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ORIGINAL ARTICLE

# Neurological Impact of COVID 19 on children.

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## INTRODUCTION

The Virus causing COVID-19Disease belongs to Coronaviruses family, which were first identified in humans in 1965 from a child with an upper respiratory infection [1]. Coronaviruses are enveloped viruses measuring 100– 150 nm in diameter with a positive-sense single-stranded RNA genome [1]. It was named SARS-CoV-2 due to its close genetic relationship to the SARS virus. The "spike proteins" of both SARS and SARS-CoV-2 [2] use the angiotensin-converting enzyme receptor type 2 (ACE-2) to bind to cells. The ACE-2 receptor is widely distributed in the lungs, oral and nasal mucosa, bone marrow and many other organs [3]. ACE 2 receptor is also expressed in the central nervous system predominantly in thalamic nuclei, cerebellum, and inferior olivary nuclei[4]. Location of these receptors in the brain may be of relevance with respect to coronavirus encephalitis [5]. Severe neurological complications of COVID-19 appear to be both infrequent and diverse in nature. Virtually any part of the nervous system appears to be susceptible to injury with SARS-CoV2. Neurological disease could be due to metabolic abnormalities triggered by the infection, direct invasion of the virus, or an autoimmune response to the viruse [6].

## CASE NO. 1

Fourteen years old previously healthy boy complains of fever,sore throat, runny nose, and mild cough 4 days before presentation to our hospital. His family sought medical advice when he got positive result forCOVID 19 PCR testing and symptomatic medication was given. Three days later the patient started to complain of intermittent attacks of numbness and paresthesia of both lower limbs specially feet with bilateral knee joint pain but without knee swelling. He claims that his legs cannot carry him and cannot walk with tendency to fall with shoulder pain and occasional flanks pain and while he is in our hospital the patient felt dizziness and fall down on his way to leave the clinic without any trigger and also without loss of consciousness and recovered quickly. he has no convulsions, headache, disturbed consciousness, no facial weakness no eye deviation or abnormal movement, no swallowing difficulties or breathing problems no upper limbs weakness or abnormal sensation and no other systems organs affections. he has no history of cardiac problems or bronchial asthma and he has no history of allergy to any medications. His past medical history and family history was irrelevant. The patient was admitted to our hospital for observation and further evaluations. On admission he has COVID-19 RT-PCR positive tests which were confirmed next day. He was found to have no antibodies against COVID-19 Ag on the same day of

admission. Clinical examinations show temperature: 63.7 C**,** Peripheral pulse: 89 beat per minute, Respiratory Rate: 20, Blood Pressure: 115/75, Oxygen Saturation: 100% in room air, Height :172.7 cm, Weight: 63.9 kg, BMI :21.42 kg/m2. General appearance he was non-dysmorphic with average built. He has normal conjunctiva with no abnormal eye movement or deviation. No abnormality was detected in head, nose, ear and throat examinations. Neck noticed to be Supple with no lymphadenopathy.Chest wasclear to auscultation, equal breath sounds, symmetrical chest wall expansion, breathing was non-laboured and no chest wall tenderness.Cardiovascular examination showed normal heart rate, regular rhythm, no murmur, no gallop, good equal pulsesin all extremities with normal peripheral perfusion and no edema.Abdomen wassoft, non-tender, non-distended with normal bowel sounds.No lymphadenopathy in neck, axilla or groin.Skin wasintact, moist, no pallor and no rash.Neurologicallythe patient was alert, oriented for time, place and persons with normal sensory and motor functions and no focal defects. Cranial Nerves were grossly intact, normal deep tendon reflexes in the upper and lower limbs with only paresthesia and decrease touch sensation in both feet and down word going planters . Laboratory tests were done and showed normal blood glucose, electrolytes, urea and creatinine. There was high direct bilirubin but liver enzymes came normal. CBC showed leukopenia. LDH and ferritin came slightly elevated while coagulations profiles were normal. Electrocardiography was carried out for our patient as he considered to havepresyncope. ECG revealed no arrythmia and no prolonged QT interval. the patient seen by Pediatrics neurologyconsultant who put provisional diagnosis of myalgia and arthralgia with Presyncope symptoms all attributed to COVID 19 and recommended No intervention but just to continue supportive management and follow up. After 48 hours of admission the patient felt better with no more body pains, paresthesia attacks or lower limb weeks. After two weeks the patient was followed by our teleconsultation team and he was normal except for some sleeping problems and excessive water drinking and feel of generally lethargy and lassitude and four weeks later there was follow up clinic visit and the child was found to have normal clinical examinations.

