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Case Series

Paediatrics Section

Rare Neurological Presentations of Paediatrics COVID-19 Cases Reported at a Tertiary Care Hospital in Mizoram, India

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ABSTRACT

Apart from the regular respiratory symptoms, neurological manifestations like headache, encephalopathy, encephalitis, seizure, coma, demyelinating disorders, and aseptic meningitis has been seen in paediatric Coronavirus Disease-2019 (COVID-19) positive cases. The present case series is about three children, of age range 9 to 15 years, who presented with encephalitis between January 2022- February 2022. All the children tested positive for COVID-19, either by Rapid Antigen Test (RAT) or by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR). One patient had necrotising encephalitis like changes in the MRI neuroimaging of the brain, but negative Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Ribonucleic Acid (RNA) PCR in Cerebrospinal Fluid (CSF). The second patient's Magnetic Resonance Imaging (MRI) brain was suggestive of acute encephalopathy, but with normal CSF analysis. The third patient presented with clinical findings suggestive of encephalitis with normal CSF study and normal MRI. The children were managed with antipyretics, antiepileptics, antibiotics, and antiviral, injection mannitol, and steroids. After the completion of the treatment, all the children were alive and were discharged from the hospital.

Keywords: Altered sensorium, Coronavirus, Encephalitis, Encephalopathy, Outcome

INTRODUCTION

The primary target of SARS-CoV-2 is the respiratory system, but neurological manifestations like encephalopathy, headache, seizure, coma, altered sensorium, encephalitis, and aseptic meningitis have been reported in the COVID-19 positive paediatric patients [1-6]. The first neurological symptoms with SARS-CoV-2 were reported in March 2020 [7] with a positive specific SARS-CoV-2 RNA in CSF followed by multiple reports of SARS-CoV-2 associated encephalitis, with only few showing viral detection in the CSF. The entry of mechanism can be through haematogenous dissemination via endothelial cells or via the cribriform plate and olfactory bulb [8]. The present case series is about three cases of CNS involvement of SARS-CoV-2 infection in children, without any respiratory symptoms.

CASE SERIES

Case 1

A previously healthy 9-year-old girl presented to the local Primary Health Centre with repeated episodes of convulsions (generalised tonic clonic) with neck rigidity, altered sensorium, projectile vomiting (three episodes), and two days history of fever. The child tested positive for SARS-CoV-2 by RAT. She was then, immediately referred to Zoram Medical College (ZMC) after initiating emergency medications (inj. midazolam for convulsion, inj. paracetamol for fever and intravenous (i.v.) fluid dextrose normal saline).

The child presented to the hospital with generalised tonic clonic seizure, Glasgow Coma Scale (GCS) score ranged from 8 to 9, muscle power were: left upper and lower limb 3/5 each, right upper and lower limb 1/5. Muscle tone was decreased in all the four limbs. Deep tendon reflexes were decreased in all the limbs. Plantar reflex was extensor response on right and flexor response on left side. Both pupils were normal in size and reaction. RT-PCR from nasopharyngeal swab was positive for SARS CoV-2. Fundus examination was normal with no signs of papilloedema. The child was given inj. mannitol 20%, inj. leveteracetum, inj. methylprednisolone and inj. cefotaxime. The CSF analysis showed white cell count (WCC) of 2/mm^3 (smear was scanty cellular, no atypical cell seen) and CSF protein was 33 mg/dL. CSF RT-PCR for SARS-CoV-2 RNA was negative. The CSF for Acid Fast Bacilli (AFB) and Gram stain were negative. There was no growth after 72 hours of incubation for both aerobic and anaerobic culture. The blood parameters were not suggestive of Multisystem Inflammatory Syndrome in Children (MIS-C).

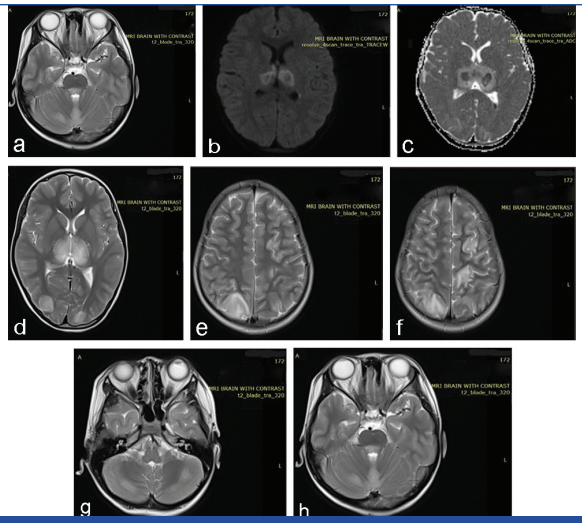
The MRI brain showed a heterogeneous mass in both thalami on Susceptibility Weighted Imaging (SWI), bilateral symmetrical areas of diffuse restriction in both thalami on Diffusion Weighted Imaging (DWI), the classic acute necrotising appearance of "tricolour/target-like appearance" or "concentric/laminar structure" in both thalami, hyperintense signals in both thalami on T2 weighted image (T2WI), multiple foci of gyral oedema, bilateral cerebellar and dorsum of brainstem involvement on T2WI. The MRI findings were consistent with necrotising encephalitis [Table/Fig-1a-f]. [Table/Fig-1g,h] shows bilateral cerebellar and dorsum of brainstem involvement on T2WI respectively. Following therapy, the patient showed clinical and neurological improvement. Her muscular weakness improved and the patient started taking orally. She was discharged on 10th day without any focal neurological deficit. The laboratory findings are shown in [Table/Fig-2].

