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Research Paper

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

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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]

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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)

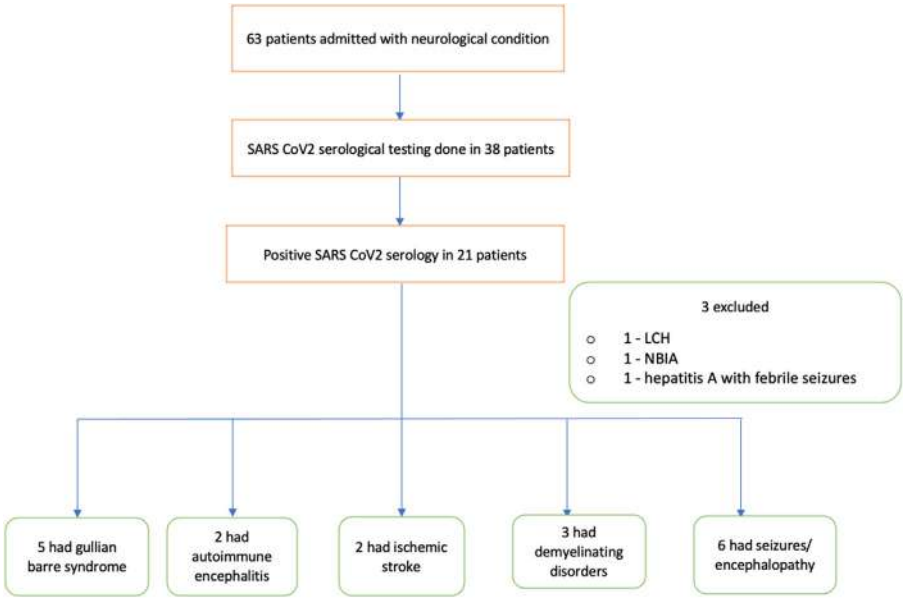

FIGURE 1. Study flow chart. The color version of this figure is available in the online edition. LCH, Langerhans cell histiocytosis; NBIA, neuronal brain iron accumulation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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