Table 1(A): COVID -19 Detection Tests:

| Test | Results | Dates |
|---|---|---|
| A 2019-n-CoV **RT-PCR** | DETECTED | 24th May 2022 |
| A 2019-n-CoV **RT-PCR** | DETECTED | 25th May 2022 |
| **COVID-19 Ag POC** | Negative | 25th May 2022 |

Table 1(B): Complete Blood Count:

| | |
|---|---|
| **WBC** | **3.0 x10^9/L LOW** |
| **RBC** | **6.51 x10^12/L HI** |
| Hgb | 140 g/L |
| Hct | 0.45 L/L |
| **MCV** | **69.4 fL LOW** |
| **MCH** | **21.5 pg LOW** |
| **MCHC** | **310 g/L LOW** |
| Platelet | 165 x10^9/L |
| **RDW-CV** | **15.1 % HI** |
| MPV | 10.10 fL |
| **Neutro Auto #** | **1.61 x10^9/L LOW** |
| Neutro % | 53.30 % NA |
| Lymph % | 33.80 % NA |
| Mono % | 10.90 % NA |
| Eos % | 1.30 % NA |

| | |
|---|---|
| Baso % | 0.70 % NA |
| Microcytes | 1+ |
| Elliptocytes | 1+ |
| Tear Cells | 1+ |
| Hypochromasia | 1+ |

Table 1(C): Renal Function and Electrolytes

| | |
|---|---|
| Sodium Lvl | 138 mmol/L |
| Potassium Lvl | 4.7 mmol/L |
| Chloride Lvl | 100 mmol/L |
| CO2 | 26 mmol/L |
| Creatinine | 77 micromole/L |
| Urea Lvl | 5.45 mmol/L |
| Glucose Random | 6.2 mmol/L |
| Calcium Lvl | 2.46 mmol/L |
| **Magnesium Lvl** | **0.92 mmol/L HI** |
| Phosphate Lvl | 1.35 mmol/L |

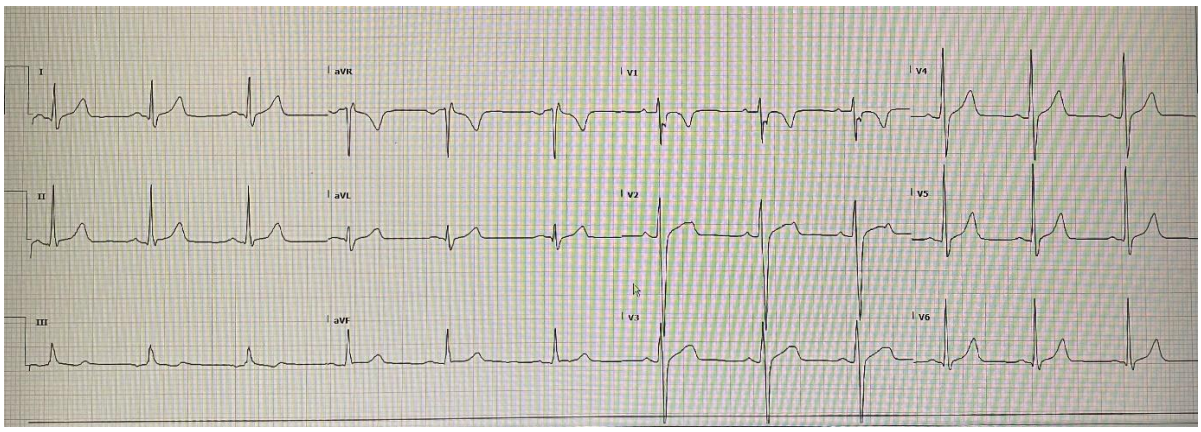
Table 1(D): Liver Function Test and Coagulation Profile:

