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Case Report

CASE REPORT

Clinical Spectrum of Neurological Manifestations in Pediatric COVID-19 Illness: A Case Series

Afreen Khan , MD[1]*, Aparna Chakravarty , MD[2], Abhinav Jain, MD[3], Rekha Harish, MD[4], Rizwan Naqishbandi, MBBS[5] *and* Twisha Ishani, MBBS[6]

[1]Department of Pediatrics, HIMSR & HAHC Hospital, New Delhi 110062, India
[2]Department of Pediatrics, HIMSR & HAHC Hospital, Fellowship Pediatric Infectious Disease (Canada), New Delhi, India
[3]Department of Radiodiagnosis, HIMSR & HAHC Hospital, New Delhi 110062, India
[4]Department of Pediatrics, HIMSR & HAHC Hospital, New Delhi 110062, India
[5]Department of Pediatrics, HIMSR & HAHC Hospital, New Delhi 110062, India
[6]Department of Pediatrics, HIMSR & HAHC Hospital, New Delhi 110062, India
*Correspondence: Afreen Khan, HIMSR & HAHC Hospital, New Delhi 110062, India.
E-mail<afreenkhan1204@yahoo.com>.

ABSTRACT

We describe a cohort of three patients with variable neurological presentations by SARS-COV-2 infection. It includes one case each of acute cerebellitis, acute encephalomyelitis and arterial ischemic stroke. To the best of our knowledge, we report the first pediatric case of acute cerebellitis due to SARS-CoV-2 infection. All critically ill patients were treated with methylprednisolone pulse therapy and dexamethasone. Patient with acute cerebellitis in addition required intravenous immunoglobulin infusion. All the patients responded to the treatment with complete neurological recovery.

INTRODUCTION

Since the emergence of COVID-19 pandemic, varied clinical manifestations are reported, which further broaden the spectrum of illness caused by SARS-CoV-2 infection. In the early phase of the pandemic, most published data were on adults with SARS-CoV-2 infection. Only mild symptoms like fever, cough, headache, rhinorrhoea, myalgia, sore throat etc. were reported in children [1]. It was therefore presumed that children had only mild symptoms with less hospitalization, until April 2020 when reports from the UK described the features suggestive of incomplete Kawasaki disease and Toxic shock syndrome in association with SARS-CoV-2 infection [2]. Since then, similar presentations have been reported in children across the globe and have been termed as Multisystem Inflammatory syndrome in children (MIS-C) [3–7]. It incorporates a spectrum of presentations from mild symptoms to severe life threatening complications like respiratory failure, shock, disseminated intravascular coagulation, renal failure etc [8]. Data on

LEARNING POINTS/TAKE HOME MESSAGES

- High index of suspicion is required to diagnose neurological disease following SARS-CoV-2 infection and the pediatrician should be prepared to have a complete set of laboratory data focusing on CNS diseases.
- Patients may present with isolated neurological involvement without affecting the respiratory system.
- Blood pressure should be monitored in all patients with MIS-C till more detailed studies are available.
- We emphasize that early intervention with intravenous immunoglobulins and steroids is beneficial in MIS-C patients with neurological disease.

pediatric neurological complications following COVID-19 are scarce and they are either reported as a part of large studies or as individual case reports. Here, we report three cases with different neurological manifestations of SARS-CoV-2 infection and also the first case of acute cerebellitis in pediatric age group. Consent was taken from the parents of all the cases.

CASE SERIES

Acute cerebellitis (Case 1)