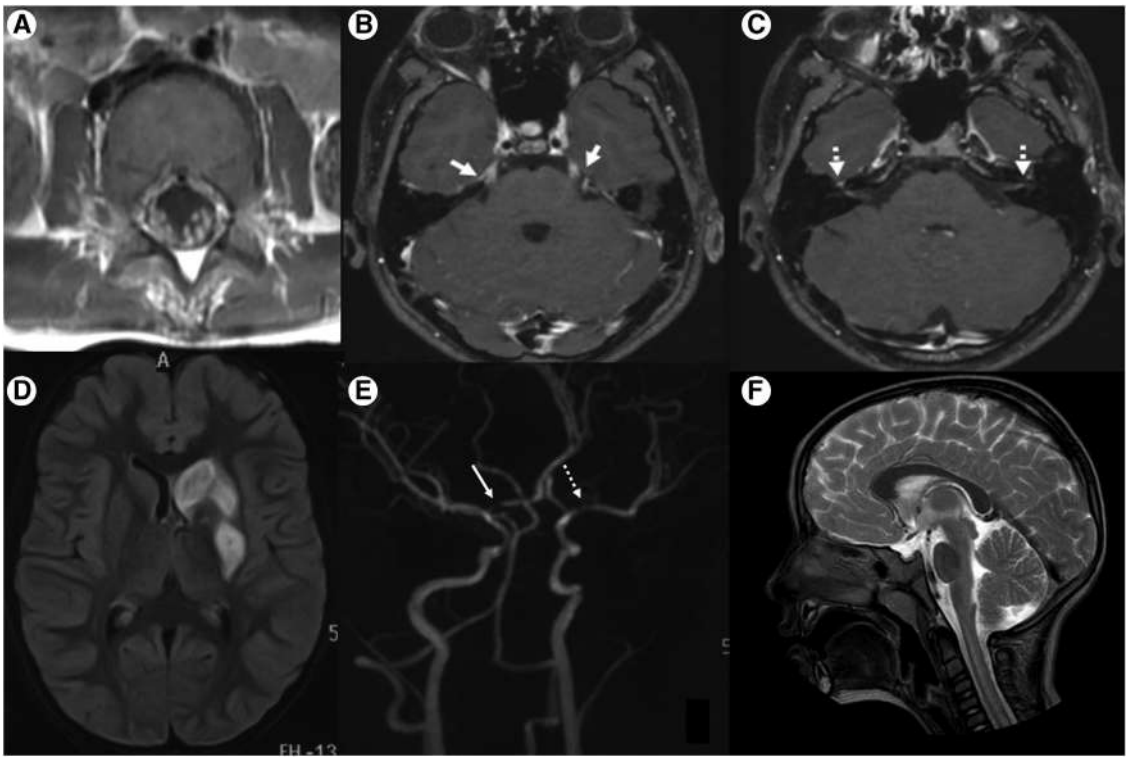

FIGURE 2. The postcontrast axial (A) images of the lumbar spine shows enhancement of the cauda equina nerve roots. The axial postcontrast T1 images of the brain (B, C) show enhancement of bilateral fifth and seventh to eighth cranial nerves depited by arrows. Correlating with the clinical details, the 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]

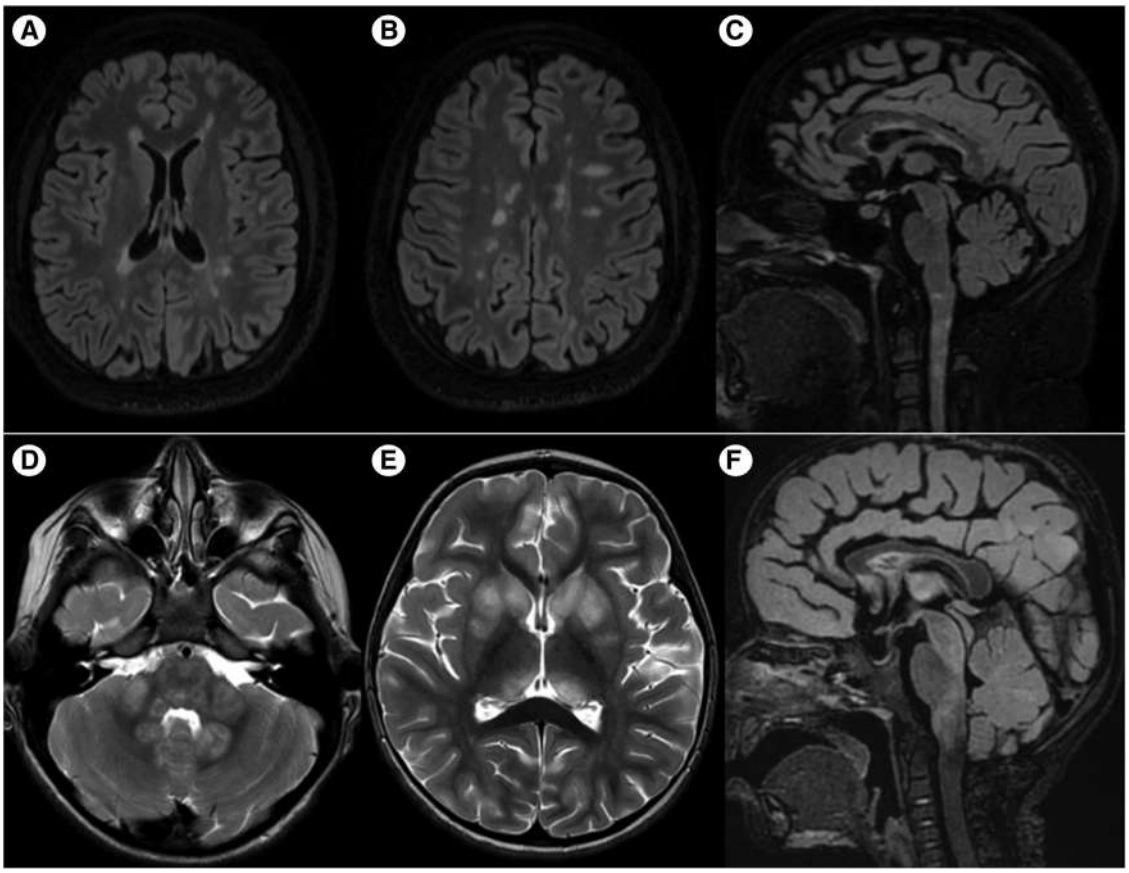

FIGURE 3. The axial fluid-attenuated inversion recovery (FLAIR) images (A, B) shows multiple oval-shaped periventricular and deep white matter lesion in perivenular distribution. The sagittal FLAIR image (C) shows multiple small demyelinating plaques at the undersurface of the corpus callosum, producing 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.