| | |
|---|---|
| Total Protein | 78 g/L |
| Albumin Lvl | 38 g/L |
| **Bili Total** | **22.6 micromole/L HI** |
| **Bili Direct** | **5.7 micromole/L HI** |
| **AlkPhos** | **238 IU/L HI** |
| AST | 24 IU/L |
| ALT | 11 IU/L |
| PT | 13.4 sec(s) |
| INR | 1.0 |
| APTT | 32.5 sec(s) |
| Fibrinogen Lvl | 3.47 g/L |
| Anticoagulant? | None |
| **D-Dimer Auto** | **1.28 mcg/mL HI** |

Table 1(E): Inflammatory Markers with Immunoglobulins Level and Blood Culture:

| | |
|---|---|
| **LDH** | **268 IU/L HI** |
| Total CK | 76 IU/L |
| Trig | 1.13 mmol/L |
| IgA | 1.70 g/L |
| IgG | 10.28 g/L |
| IgM | 0.70 g/L |
| **Ferritin Lvl** | **119 mcg/L HI** |
| Interleukin 6 | 4.0 pg/mL |
| NT-pro BNP | <5.0 ng/L |
| Troponin-T | 4.590 ng/L |
| Procalcitonin | 0.04 ng/mL |
| C Reactive Prot | 1.28 mg/L |
| **Blood Culture** | No Growth |

**FIGURE 1:** ECG shows Normal Heart Rate with Sinus Rhythm with No prolonged QT Interval or any other Arrhythmia.




**CASE NO. 2**

Nine years old male child, previously healthy, presented with 2 days history ofhigh-grade fever,temperature was 39.8Celsius that was associated with rigors , abdominal pain and frequent vomiting, mainly gastric content, non-bloody, non-bilious and non-projectile. Severe headache which was intermittent, frontal and sometimes occipital, with photophobia, phonophobia and hallucination. The mother sought medical advice and the child discovered to be PCR COVID 19 Positive. He was contact with family member with COVID 19 ahead of developing symptoms. As per the mother he is not himself since yesterday night, acting weird and saying wrong wordings. He has no slurred speech and mother denied abnormal gait, any weakness, vision change, nystagmus, hoarseness of voice or facial asymmetry. mother denied also any history of seizure, abnormal movements, starring attack and he is not on any medications. Other associated symptoms includes: nausea, sore throat, poor oral intake, fatigue and body aches. No diarrhoea , constipation, no change in urine amount, colour or smell. No eyes redness or discharge , no red tongue nor cracked lips, no ear pain or discharge, no skin rash. No cough, no chest pain, no shortness of breath, no swallowing difficulties . No history of trauma or fall, no history of drug ingestion as per family. Has has a pet cat living at home for 1 year . No history of recent travel. Past medical history and family history are irrelevant. Vaccination history is up to date. Upon Assessment in emergency department**:** he was consciousbut less responsive, drowsy ,looks lethargic and toxic appearance . He had dry and pale lips. He was doing purposeless movements with hands and legs, funny movements with tongue and eyes. Was laughing hysterically with no reason, not answering questions, not looking at doctor or at his mother. Disoriented, answering few questions incorrectly. GCS initially 13/15 . No nystagmus. No facial asymmetry. Oral cavity showed uvula in place, normal tongue no fasciculation, normal throat and tonsils. No neck stiffness, negative Brudzinski and kerning's signs.Initial Investigationsin the ER showed: PCO2 28 mmHg, HCO3 17 mmol/l, Base Excess -9 mmol/l with Low pHpointing to metabolic acidosis. Blood Glucose was initially 3.3mmol/l, poor oral intake related hypoglycaemia. Mild hyponatremia as Sodium was 134mmol/l , hypochloraemiaas Chloride was 96mmol/l, but normal Potassium, Phosphorusand Magnesium. Renal function within acceptable limit. Complete blood count showed:mild leukopenia with lymphopenia with normal Haemoglobinand Platlets. CRP and Procalcitonin were normal also LDH, Ferritin and triglyceride came within acceptable limits. CPK normal, IL-6 2.7, Cardiac enzymes normal, Liver function tests came all normal but Coagulation profile was slightly deranged as PT 17, INR 1.4, normal fibrinogen and D-Dimer. COVID-19 RT-PCR Positive and Chest x-ray unremarkable. The patient received one bolus of IVnormal saline and IV bolusD10% IV bolus along with ondansetron IV and IV paracetamol. After initial stabilization the patient was admitted for hydration, Neuro-observation, further investigations and management. On