Eleven year old male child presented to the Emergency Department with two episodes of generalized tonic-clonic seizures. There was a history of fever, headache, vomiting and abdominal pain for last 3 days. On examination, the child was delirious and had horizontal nystagmus, dysarthria, nuchal rigidity, features of raised intracranial tension (ICT) and shock. In view of raised ICT 3% normal saline was infused. Broad spectrum antibiotics (ceftriaxone and acyclovir) along with intravenous fluids, inotropes were administered. Contrast-enhanced magnetic resonance imaging (CEMRI) brain revealed features of acute cerebellitis (Fig. 1a and 1b). Initial laboratory investigations were unremarkable. Intravenous Methylprednisolone pulse therapy (30 mg/kg/day for 3 days) was started. On third day, the child deteriorated neurologically however, his hemodynamical parameters stabilized and was weaned off the inotropic infusion. Serial MRI revealed increasing cerebellar edema. Further laboratory evaluation showed elevated inflammatory markers along with positive COVID serology, fulfilling the criteria for MIS-C (Table 1). Other laboratory investigations were not suggestive of any viral, bacterial or immunological abnormality (Table1). Cerebrospinal fluid (CSF) analysis could not be performed due to persistent raised ICT. Intravenous immunoglobulin (IVIG) infusion (2 g/kg of body weight single dose), mannitol and steroids (intravenous dexamethasone 0.15 mg/kg/dose six hourly) were added. Child improved gradually. Cognition improved in next 4 days but cerebellar signs -ataxia, dysarthria and nystagmus persisted. CEMRI brain performed on Day 7 also displayed slow resolution of cerebellar edema. Oral steroids (prednisolone 2 mg/kg/day), antiepileptic drugs, osmotic agents along with physiotherapy were continued. Steroids were gradually tapered over a period of 6–8 weeks. On follow-up at 4 months, child is stable with normal neurological examination and neuroimaging demonstrated complete resolution.

Encephalomyelitis (Case 2)

Seven year old female, known case of right temporal epilepsy on multiple antiepileptic drugs since 5 years of age presented with a history of high grade fever, loose stools, vomiting and throat pain for 4 days.

On examination she was sick, febrile with generalized erythematous rash, swollen lips and non-suppurative tonsillo-pharyngitis. She was hemodynamically stable with normal systemic examination. Intravenous antibiotics—Injection ceftriaxone 100 mg/kg/day and clindamycin-30 mg/kg/day—along with symptomatic treatment were started. SARS-CoV-2 RT–PCR was

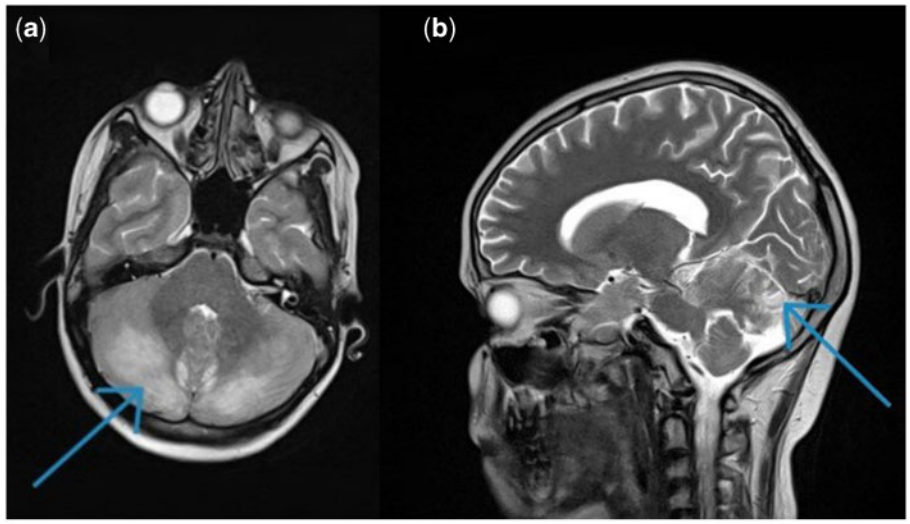

FIG. 1a and 1b. Diffuse cerebellar swelling with T2/FLAIR hyper intensity (arrows).These areas showed diffusion restriction on DW images and post-contrast enhancement with mass effect suggestive of acute cerebellitis.