Case 2

A previously healthy 13-year-old boy presented at a primary health centre with altered sensorium, seizures and two days history of fever. The boy was referred to the Institute (tertiary hospital). He showed positivity for SARS-CoV-2 rapid antigen.

On the way to the hospital, his consciousness deteriorated and became unresponsive. On admission, his vitals were unstable pulse rate 138 per minute, respiratory rate 24/minute, blood pressure 100/80 mmHg, temperature 101° F, room air SpO_2 was 85%.

On Central Nervous System (CNS) examination, both pupils were equal in size and reactive to light; no cranial nerve palsy or neck rigidity. All the deep tendon reflexes were normally elicitable. Plantar reflex was flexion response on both side. The fundus examination showed no papilloedema. The boy had GCS of 10 (E4V1M5). He did not require intubation. The patient was started on injection remdesivir, inj. dexamethasone, empirical i.v. antibiotics, and



[Table/Fig-1]: a) Shows heterogeneous mass in both thalami on SWI; b) Shows bilateral symmetrical areas of diffuse restriction in both thalami on DWI; c) Shows classic acute necrotising encephalopathy of childhood (ANEC) appearance of tricolour/target like appearance or concentric/laminar structure in both thalami on ADC; d-f) Shows multiple foci of gyral oedema. g,h) shows bilateral cerebellar and dorsum of brainstem involvement on T2WI.

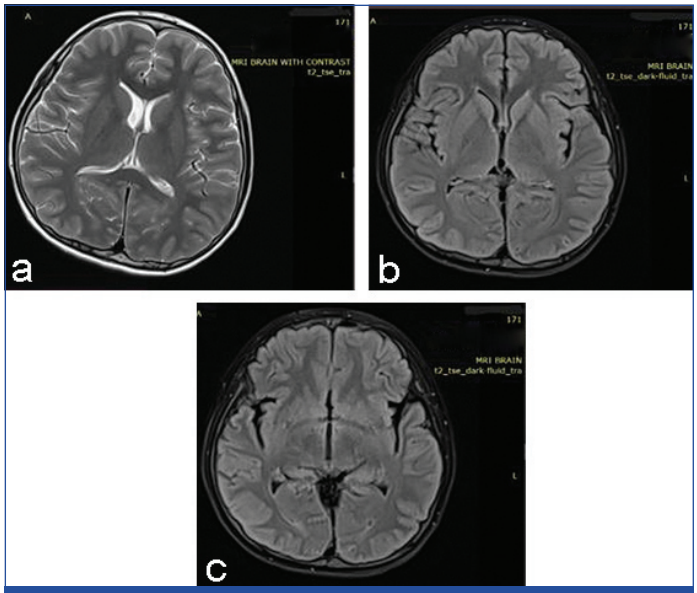
CSF		
Parameters	**Result**	**Reference range**
Volume (mL)	0.6 mL	-
Appearance	Clear	Clear
Sugar (mg/dL)	56	50-80
Protein (mg/dL)	33	<50
Colour	Colourless	
Clot formation	Absent	Absent
Total leucocyte count (cells/cumm)	2	Transudate: <1000 Exudate: >1000
RBC	Nil	Nil
Cytology	Smear was scantly cellular No atypical cell seen	
Gram stain	Negative	
Ziehl–Neelsen staining	Negative	
Culture	No growth	
Test	**Result**	**Reference range**
Liver function test		
Bilirubin (Total) (mg/dL)	0.4	0.3-1.3
Direct (Conjugated) (mg/dL)	0.2	0.1-0.4
Indirect (Unconjugated) (mg/dL)	0.2	0.2-0.9
Total protein (gm/dL)	5.9	6.7-8.6
Albumin (gm/dL)	3.4	3.5-5.5
Globulin (gm/dL)	2.5	2.0-3.5
SGOT (AST) (U/L)	54	12-38
SGPT (ALT) (U/L)	76	7-41
Alkaline phosphatase (U/L)	158	<20 yrs: 54-369
Kidney function test/Renal function test		
Blood urea (mg/dL)	50	15-45
Serum creatinine (mg/dL)	0.6	M:0.6-1.2 F:0.5-0.9
Serum electrolyte		
Sodium (meq/L)	138	136-146
Potassium (meq/L)	3.8	3.5-5.0
Calcium (Total) (mg/dL)	9.7	8.7-10.2
CRP (mg/dL)	7.5	<6
D-dimer (ng/dL)	200.18	<500