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Clinical Profile, Follow-up, and Role of Neuroimaging in Pediatric Guillain-Barré Syndrome in the COVID Era: An Ambispective Study

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Abstract

Background: To define the varied presentations of Guillain-Barré syndrome in children in the COVID era and 6 months' follow-up outcome. **Methods:** Ambispective study of 15 months' duration involving children with Guillain-Barré syndrome aged 1 month to 18 years at a tertiary care pediatric hospital. They were categorized into groups A and B based on COVID-19 serology testing. Hughes Disability Scale was used for disability assessment. Modified Rankin scale was used for improvement assessment in follow-up. **Results:** Of 19 children with Guillain-Barré syndrome, 9 (47%) were females and 10 (53%) were males. Groups A and B had children with negative (8) and positive serology (11), respectively. The most common presentation in both groups was motor weakness. Post-COVID pediatric Guillain-Barré syndrome presented with variants of Guillain-Barré syndrome rather than the classical form ($P = .03$). In group B, patients with elevated inflammatory markers had poor response to intravenous immunoglobulin, and 5 of 11 patients had good response to pulse steroids, probably depicting an inflammation-predominant pathology. **Conclusion:** Post-COVID Guillain-Barré syndrome in children presented with Guillain-Barré syndrome variants rather than the classic form. Neuroimaging is of great value in both confirming Guillain-Barré syndrome diagnosis and excluding differentials. Patients with elevated inflammatory markers and residual weakness may be given a pulse steroid trial.

Keywords

Guillain-Barré syndrome, pediatrics, post-COVID, neuroimaging

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Coronavirus disease–2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in children manifests commonly with respiratory and gastrointestinal symptoms.[1] Multisystem inflammatory disease–children (MIS-C) or Kawasaki disease-like presentation and neurologic manifestations are the other presentations.[2] Among the neurologic manifestations, encephalopathy/encephalitis, seizures, headache, and vomiting are common and intracranial hemorrhages, cranial nerve palsies, Guillain-Barré syndrome, and vision problems are the rare presentations.[2-5] The post-COVID neurologic manifestations are similar to those of other conditions resulting in either (1) direct injury due to neurotropism or (2) an immune-mediated phenomenon resulting in central and peripheral nervous system injuries.[2,6] The pathophysiology of Guillain-Barré syndrome is the postinfectious immune-mediated interdependent generation of antibodies by both cell-mediated and antibody-mediated immune responses

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(cellular and humoral), cross-reacting with gangliosides in peripheral nerve membranes resulting in their destruction.[7,8] The annual incidence of pediatric Guillain-Barré syndrome based on epidemiology studies is estimated at 0.34 to 1.34 per 100 000 person-years.[9,10] However, the incidence of pediatric Guillain-Barré syndrome due to COVID-19 is yet to be determined. Khalifa et al[11] reported probably the first case of post-COVID pediatric Guillain-Barré syndrome. Following this, more similar cases were reported.[12-34] Neuroimaging contributes a significant value in children with Guillain-Barré syndrome in confirming the diagnosis and excluding the differentials, especially in atypical presentations. Our study aimed to analyze the characteristics and outcomes of post-COVID Guillain-Barré syndrome in children and explored the utility of neuroimaging as an upfront diagnostic modality.

Methodology

This study was an ambispective study conducted for 15 months (May 2021 to July 2022) at a tertiary care pediatric hospital. The records were retrospectively reviewed from May 2021 to January 2022 (9 months). The cohort was prospectively followed up from February 2022 to July 2022 (6 months). Ethical approval from the institutional ethics committee was obtained (AIIMS/IEC/2022/5066). Inclusion criterion was children aged between 1 month and 18 years with a diagnosis of Guillain-Barré syndrome or its variants admitted to the inpatient ward and intensive care unit at the department of pediatrics. The National Institute of Neurological Disorders and Stroke (NINDS) Committee's diagnostic criteria modified by Asbury et al[35] were used to diagnose Guillain-Barré syndrome and its variants. Exclusion criterion was a diagnosis not consistent with Guillain-Barré syndrome. Informed assent or consent was obtained before enrollment. The basic demographic data, clinical manifestations, history of SARS-CoV-2 infection or exposure, investigations, treatment, and outcomes were recorded in a prestructured questionnaire. Inflammatory markers, including C-reactive protein, ferritin, and interleukin-6 levels, were done in all children.