negative and initial laboratory parameters were normal except renal profile suggestive of prerenal AKI. Next day, she developed toxic shock syndrome. Significant laboratory parameters were leucocytosis, thrombocytopenia, raised inflammatory markers with slightly deranged renal profile and hypo-albuminemia (Table 1). Child was shifted to Pediatric Intensive Care Unit, started on inotrope (norepinephrine @ 1 µg/kg/min) and antibiotics were upgraded to injection meropenem @ 60 mg/kg/day and vancomycin @ 45 mg/kg/day. Over next 36 h the body rash and pharyngitis improved. However, on Day 4, there was a sudden neurological deterioration with Glasgow Coma Scale of 5/15 and poor respiratory efforts, and thus was mechanically ventilated. Chest X-ray was normal. CSF analysis was performed, which did not reveal any evidence of viral/bacterial meningitis and RT–PCR for COVID-19 was also negative. However, CEMRI brain suggested possibility of encephalitis with myelitis (Fig. 2a and 2b) and serology for SARS-CoV-2 was positive. Child met all the criteria of Multisystem Inflammatory Response Syndrome-Children (toxic shock syndrome, multisystem involvement, raised inflammatory markers, no other obvious cause of inflammation, positive SARS-CoV-2 serology). In setting of MIS-C with no other explainable cause for neurological involvement, it was attributed to SARS-CoV-2 infection. Pulse methylprednisolone therapy (30 mg/kg/day) for 5 days followed by intravenous dexamethasone 0.15 mg/kg/dose six hourly was started. Child was extubated after 2 days of ventilation. After receiving pulse methylprednisolone therapy, she developed hypertension, which was managed with antihypertensive drugs. She responded well to the therapy and was discharged after 16 days on oral steroids, which were continued 6 weeks and stopped after tapering. At 2-month follow-up, patient had no neurological deficit.

Arterial ischemic stroke (Case 3)

Fifteen years old female with no chronic medical history presented to Emergency Department with brief history of headache and multiple episodes of generalized tonic-clonic seizures in the last 24 h. On examination, child was apprehensive, sick looking, conscious and had respiratory distress. The saturation on oxygen by mask @ 6 l/min was 86%. Initial stabilization started with administration of high flow oxygen by mask with reservoir bag, intravenous fluids and antiepileptic drug. Her condition soon deteriorated and patient had gasping respiration for which she was mechanically ventilated. A probable diagnosis of severe acute respiratory infection (SARI) was made. Initially the seizures were attributed to hypoxia. Complete neurological examination could not be performed as child was sedated during ventilation. Empirical antibiotics ceftriaxone,

Table 1. Laboratory features of three children with neurological involvement

	Case1: acute cerebeliitis	Case 2: encephalomyelitis	Case 3: arterial ischemic stroke
Hemoglobin(g/dl)	9.9	10.2	8
TLC (thousand/cmm)	11.51×10^3	22×10^3	9.7×10^3
DLC (polymorphs (P), lymphocytes (L) in %)	P88L9	P60L30	P85L11
Platelet counts (lacs/cmm)	1.32	1.2	1.49
Blood urea(mg/dl)	24.9	32.8	18
Creatinine (mg/dl)	0.38	0.5	0.75
SGOT (IU/l)	30	56	45
SGPT (IU/l)	19	71	13
Albumin (g/dl)	2.1	2.5	2.9
CRP (mg/dl)	4.8	Positive (qualitative)	18.3
ESR (mm/h)	60	60	
S. Ferritin (ng/ml)	336	362.5	265.9
D-dimer (FEU/l)	1.47	1.51	4.08
Coagulation profile	Prothrombin time: 14.0 s INR: 1.04	Prothrombin time: 15.6 s INR: 1.16	Prothrombin time =19.9 INR=1.49
Urine R/M	RBC: 8–10/hpf	WNL	WNL
Culture	Blood c/s: sterile	Blood c/s: sterile CSF c/s: sterile Throat swab c/s: sterile	Blood c/s: sterile
COVID RT–PCR	Negative	Negative	Negative
SARS CoV-2 antibody (AU/ml)	185	149.0	42.5
Others	Influenza A & B RT–PCR: negative Serology for HSV, RSV, EBV, JE, rotavirus, Parvovirus B-19 were negative ANA: negative Immunoglobulin profile: WNL	Malaria serology: negative Typhidot IgM: negative NS1Antigen: negative Dengue serology; negative Scrub typhus: negative	ANA: negative APLA: negative Influenza PCR: negative
ECG	WNL	WNL	WNL
Echocardiography	WNL	Mild pericardial effusion	WNL
CSF analysis	–	HSV-I: negative HSV II- negative JE PCR: negative CMV IgM: negative	–
USG whole abdomen	Mesentric adenitis with minimal free fluid	Malrotated right kidney Mild gall bladder wall edema & pelvic ascites	
Neuroimaging	Fig. 1a and 1b	Fig. 2a and2b	Fig. 3