[Table/Fig-2]: Laboratory findings of patient 1.
*RBC: Red blood cells; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; CRP: C-reactive protein

levetiracetam immediately on reaching to our Paediatrics Intensive Care Unit (PICU). Nasopharyngeal RT-PCR was tested positive for SARS-CoV-2 at time of admission. CSF analysis are showed in [Table/Fig-3] and was negative for SARS-CoV-2 RNA. The contrast MRI brain showed cortical enhancement in left frontal lobe on T2 and Fluid Attenuated Inversion Recovery (FLAIR) images suggestive of acute encephalopathy [Table/Fig-4].

Test: CSF fluid	Result	Reference range
Sugar (mg/dL)	70	50-80
Protein (mg/dL)	20.9	<50
Appearance	Clear	Clear
Clot formation	Absent	Absent
Total leucocyte count (cells/cumm)	7	Transudate: <1000 Exudate: >1000
Red cells	Nil	Nil
Cytology	Scantly cellular smear shows few intact and degenerated cells comprising mainly lymphocytes. No atypical cell seen on the smear examined DLC- L 98% N 2%	
Gram stain	Negative	
Ziehl–Neelsen staining	Negative	
Culture	No growth	
Liver function test		
Bilirubin (Total) (mg/dL)	0.5	0.3-1.3
Direct (Conjugated) (mg/dL)	0.2	0.1-0.4
Indirect (Unconjugated) (mg/dL)	0.3	0.2-0.9
Albumin (mg/dL)	4.1	3.5-5.5
SGOT (AST) (U/L)	48	12-38
SGPT (ALT) (U/L)	44	7-41
Alkaline phosphatase (U/L)	509	<20 yrs: 54-369
Kidney function test		
Blood urea (mg/dL)	21	15-45
Serum creatinine (mg/dL)	0.6	M:0.6-1.2 F:0.5-0.9
Serum electrolytes		
Sodium (meq/L)	138	136-146
Potassium (meq/L)	4.0	3.5-5.0
Test	**Results**	
D-dimer (ng/dL)	293.8	<500
CRP (mg/dL)	6	<6

[Table/Fig-3]: Laboratory findings of patient 2.



[Table/Fig-4]: a-c) Show minimal cortical enhancement in left frontal lobe on T2 and FLAIR images in a patient with acute encephalopathy.

The patient responded to the treatment. On the third day, the child became conscious, there was no episode of convulsion, he could sit without support, walk with support and he could take semi-solid diet. The boy was discharged on the 7th day after completion of the dose of remdesivir. At the time of discharge, he was active, stable, no focal neurological defecit and was accepting food orally.

Case 3

A previously healthy 15-year-old male presented at a district hospital with fever associated with headache for four days, mulitple episodes of seizures for three days and altered sensorium for one day. The patient was found positive for RAT for SARS-CoV-2 and then referred to the tertiary centre Zoram Medical College (ZMC). The patient reached the Institute after three hours of journey, during which his consciousness deteriorated.

On admission, the patient had altered sensorium vitals Heart Rate (HR) 140/minute, Temperature 102°F, Blood Pressure (BP) 100/ 80 mmHg, Room Air SPO_2 85%. He was drowsy with GCS -- E1V2M5, with GCS scores 8/10, neck rigidity was present. There were no signs of dehydration, his pupils were equal in size and bilaterally reactive to light; he had no cranial nerve palsies, plantar bilateral were extensors response and the deep tendon reflex on knee bilateral were 3+, ankles bilateral were 3+, The fundus examination showed no papilloedema. He was managed with intravenous antibiotic (ceftriaxone), inj. paracetamol, inj. dexamethasone, inj. 20% mannitol and inj. phenytoin, immediately on reaching to the (PICU). Nasopharyngeal RT-PCR was positive for SARS-CoV-2 at time of admission. Lumbar puncture was done on the next day of admission and CSF analysis showed in [Table/Fig-5] and was negative for SARS-CoV-2 RNA. The MRI brain showed normal findings. The child responded to the medical treatment. The child regained consciousness next day and there was no episode of convulsion, he could sit without support. He could walk with support on the 3rd day. Rest of the hospital stay was uneventful. The boy was discharged on the 10th day. Patient was well and had no neurological deficit at the time of discharge.