admission he was settled and looks well hydrated and improvement in GCS was noticed. He was not toxic, not in distress. Afebrile and hemodynamically stable no bradycardia or hypertension and on other signs of raised ICP. The patient was maintaining his oxygen saturation on room air and well perfused with capillary refile below2 seconds. Chest was clear on auscultation and cardiovascular examinations showed normal first and second heart sounds with no murmur appreciated. Abdomen was soft, lax, not tender with no organomegaly. To exlude any intracranial problems or encephalitis Computed tomography on head was donewhich showednormal appearance of the brain parenchyma without focal lesion , haemorrhage or extra-axial collection.To exclude any toxic substance ingesion , Toxic Drugs Screening in urine was done which revealed no concern. The patient stayed in hospital for 48 hours under observation in which he did not have any abnormal movement or any seizures and he started to take oral feeding gradually and take only supportive treatment after that he was discharged with the diagnosis of COVID 19 Induced encephalopathy for follow up.

**Table 2(A): COVID -19 Detection Test:**

| Test | Result | Date |
|---|---|---|
| **2019-n-CoV RT-PCR** | Not Detected | 26/05/2022 |
| **2019-n-CoV RT-PCR** | Detected | 27/05/2022 |
| 2019-n-CoV RT-PCR | Detected | 28/05/2022 |
| **COVID-19 Ag POC** | Positive | 28/05/2022 |

Table 2(B): Blood Glucose Levels with Venous Blood Gas:

| Test | Level | Date and Time |
|---|---|---|
| Glucose (POC) | **3.6 mmol/L LOW** | 28/5/2022 16:46 PM |
| **Glucose Random** | **3.3 mmol/L LOW** | 28/5/2022 16:30 PM |
| **Glucose (POC)** | **5.4 mmol/L** | 28/5/2022 18:18 PM |
| Glucose (POC) | 5.9mmol/L | 28/5/2022 23:31 PM |
| **TCO2 (iSTAT)** | **17 mmol/L LOW** | 28/5/2022 16:46 PM |
| Lactate (iSTAT) | 2.14 mmol/L | 28/5/2022 16:46 PM |
| pH ven (iSTAT) | 7.37 | 28/5/2022 16:46 PM |
| **pCO2 ven(iSTAT)** | **28 LOW** | 28/5/2022 16:46 PM |
| pO2 ven(iSTAT) | 46 | 28/5/2022 16:46 PM |
| **HCO3 ven(iSTAT)** | **16 mmol/L CRIT** | 28/5/2022 16:46 PM |
| **BE ven (iSTAT)** | **-9.00 mmol/L LOW** | 28/5/2022 16:46 PM |
| **sO2 ven(iSTAT)** | **81.00 % LOW** | 28/5/2022 16:46 PM |

Table 2(C): Renal Function and Electrolytes

| | |
|---|---|
| Sodium Lvl | **134 mmol/L LOW** |
| Potassium Lvl | 4.4 mmol/L |
| Chloride Lvl | **96 mmol/L LOW** |
| CO2 | **14 mmol/L LOW** |
| Creatinine | 52 micromol/L |
| Urea Lvl | 4.06 mmol/L |
| Calcium Lvl | 2.51 mmol/L |
| **Magnesium Lvl** | 0.86 mmol/L |
| Phosphate Lvl | 1.64 mmol/L |