TLC, total leucocyte count; DLC, differential leucocyte count; CRP, C- reactive protein; ESR, erythrocyte sedimentation rate; S. ferritin, serum ferritin; R/M, routine microscopy; WNL, within normal limits; C/S, culture and sensitivity; CSF, cerebrospinal fluid; HSV, herpes simplex virus; JE, Japanese encephalitis; EBV, Epstein–Barr virus; VZ, varicella zoster virus; RSV, respiratory syncytial virus; ANA, antinuclear antibody; APLA, antiphospholipid antibody; PCR, polymerase chain reaction; EEG, electroencephalogram; PS, peripheral smear; MP, malarial parasite; USG, ultrasonography; CEMRI, contrast-enhanced magnetic resonance imaging.

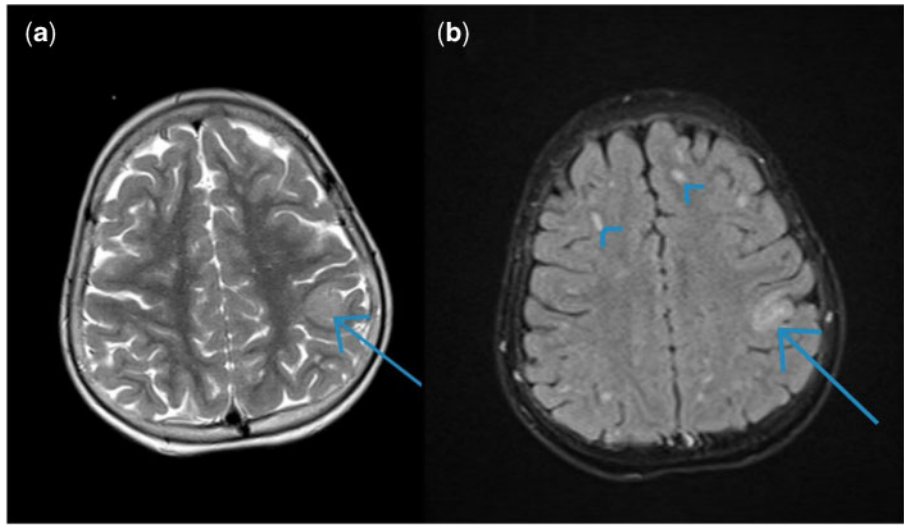

FIG. 2a and 2b. Area of gyral swelling with hyper intensity in left frontal lobe on T2WI (arrow). Multiple smaller areas of hyper intensity are seen in the bilateral frontal and parietal lobes (arrowheads). On post-contrast T1FS image, these show enhancements. Findings favored encephalomyelitis.

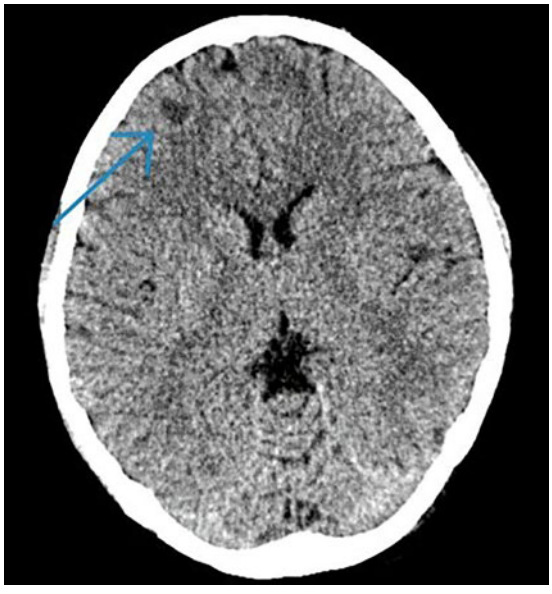

FIG. 3. Focal area of hypodensity (arrow) present in right frontal lobe suggesting ischemic change.

