MOG, anti-NMDAR, and any others available, should be performed when evaluating children with neurological diseases. The results will aid in both establishing the underlying etiology and providing epidemiologic data. We also want to convey that although children are relatively immune to the severe health effects of coronavirus infections compared with adults, one should be aware of post-COVID-19 systemic manifestations, which can be life-threatening. Early anticipation and treatment with immunomodulation are rewarding. The addition of pulse steroids should be considered in the presence of high inflammatory markers, wherever treatment response is not satisfactory to first-line immunotherapy.

Limitations of the study

Immune-mediated conditions occur following various viral infections, and at times they can occur even without any viral trigger. We have tried to exclude other prevalent known infectious triggers in our region. However, the list is endless; hence it is challenging to conclude that the presentation is solely secondary to COVID. More extensive multicentric studies are required for recognizing different clinical phenotypes, treatment strategies, and long-term outcomes for post-SARS-COV-2 immune-mediated neurological illnesses.

References

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–733.
2. Gulko E, Overby P, Ali S, Mehta H, Al-Mufti F, Gomes W. Vessel wall enhancement and focal cerebral arteriopathy in a pediatric patient with acute infarct and COVID-19 infection. AJNR Am J Neuroradiol. 2020;41:2348–2350.
3. Song E, Zhang C, Israelow B, et al. Neuroinvasion of SARS-CoV-2 in human and mouse brain. J Exp Med. 2021;218, e20202135.
4. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020;191:145–147.
5. Carter MJ, Fish M, Jennings A, et al. Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection. Nat Med. 2020;26:1701–1707.
6. Dalakas MC. Guillain-Barré syndrome: the first documented COVID-19–triggered autoimmune neurologic disease: more to come with myositis in the offing. Neurol Neuroimmunol Neuroinflamm. 2020;7, e781.
7. Cataldi M, Pignataro G, Taglialatela M. Neurobiology of coronaviruses: potential relevance for COVID-19. Neurobiol Dis. 2020;143, 105007.
8. Kaur S, Bansal R, Kollimuttathuillam S, et al. The looming storm: blood and cytokines in COVID-19. Blood Rev. 2021;46, 100743.
9. Blank M, Barzilai O, Shoenfeld Y. Molecular mimicry and auto-immunity. Clin Rev Allergy Immunol. 2007;32:111–118.
10. Damian RT. Molecular mimicry in biological adaptation. Science. 1965;147:824.
11. Hotta-Iwamura C, Benck C, Coley WD, et al. Low CD25 on autoreactive Tregs impairs tolerance via low dose IL-2 and antigen delivery. J Autoimmun. 2018;90:39–48.
12. Pacheco Y, Acosta-Ampudia Y, Monsalve DM, Chang C, Gershwin ME, Anaya J-M. Bystander activation and autoimmunity. J Autoimmun. 2019;103, 102301.
13. Varatharaj A, Galea I. The blood-brain barrier in systemic inflammation. Brain Behav Immun. 2017;60:1–12.
14. Tatu L, Nono S, Grácio S, Koçer S. Guillain-Barré syndrome in the COVID-19 era: another occasional cluster? J Neurol. 2021;268:1198–1200.
15. Gutiérrez-Ortiz C, Méndez-Guerrero A, Rodrigo-Rey S, et al. Miller Fisher syndrome and polyneuritis cranialis in COVID-19. Neurology. 2020;95:e601–e605.
16. Curtis M, Bhumbra S, Felker MV, et al. Guillain-Barré syndrome in a child with COVID-19 infection. Pediatrics. 2021;147, e2020015115.
17. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain–Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases. J Neurol. 2021;268:1133–1170.
18. Sarigecili E, Arslan I, Ucar HK, Celik U. Pediatric anti-NMDA receptor encephalitis associated with COVID-19. Childs Nerv Syst. 2021;37:3919–3922.
19. Monti G, Giovannini G, Marudi A, et al. Anti-NMDA receptor encephalitis presenting as new-onset refractory status epilepticus in COVID-19. Seizure. 2020;81:18–20.
20. Appavu B, Deng D, Dowling MM, et al. Arteritis and large vessel occlusive strokes in children after COVID-19 infection. Pediatrics. 2021;147, e2020023440.
21. Nikbakht F, Mohammadkhanizadeh A, Mohammadi E. How does the COVID-19 cause seizure and epilepsy in patients? The potential mechanisms. Mult Scler Relat Disord. 2020;46, 102535.
22. Udani V, Badheka R, Desai N. Prolonged fever: an atypical presentation in MOG antibody-associated disorders. Pediatr Neurol. 2021;122:1–6.
23. McLendon LA, Rao CK, Da Hora CC, Islamovic F, Galan FN. Post-COVID-19 acute disseminated encephalomyelitis in a 17-month-old. Pediatrics. 2021;147, e2020049678.