Table (D): Liver Function Test and Coagulation Profile:

| | |
|---|---|
| Total Protein | 79 g/L |
| Albumin Lvl | 44 g/L |
| **Bili Total** | 4.5 micromol/L |
| **Bili Direct** | 2.3 micromol/L |
| **AlkPhos** | **174 IU/L HI** |
| AST | 37 IU/L |
| ALT | 18 IU/L |
| PT | **17.6 sec(s) HI** |
| INR | **1.4 HI** |
| APTT | 38.1 sec(s) |
| Fibrinogen Lvl | 3.26 g/L |
| Anticoagulant? | None |
| **D-Dimer Auto** | 0.25 mcg/mL |

Table 2(E): Inflammatory Markers with Immunoglobulins Levels:

| | |
|---|---|
| **LDH** | **246 IU/L HI** |
| Total CK | 82 IU/L |
| Trig | 0.61 mmol/L |
| IgA | 0.89 g/L |
| IgG | 10.48 g/L |
| IgM | 0.78 g/L |
| **Ferritin Lvl** | **97 mcg/L HI** |
| Interleukin 6 | 2.7 pg/mL |
| NT-pro BNP | 19.1 ng/L |
| Troponin-T | <3.000 ng/L |
| Procalcitonin | 0.18 ng/mL |
| C Reactive Prot | 3.27 mg/L |

Table 2(F): Complete Blood Count:

| | |
|---|---|
| **WBC** | **3.4 x10^9/L LOW** |
| **RBC** | 5.09 x10^12/L |
| Hgb | 137 g/L |
| Hct | 0.41 L/L |
| **MCV** | 80.2 fL |
| **MCH** | 26.9 pg |
| **MCHC** | 336 g/L |
| Platelet | 317 x10^9/L |
| **RDW-CV** | 12.8 % |
| MPV | **8.70 fL LOW** |
| **Neutro Auto #** | 1.0 NA |
| Neutro % | 1.93 x10^9/L |
| Lymph % | 57.40 % NA |
| Mono % | 27.70 % NA |
| Eos % | 14.90 % NA |
| Baso % | 0.00 % NA |
| Neutro # | 0.00 % NA |
| **Lymph #** | 1.93 x10^9/L |
| Mono # | **0.93 x10^9/L LOW** |
| Eos # | 0.50 x10^9/L |
| Baso # | 0.00 x10^9/L |

Table 2(G): To exclude any toxic substance ingesion Toxic Drugs Screening in Urin was done:

| Toxic Substance in Urin | Result |
|---|---|
| U Barb Scrn | Not detected |
| U BenzodiaScrn | Not detected |
| U Canab (THC) | Not detected |
| U Cocaine Scrn | Not detected |
| U MethamphScrn | Not detected |
| U Opiate Scrn | Not detected |
| U Tricyscrn | Not detected |
| U Meth Metab (EDDP) | Not detected |