The SARS-CoV-2 serology test (IgM antibodies) was done in all patients at admission. The cohort was further divided into 2 subgroups based on the serology: group A consisted of children with negative SARS-CoV-2 serology, and group B included those with positive SARS-CoV-2 serology (post-COVID Guillain-Barré syndrome). The oropharyngeal swabs from all children were tested for COVID-19 by the reverse transcription polymerase chain reaction (RT-PCR). The electrophysiological study was done on 4 motor nerves and 2 sensory nerves in the upper limbs and lower limbs in all children, and the electrophysiological criteria by Hadden et al[36] were used for the classification of Guillain-Barré syndrome. The Guillain-Barré syndrome diagnosis was classified into subtypes, including acute motor axonal neuropathy, acute inflammatory demyelinating polyradiculoneuropathy, Miller-Fisher syndrome, polyneuritis cranialis variant, and descending variant of Guillain-Barré syndrome. The Hughes Disability Scale[37] was used for disability assessment. The modified Rankin Scale[38] was used for the assessment of improvement in follow-up at 1, 3, and 6 months after discharge from the hospital.

Hughes Disability Scale

The Hughes Guillain-Barré syndrome disability score was devised to assess the functional status of Guillain-Barré syndrome patients by Hughes et al in 1978.[37] The scoring of the scale ranges from 0 to 6, where 0 = healthy, 1 = minor symptoms and can run, 2 = can walk 10 meters or more without assistance but cannot run, 3 = can walk 10 meters only with assistance, 4 = bedridden, 5 = need for assisted ventilation, and 6 = dead.

Modified Rankin Scale

The Rankin Scale was devised to assess the degree of disability or the dependence for activities of daily living (ADL) of people with stroke or other causes of neurologic disabilities by Rankin et al[38] in 1957 and later modified in 2008. The scoring of the scale ranges from 0 to 6, where 0 = no symptoms; 1 = can carry out usual activities, despite symptoms; 2 = slight disability: able to look after own affairs without assistance, but cannot carry out all prior activities; 3 = moderate disability: needs help for previous activities, but can walk without assistance; 4 = moderately severe disability: cannot attend to own bodily needs or walk without assistance; 5 = severe disability: needs constant nursing, bedridden; and 6 = dead.

Results

Nineteen patients admitted during the study period with a diagnosis of Guillain-Barré syndrome or its variants in the department of pediatrics were enrolled.

Demographics and Clinical Presentation

Among the 19 children, 9 (47%) were female and 10 (53%) were male. The mean (SD) age in group A was 6 (±4.6) years and in group B was 8.4 (±4.7) years. Among them, 15 children had a history of COVID-like symptoms or in the family members at 1-4 weeks before the presentation. None of the children received COVID-19 vaccines. Only 1 patient previously had a history of Guillain-Barré syndrome–like illness 4 years back, which gradually recovered in 6 months. The rest had no preexisting neurologic disease or any other comorbidity. On serology testing, 11 tested positive, with very high titers of COVID-19 antibodies. On RT-PCR testing, all were negative at admission.

The most common presentation in both groups was motor weakness. In group A, all 8 children presented with weakness; in group B, 8 of 11 children presented with weakness. The other prominent manifestation in group B was the involvement of cranial nerves. The other symptoms included ataxia and paresthesias.

Guillain-Barré Syndrome and Its Variants

Seven of the 8 children in group A had classical Guillain-Barré syndrome, and 1 had a descending variant of Guillain-Barré syndrome.

In group B, 4 children had classical Guillain-Barré syndrome, and 7 children presented with Guillain-Barré syndrome variants, including polyneuritis cranialis variant of Guillain-Barré syndrome in 4 children, descending variant of Guillain-Barré syndrome in 2 children, and Miller-Fisher syndrome variant of Guillain-Barré syndrome in 1 child. These descending variants were already reported in our previous study on post-COVID neurologic complications in children.[5] Therefore, those with post-COVID Guillain-Barré syndrome presented with variants of Guillain-Barré syndrome rather than the classical symmetric ascending type of Guillain-Barré syndrome, and this association was found to be statistically significant ($P = .03$).