Test : CSF fluid	Result	Reference range
Sugar (mg/dL)	60	50-80
Protein (mg/dL)	30.9	<50
Appearance	Clear	Clear
Clot formation	Absent	Absent
Total leucocyte count (cells/cumm)	5	0-5/cumm
Red cells	Nil	Nil
Cytology	Scantly cellular smear shows few intact and degenerated cells comprising mainly lymphocytes. No atypical cell seen on the smear examined DLC- L 89%, N 11%	
Gram stain	Negative	
Ziehl–Neelsen staining	Negative	
Culture	No growth	
Liver function test		
Bilirubin (Total) (mg/dL)	0.4	0.3-1.3
Direct (Conjugated) (mg/dL)	0.2	0.1-0.4
Indirect (Unconjugated) (mg/dL)	0.3	0.2-0.9
Albumin (mg/dL)	4.1	3.5-5.5
SGOT (AST) (U/L)	28	12-38
SGPT (ALT) (U/L)	24	7-41
Alkaline phosphatase (U/L)	263	<20 years: 54-369
Kidney function test		
Blood urea (mg/dL)	40	15-45
Serum creatinine (mg/dL)	1.2	M:0.6-1.2; F:0.5-0.9
Serum electrolytes		
Sodium (meq/L)	140	136-146
Potassium (meq/L)	4.0	3.5-5.0
Test results		
D-dimer (ng/dL)	245	<500
CRP (mg/dL)	7.5	<6

[Table/Fig-5]: Laboratory findings of patient 3.

DISCUSSION

The virus enters the lungs via Angiotensin-Converting Enzyme 2 (ACE-2) receptor for SARS-CoV-2 and the virus uses the Transmembrane protease, serine 2 (TMPRSS2) for S protein priming [8]. Recent studies have demonstrated that SARS-CoV-2 exhibits neurotropic properties [9,10]. A direct neuroinvasive effect of the virus could be explained by its retrograde movement along the olfactory or the peripheral lung nerves to the CNS or via haematogenic migration through the CNS endothelia that express ACE-2 receptors. An indirect effect can result from the leakage of inflammatory mediators through a permeable blood-brain barrier [11].

Neither of three patients had respiratory symptoms or signs of MISC/ PIMS-TS (Multisystem Inflammatory, Syndrome, in Children/Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2) or history suggestive of SARS-CoV-2 infection prior to the present infection. The symptoms of encephalopathy, muscle weakness, and reduced reflexes of the 1st case was in consistent with the findings of Tandon M et al., [12]. However, the latter study was a systematic review and the age of the study population was greater than 18 years.

The temporal sequence of signs of encephalopathy and neurological symptoms, in a known COVID-19 infection, along with the later MRI brain changes as seen in the first two cases are suggestive of neuroinflammatory process triggered by SARS-CoV-2. The laboratory parameters and the MRI brain findings of the 1st case was similar to the case presented by Lazarte-Rantes C et al., [13] and Tandon M et al., [12]. The study by Tandon M et al., in a systematic review of CSF findings of 113 patients from 67 studies [12]. The CSF protein levels were elevated in 74.5% (38/51) patients with non-severe COVID-19 and 68.6% (24/35) in those with a severe COVID-19 infection.

All the three cases showed reduced pleocytosis in the CSF, and it was common to see MRI changes during the acute phase of the encephalopathic illness rather than during the recovery phase which was similar with the findings by Ellul MA et al., [6] and Tandon M et al., [12]. The normal MRI findings in patients having CNS manifestation with COVID-19 infection had been reported [13].

None of the patients had any other positive viral markers except for SARS-CoV-2. In all the index patients, other infectious causes with CNS manifestations were excluded. As all the three patients had no laboratory findings suggestive of MISC, it was concluded that, these patients had COVID-19 infections with rare neurological manifestations.

CONCLUSION(S)

Although, SARS-CoV-2 can trigger an inflammatory process which can present as encephalitis features clinically, it is important to exhaust all means of investigations before labelling an encephalopathy as acute COVID-19 encephalitis. Paediatricians need to be aware of this association in paediatrics patients with COVID-19 presenting to the emergency room with neurologic symptoms and clinical worsening. Though acute necrotising encephalitis associated with SARS-CoV-2 due to autoimmune-mediated mechanisms has been described in the adult population, children could also be at risk of developing this disease, following COVID-19 infection.

The SARS-CoV-2 CSF RNA test was negative in all the three cases. The detection of anti-SARS-CoV-2 antibodies in CSF could have

supported the diagnosis of patients with COVID-19 encephalitis, but this facility was unavailable in the study centre.

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