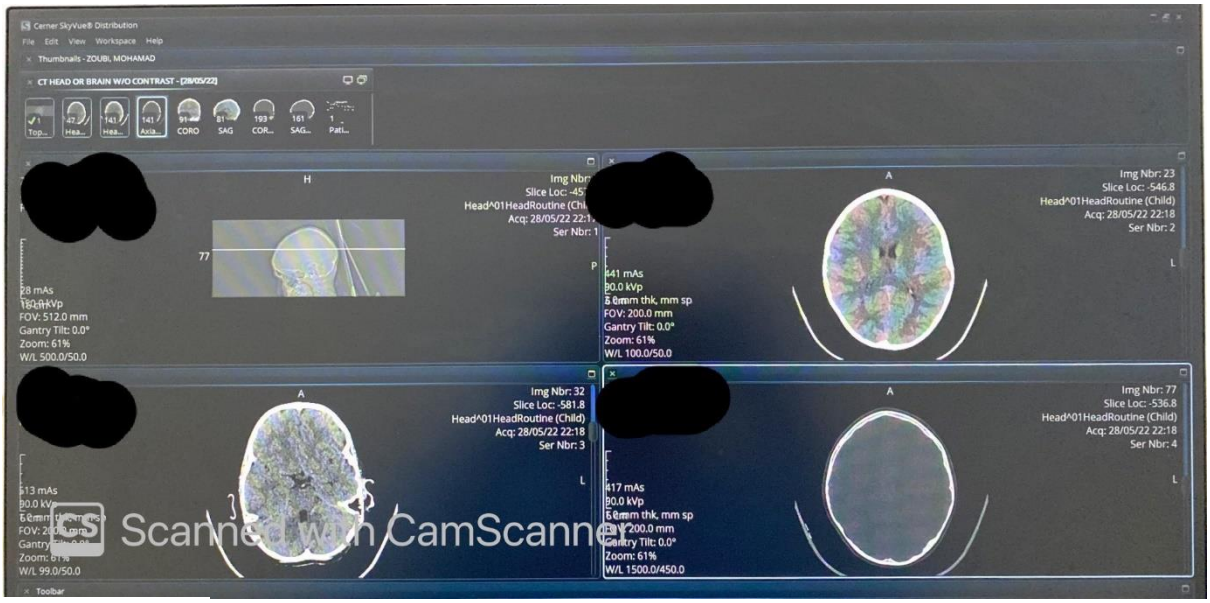



**Figure No. 2 (A):** CT Head was done and shows Normal appearance of the brain parenchyma without focal lesion.

**Figure No. 2 (B):** CT Head was done and shows No haemorrhage or extra-axial collection, No any intracranial problems or Signs of encephalitis

## DISCUSSION

On 10th of March, 2020, COVID-19 has been responsible for more than 110,000 infections and 4000 deaths worldwide, in contrast with infected adults, most infected children appear to have a milder clinical course and asymptomatic infections were not uncommon [10]. No neurological complications were reported in the 171 children from Wuhan Children's Hospital [2]. Neurological involvement with SARS-CoV-2 in pediatrics age groups has been rarely reported and these two cases report trigger researchers to ask many questions regarding pathogenic mechanisms that underlie the occurrence of neurologic injury in our young patients. In other words, is it related to specific host factors in those children that increase their susceptibilityto be involved or related to a newly acquired antigenic virulence that enhance SARS-CoV-2 to have more predilections to Nervous system. SARS-CoV-2 infection causes multiple organ involvement including pulmonary, cardiovascular, renal, coagulation, gastrointestinal tract, and muscles. Central nervous system disorders should not be unanticipated with SARS-CoV-2., as it has been reported with other coronaviruses; SARS-CoV-1 that was detected by polymerase chain reaction in the cerebrospinal fluid of a 32- year-old woman

with SARS presenting with generalized tonic-colonic seizures [6]. Similar to my two case reports RajS. et al. 2020[12] reported three children of COVID-19 who presented with only neurological symptoms. McAbee, et al. 2020[11] reported an 11-year- old male child with encephalitis whose nasopharyngeal swab was positive for COVID-19, whereas CSF was negative and fortunately the baby recovered with supportive treatment without sequalae within one week. Natarajan S. et al. 2020[8] reported a 13 years old girl with neurological symptoms as she has Seizures and disturbed consciousness and nasopharyngeal swab RT-PCR was positive for COVID-19 virus. Therewas a limitation in my observation as CSF analysis were not done for both cases because our consultant physician approached the cases without rushing to exaggerated investigations that could be financially exhaustive and also the context of COVID-19 makes the approach easier. Neurological presentations of COVID-19 may go unrecognized due to misconception that it is only respiratory virus but in this pandemic situation, any child with primary neurologic symptoms and fever, with mild or absent respiratory symptoms, could be either a part of MIS-C or a self-limiting finding of paediatric COVID-19 infection. In my observation it is noticeable that both children had favourable outcomes with only supportive treatment.

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