vancomycin and oseltamivir were started. Initial laboratory values showed total normal leucocyte count with lymphocytopenia and raised inflammatory markers (CRP, ESR, ferritin and D-dimer). Chest X-ray was consistent with acute respiratory distress syndrome (bilateral coalescent opacities predominantly in the lower zones and parahilar location) but three subsequent samples from nasopharynx and tracheal aspirate were negative for SARS-CoV-2 RT–PCR. She was gradually weaned off the ventilator support and shifted to Bilevel Positive Airway Pressure mode of NIV after 5 days of admission. Post-extubation, on neurological examination she had tremulousness of tongue and horizontal nystagmus. Neuroimaging showed a small hypo-dense area involving subcortical white matter in the right frontal lobe suggestive of infarct (Fig. 3) and a small intracerebral hematoma in left frontal lobe with mild perilesional edema.

Her antibody titers for COVID were significantly raised with raised inflammatory markers. A diagnosis of MIS-C was made. She was started on IV dexamethasone (0.15 mg/kg/dose six hourly) followed by oral steroids for 1 week. Child also had hypertension for period of 2 days the cause of which could not be ascertained. She gradually improved and was discharged after 17 days. A follow-up at 4 month showed no neurological deficit.

DISCUSSION

We report a cohort of three patients with distinct neurological involvement due to SARS-CoV-2 infection: one case each of acute cerebellitis, arterial

ischemic stroke (AIS) and encephalomyelitis. Evidence of infection was positive antibodies against SARS-CoV-2 in all. The IgG antibodies were measured in patient's serum by using indirect chemiluminescence immunoassay technology for the quantitative determination of Anti-S1- and Anti-S2-specific IgG antibodies to SARS-CoV-2, a value of more than 15 AU/ml was considered positive. Recent studies have suggested that COVID serology has high sensitivity and specificity in COVID-19 detection [9, 10]. A meta-analysis performed by Zhang, *et al.* [9] to study the diagnostic efficacy of anti SARS- CoV-2 IgG/IgM test for COVID-19 reported pooled sensitivity and specificity of 0.85 (95% CI 0.79–0.90) and 0.99 (95% CI 0.98–1.0). The diagnosis of MIS-C was made when all the criteria suggested by CDC or WHO were fulfilled [11, 12]. In the current series, all three patients had specific neurological complications, were seriously ill, had MIS-C and definite neuroimaging finding. It was consistent with the reports showing association of specific neurological complications with seriously ill patients [13, 14].

In adults, cerebrovascular problems due to thrombotic complications are the most common neurological sequel followed by meningitis and encephalitis [15]. There is limited information about detailed neurological involvement by SARS-COV-2 virus in children and no large case series or studies on the same are available till date. They are also underreported in preverbal and critically ill children. To study these complications, Panda, *et al.* [13] conducted a systematic review and meta-analysis. They included all articles published from December 2019 to July 2020 in children <18 years with confirmed neurological complications due to COVID-19. The review showed that amongst 41 children with COVID-19 associated definite neurological complications, encephalopathy was a predominant neurological manifestation (25 children) followed by meningeal signs (17 children) and seizures (12 children). Similarly encephalopathy was the most common finding in the present series. In the review by Panda, *et al.* [13] neuroimaging findings were available only for few patients but most of them were normal. In contrast to this Lindan, *et al.* [16] described post-infectious immune-mediated acute disseminated encephalomyelitis as the most common neuroimaging abnormality followed by myelitis and neural enhancement in 38 children with neurological disease related to SARS-CoV-2 infection. However, we cannot assign such ranks to our findings due to small cohort with three different neuroimaging findings.

At the time of presentation, one patient had no respiratory involvement, one presented with SARI and other with pharyngitis that later developed pneumonia. This is consistent with the study by Ahmad, *et al.* [14]. They suggested that neurological symptoms may precede respiratory symptoms or may be the only symptom of COVID-19.