Hughes Disability Score

Hughes disability score in our cohort ranged from 2 to 5. There was no mortality in our cohort (score of 6). The demographic details and clinical characteristics are summarized in Table 1.

Table 1. Demographics and Clinical Characteristics.

	COVID-19 serology	
	Negative: Group A, n (%) (n = 8)	Positive: Group B, n (%) (n = 11)
Gender		
Male	5 (62.5)	5 (45.5)
Female	3 (37.5)	6 (54.5)
Symptoms		
Weakness		
Upper limb predominant	1 (12.5)	3 (27.3)
Lower limb predominant	2 (25)	2 (18.2)
Quadriparesis	5 (62.5)	3 (27.3)
Cranial nerve involvement		
Facial palsy	3 (37.5)	4 (45.5)
Ocular palsy	–	3 (27.3)
Bulbar palsy	–	2 (18.2)
Paresthesia	1 (12.5)	4 (36.4)
Ataxia	–	1 (9.1)
Respiratory involvement	4 (50)	4 (36.4)
GBS variants		
Classical GBS	7 (87.5)	4 (36.4)
Descending variant	1 (12.5)	2 (18.2)
MFS	–	1 (9.1)
Polyneuritis cranialis	–	4 (36.4)
Hughes GBS Disability Score		
0-1	–	–
2	–	3 (27.3)
3	3 (37.5)	2 (18.2)
4	1 (12.5)	2 (18.2)
5	4 (50)	4 (36.4)
6	–	–

Abbreviations: GBS, Guillain-Barré syndrome; MFS, Miller-Fisher syndrome.

Investigations

The inflammatory markers were elevated in 6 children in group B and none in group A. Nerve conduction studies (NCS) were performed in all patients. Of them, 13 children had the demyelinating variants, 5 had the axonal variants, and 1 had no elicitable waveforms. Five children in group A and 8 in group B had the demyelinating variants. Among the children with the axonal variants, 3 were from group A and 2 were from group B. Lumbar puncture was done in all (19/19) patients and all had albumino-cytologic dissociation. Neuroimaging was done in all (19/19) patients. In children with classical and descending variants of Guillain-Barré syndrome, gadolinium enhancement of ventral nerve roots and cauda equina nerve roots were noted. In children with polyneuritis cranialis variant of Guillain-Barré syndrome, enhancement of multiple cranial nerves was noted (Figure 1A-F).

Clinical Complications

In our study, 8 of 19 children were admitted to the pediatric intensive care unit, and all 8 (4 each from groups A and B) required ventilatory support. Among the 19 children, 14 children had autonomic dysfunction (6 from group A and 8 from group B). One child from group B had syndrome of inappropriate antidiuretic hormone. The same child had posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome due to fluctuation in blood pressure. The investigations and clinical complications are summarized in Table 2.

Treatment

All children received intravenous immunoglobulin at 2 g/kg as per treatment protocol at admission. However, 3 children received a second dose of intravenous immunoglobulin at 2 g/kg in group B compared to 1 in group A, and 2 children (1 from each group) required plasma exchange as there was no significant improvement after 1 week of the first dose of intravenous immunoglobulin. In children with poor response to the first dose of intravenous immunoglobulin with elevated inflammatory markers, pulse steroids (5/11) were given, following which they showed brisk recovery. In children with poor clinical improvement in terms of persistent weakness, ventilator requirement, or autonomic dysfunctions after 2 weeks of second dose intravenous immunoglobulin or pulse steroids, third-line therapies including cyclophosphamide or rituximab were used. One child in group A required cyclophosphamide. In group B, 2 children received cyclophosphamide, and 1 required rituximab because of an unsatisfactory treatment response.

Outcome and Follow-up

Children were followed up at regular intervals and assessed with the mRS. The mean follow-up postdiagnosis was 12.4 ±