Till date, only few cases of AIS were reported in children whereas none of acute cerebellitis and acute hemorrhagic encephalopathy [13, 16–19]. To the best of our knowledge we here report the first case of acute cerebellitis associated with SARS-CoV-2 in children. After the onset of COVID pandemic, only 10 cases of cerebellar symptoms, associated with SARS-COV-2 infection have been reported. All patients were adult males and only one had serious neurocognitive impairment. Abnormal neuroimaging (bilateral cerebellar edema) was present only in one patient. Seven patients were treated with combination of IVIG and steroids or either of them whereas three patients did not receive any specific therapy. There was mortality of one patient who had severe respiratory involvement. Rest recovered completely within a short duration [20–26]. In contrast to these reported patients with cerebellar symptoms, our patient was an adolescent male who had serious neurological involvement with significant MRI changes. He was treated with IVIG and steroids. Though he responded gradually but recovered completely.

In adults, cerebrovascular accidents (CVA) are more commonly seen neurological complication of SARS-CoV-2. CVA are rarely seen in children. Only few case reports are available till date in pediatric age group [19, 27, 28]. Beslow, *et al.* [29] performed a survey including 61 international sites with pediatric stroke expertise and found that 4.6% of all the patients who had stroke were found to be positive for SARS-CoV-2 however, most of them had additional established risk factor. No such risk factors suggestive of thrombophilia were found in our patient. The main presenting complaints in previous

reports were headache, vomiting and weakness of extremities but in our patient with AIS had no previous history and presented with seizures and severe respiratory distress.

In this series, all patients were treated with intravenous dexamethasone and pulse methylprednisolone therapy while one patient with acute cerebellitis required IVIG. These patients responded gradually to the treatment. On follow-up visits, none had any neurological deficits. Recent studies have also shown that steroids, IVIG and supportive therapy are mainstay of management [30].

Various pathogenic mechanisms have been proposed but nothing confirmatory has been known so far. ACE2 receptors present on glial cells in brain and spinal neurons serve as a target receptor for attachment and internalization of virus followed by multiplication and damage. The virus enters the brain either through the circulatory or neuronal pathway. The cytokines disrupt the blood brain barrier during the cytokine storm through enabling the virus brain entry. Virus can also reach the brain through the nasal epithelium via olfactory neurons and olfactory bulb or through peripheral nervous system in a retrograde manner through neurons. Virus damages the cells either directly or through post-infectious autoimmune process. The above two mechanisms can explain the occurrence of encephalitis, autoimmune disseminated encephalomyelitis etc. [31–33]. In our series, both patients with cerebellitis and encephalomyelitis had negative SARS-CoV-2 RT–PCR, positive serology, elevated inflammatory markers and responded to immunosuppressive therapy, which favors an immune-mediated phenomenon.

Cerebrovascular complications have resulted from thrombotic events supported by various studies demonstrating a hypercoagulable state in COVID; the cause of which is multifactorial like endothelial dysfunction, inflammation, hypoxia etc. [34, 35].

Binding to ACE-2 receptors may also cause abnormally elevated blood pressure, which increases the risk of cerebral hemorrhage. In three of our patients who were seriously ill transient hypertension was present. In patient with acute cerebellitis, it was attributed to raise ICT but in other two patients, it could be explained by either steroids or above-mentioned mechanism. Detailed studies can help to analyze the association of hypertension with SARS-CoV-2 infection.

In conclusion, though the vaccine has been introduced in many countries across the globe, it is not yet recommended in children <18 years of age [36]. Even after recommendation follow-up studies are required to assess the neuro-protective efficacy. Poor immunization coverage especially in resource limited countries and emergence of new mutant strains are other potential challenges. Identifying a neurological disease associated with SARS-CoV-2 in patients with mild or no respiratory involvement is often difficult. We hereby emphasize that any neurological symptom in a SARS-CoV-2 infections needs to be investigated appropriately and reported in detail to create a better understanding of the disease spectrum. This will enable treating physician for timely diagnosis and management failure of which might leave patients with severe neurological sequelae. More detailed studies are required to further comment on the association between hypertension and COVID-19 illness, till then careful blood pressure monitoring will help to detect hypertension and its complications.

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