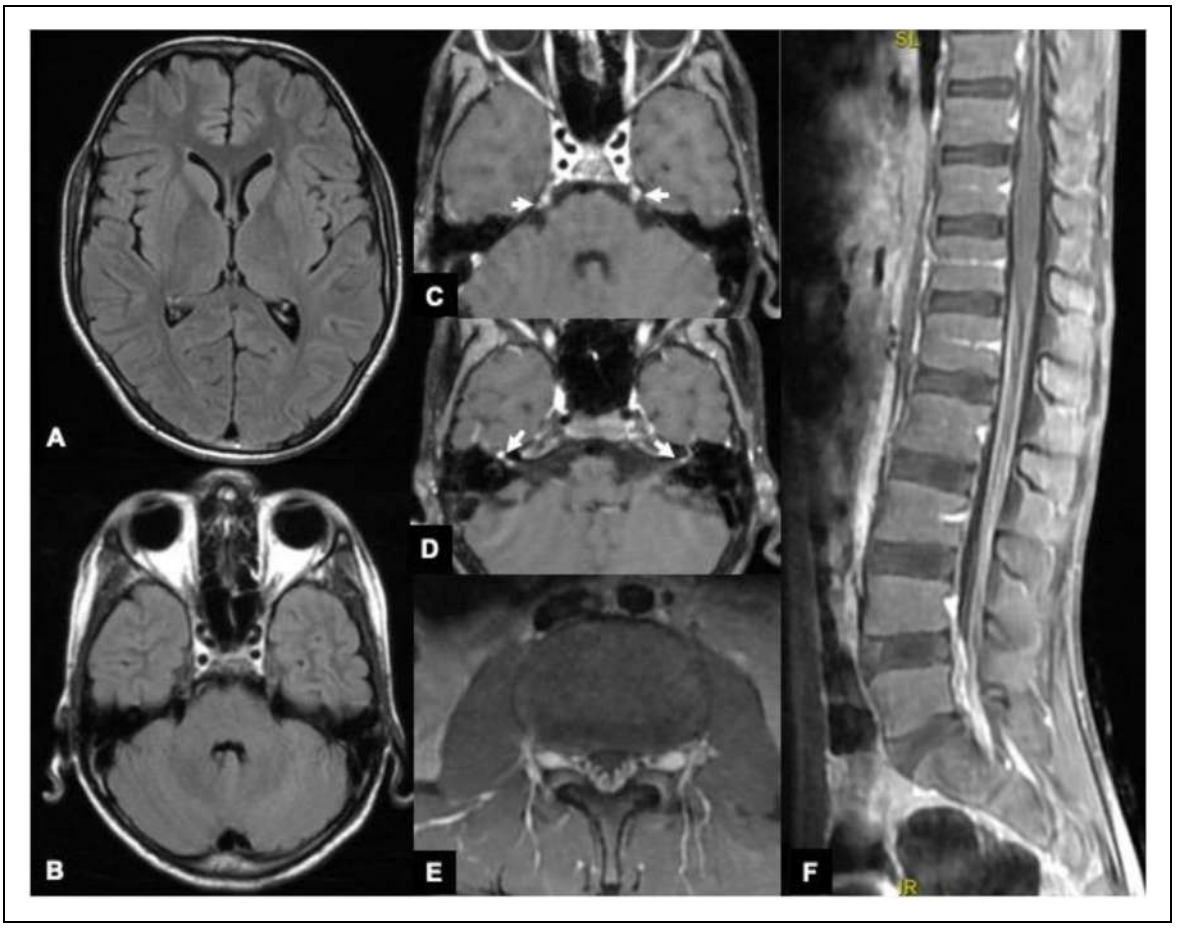

Figure 1. Neuroimaging in Guillain-Barré syndrome: (A and B) The axial fluid-attenuated inversion recovery images of brain does not reveal any abnormal parenchymal signal abnormality. (C and D) The postcontrast T1 fat-suppressed images shows enhancement bilateral fifth and seventh cranial nerves (white arrows). The postcontrast (E) axial and (F) sagittal T1-weighted images of lumbar spine showed enhancement of the cauda equina nerve roots without clumping.

3.8 months. On follow-up at 3 months, in group A, the predominant mRS score was 1. In group B, the predominant mRS score was 0, and one child scored 4, because of complications of Guillain-Barré syndrome. On follow-up at 6 months, in group A, 8 of 8 children scored 0-1. In group B, 10 of 11 children scored 0-1. There was no mortality in our cohort (score of 6). The predominant residual symptom on follow-up was weakness. None were lost to follow-up. The treatment and outcomes are summarized in Table 3.

Discussion

Guillain-Barré syndrome is a clinical diagnosis further supported by lumbar puncture and NCS. However, when a child presents with manifestations apart from classic symptoms of Guillain-Barré syndrome (symmetric ascending flaccid paralysis), neuroimaging may be of value both to confirm the diagnosis of Guillain-Barré syndrome and simultaneously exclude the other differentials, which commonly arise whenever we encounter an uncommon variant of Guillain-Barré syndrome. In our cohort, we found that the children with positive SARS-CoV-2 serology presenting with variants were more than classical Guillain-Barré syndrome. The Miller-Fisher syndrome variant, polyneuritis cranialis variant, and a descending variant of Guillain-Barré syndrome were diagnosed. A similar unexcitable Guillain-Barré syndrome variant was reported in an Indian child with post-COVID Guillain-Barré syndrome.[18] In a systematic review by Abu-Rumeileh et al, including 73 patients aged 11-94 years with COVID-19–associated Guillain-Barré syndrome, they concluded that the most common presentation was a classic sensorimotor variant, even though few other variants were also reported.[39] A systematic review by Sansone et al reported that the demyelinating variety was more common in Western countries; however, a quarter of patients had the Miller-Fisher syndrome variant of Guillain-Barré syndrome.[40] In a systematic review by Jaberi et al,[16] among the reported Guillain-Barré syndrome variants available, classic Guillain-Barré syndrome was the predominant type in 15 patients,[11,17,20,22,23,27-29,31-34] Miller-Fisher syndrome variant in 4 patients,[21,25,26,30] and only 1 had polyneuritis cranialis variant.[24] In our cohort, 2 descending variants of post-COVID Guillain-Barré syndrome were diagnosed, and a

Table 2. Investigations and Clinical Complications.

	COVID-19 serology[a]	
	Negative: Group A (n = 8)	Positive: Group B (n = 11)
Investigations		
Inflammatory markers		
CRP, mg/L, mean (range)	2.9 (4.2)	49.6 (331.3)
Ferritin, ng/mL, mean (range)	165.9 (197)	261.1 (436)
IL-6 levels, pg/mL, mean (range)	3.3 (2.4)	64.1 (347.8)
Nerve conduction studies		
Demyelinating	5 (62.5)	8 (72.7)
Axonal	3 (37.5)	2 (18.2)
Uncharacterizable	-	1 (9.1)
CSF examination		
Albumino-cytological dissociation	8 (100)	11 (100)
Neuroimaging: (suggestive of GBS)		
Nerve root enhancement	8 (100)	11 (100)
Complications		
Dysautonomias		
Hypertension	5 (62.5)	6 (54.5)
Sweating	–	1 (9.1)
Tachycardia	1 (12.5)	1 (9.1)
SIADH	–	1 (9.1)
RCVS	–	1 (9.1)
PRES	–	1 (9.1)

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; GBS, Guillain-Barré syndrome; IL-6, interleukin-6; PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome; SIADH, syndrome of inappropriate antidiuretic hormone. Unless otherwise noted, values are n (%).

Table 3. Treatment and Outcomes.

	COVID-19 serology	
	Negative: Group A (n = 8)	Positive: Group B (n = 11)
Treatment		
Intravenous immunoglobulin		
Single dose	7 (87.5)	8 (72.7)
Two doses	1 (12.5)	3 (27.3)
Plasma exchange	1 (12.5)	1 (9.1)
Steroids	–	5 (45.5)
Cyclophosphamide/Rituximab	1 (12.5)	3 (27.3)
Ventilatory support	4 (50)	4 (36.4)
Outcomes		
mRS score at 3-mo follow-up		
0	2 (25)	5 (45.4)
1	3 (37.5)	2 (18.2)
2	2 (25)	2 (18.2)
3	1 (12.5)	1 (9.1)
4	–	1 (9.1)
5-6	–	–
mRS score at 6-mo follow-up		
0	6 (75)	7 (63.6)
1	2 (25)	3 (27.3)
2	–	1 (9.1)
3-6	–	–

Abbreviation: mRS, Modified Rankin Scale.

similar variant was reported by Michael et al[41] in a 4-year-old Indian child in 2021.

In a study by Garg et al on Indian children with pediatric Guillain-Barré syndrome, they reported that the COVID-19 pandemic led to a marked decline in the incidence of pediatric Guillain-Barré syndrome, and also, the electrophysiological profile was similar to that of the prepandemic era.[14] In a study by La Rovere et al in 2021, among 365 children and adolescents with COVID-19–related neurologic involvement, only 4 (1.1%) patients had Guillain-Barré syndrome, of whom 2 were positive for COVID-19 antibodies and 2 were positive for COVID-19 RT-PCR and antibodies.[5] In contrast to these studies, in the index study, there is an increased incidence of Guillain-Barré syndrome during the era of COVID-19, and also, post-COVID Guillain-Barré syndrome presented with variants of Guillain-Barré syndrome rather than classic forms of Guillain-Barré syndrome.

In our study, magnetic resonance imaging (MRI) was done on all the patients to explore the utility of neuroimaging as an upfront diagnostic modality and also to rule out differential diagnosis. Those who had classical Guillain-Barré syndrome revealed post-gadolinium enhancement of ventral nerve roots. In patients with polyneuritis cranialis variant, enhancement of involved cranial nerves was also noted. The post-gadolinium enhancement of nerve roots may also be seen in inherited neuropathies.[42] Intravenous immunoglobulin was used as the first line of management in all the children. Among the children with poor response to intravenous immunoglobulin, either a second dose of intravenous immunoglobulin or plasma exchange (PLEX) was tried.

The use of corticosteroids has been shown to be ineffective in the treatment of traditional forms of Guillain-Barré syndrome.[43] In our center, we do not routinely use and recommend using steroids in Guillain-Barré syndrome patients. But in the index study, pulse steroids were also used in addition to intravenous immunoglobulin and PLEX, as few patients affected with COVID-19 had underlying cytokine storms and intense inflammation, resulting in the severity of illness. These elevated cytokines contributed to dysregulation of the immune process, resulting in multisystem inflammatory syndrome in children (MIS-C) and other neurologic disorders, including Guillain-Barré syndrome. This possible altered pathophysiology of post-COVID Guillain-Barré syndrome compared to typical Guillain-Barré syndrome could be attributed to the good response to steroids and immunosuppressive agents, including cyclophosphamide and rituximab. In a systemic review by Jaberi et al,[16] among 35 patients included from 26 case series/reports, serology reports were available for 13 patients, and of them, 2 patients who received steroids along with intravenous immunoglobulin had a good response.[32] A

good response was noted for steroids, intravenous immunoglobulin, and plasmapheresis in 3 pediatric Guillain-Barré syndrome patients who were positive for COVID-19 RT-PCR without COVID-19 serology reports.[17,21,34]

In the index study, patients with post-COVID Guillain-Barré syndrome with elevated inflammatory markers had poor responses to intravenous immunoglobulin but responded better to steroids. Therefore, in patients with elevated inflammatory markers, steroids may be helpful by causing immunosuppression and varying responsiveness. Similarly, we noted that those with elevated inflammatory markers and residual weakness responded better to steroids. Although there could have been multiple exposures that could have resulted in Guillain-Barré syndrome, COVID-19 infection is known to trigger Guillain-Barré syndrome. We highlight the need for better-structured prospective multicentric studies with testing of antibody titers.

The limitations of this study include its design and the sample size being small to conclude the clinical features of post-COVID Guillain-Barré syndrome. The titers of serum auto-antibodies were not tested and clinically correlated. These children were not tested for all the possible viral infections that could have triggered the Guillain-Barré syndrome.

Conclusion

Post-COVID Guillain-Barré syndrome in children presented with variants of Guillain-Barré syndrome rather than the classical symmetric ascending type of Guillain-Barré syndrome. Neuroimaging is of great value in confirming Guillain-Barré syndrome diagnosis and excluding differentials and can be utilized in atypical presentations of Guillain-Barré syndrome. Post-COVID pediatric Guillain-Barré syndrome patients with elevated inflammatory markers and residual weakness may be given a pulse steroids trial after the first-line therapy (intravenous immunoglobulin). Early diagnosis, monitoring, and prevention of complications, including secondary infections, decubitus ulcers, and autonomic dysfunction, can improve the overall outcome in these children.

Authors Contributions

LS and ST contributed to the concept and study design; LS, DK, ST, PK, JPG, DK, BC, SD, and RG collected the clinical and MRI data; LS, DK, and PKG performed the analyses; LS, PK, JPG, DK, SP, and KS interpreted the data; LS, DK, PKG, and ST wrote the main manuscript text and figures. All authors reviewed and approved the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Compliance Statements

Ethical approval was obtained from the institutional review board. Informed written consent/assent to participate/publish were obtained from the parents/guardians/patients.

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