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ORIGINAL RESEARCH

# Unusual neurologic manifestations in children during the COVID-19 pandemic: A cross-sectional study in Trinidad and Tobago

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## Abstract

*Importance:* The effects of COVID-19 on the neurologic system warrant recognition in our pediatric population. The long-term effects on development should be closely monitored, especially if autoimmunity is suspected.

*Objective:* To present pediatric cases of unusual neuroinflammatory conditions encountered during the COVID-19 pandemic in Trinidad and Tobago.

*Design:* Observational cross-sectional study.

*Setting:* Hospital – Eric Williams Medical Sciences Complex.

*Participants:* Paediatric inpatients (aged 0–16 years) hospitalized for neurologic complaints during the period June 2020–August 2021.

*Exposure:* COVID-19/SARS-CoV-2 virus.

*Main Outcomes:* Age, gender, ethnicity, COVID-19 status, diagnosis, radiological findings, blood and cerebrospinal fluid findings, treatment, outcomes, and other systems involved.

*Results:* Twenty patients (aged 4 months to 15 years) had documented neurologic involvement – 10 acute demyelinating encephalomyelitis/acute demyelinating syndrome/acute hemorrhagic necrotizing encephalopathy, three central nervous system (CNS) vasculitis, three autoimmune encephalitis (AE), three Guillain-Barré syndrome (GBS) and one acute COVID-19 encephalitis. 70% ($n$ = 14) were of African descent. The youngest age group (0–4 years) ($n$ = 11) constituted more males while the eldest age group (10–15 years) ($n$ = 3) were all females. 14/18 patients tested were either SARS-CoV-2 polymerase chain reaction positive or COVID-19 antibodies positive. Neuroimaging findings were corpus callosal lesions; deep white matter T2 hyperintensities; cerebellar involvement; area postrema and brainstem/C-spine involvement; microhemorrhages and necrotizing/hemorrhagic lesions (peripheral/central). Eight patients had other systemic inflammatory involvement of whom five had cardiac involvement (myocarditis, coronary arteries dilatation, valve regurgitation) and three had pancreatic involvement (autoimmune pancreatitis, type 1 diabetes mellitus). Treatment modalities for CNS manifestations ($n$ = 17) were clinically based – four requiring third-line treatment. All three patients with a diagnosis of GBS responded appropriately to IVIG. Outcomes were worse in patients with a diagnosis of AE and positive ANA.

*Conclusion/Relevance:* There has been an upsurge in neuroinflammatory cases since the COVID-19 pandemic began. The range of neuroradiological diagnoses and other systemic involvement (including meeting the criteria for pediatric inflammatory multisystem syndrome) alludes to a neuroinflammatory mechanism. Effects on long-term sequelae and developmental outcomes are concerning; however, at this early stage, they are still unknown.

**Keywords:** COVID-19, ADEM, Autoimmune encephalitis, Neuroinflammatory, GBS, PIMS-UK, MIS-C.

**Key points**

Question: Should there be a concern about pediatric COVID-19 related neurologic manifestations?

Findings: In this observational single-center study in Trinidad and Tobago, conducted from June 2020 to August 2021, 20 pediatric patients had documented neuroinflammatory involvement at a higher-than-expected population prevalence.

Meaning: The spectrum of neurologic manifestations and associated multi-system involvement during the COVID-19 pandemic alludes to a neuroinflammatory mechanism.

## Introduction

### Background/rationale

Early in the COVID-19 pandemic, there was a belief that children were unaffected. Then, a Kawasaki-like syndrome labelled Pediatric Inflammatory Multisystem Syndrome (PIMS) emerged. However, neurologic complications in children were still rarely reported [1].

The first case of COVID-19 was reported in Trinidad and Tobago on 12 March 2020. An increase in various, rare post-inflammatory neurologic manifestations in children was then observed. In a Netherlands study collating results over four years, the mean incidence rates were 1.54 children/million (95% CI 0.95–2.35) and 2.49 children/million (95% CI 1.73–3.48) for autoimmune encephalitis (AE) and acute demyelinating encephalomyelitis (ADEM), respectively. Extrapolating these data, with our population statistics (352,271 persons aged 0–18 years old), the incidence of ADEM in children should be about one case per year, and the incidence of AE in both children and adults should be about one case every two years [2–4]. Prior to 2020, the diagnosis of ADEM and AE in Trinidad and Tobago was made in no more than one to two pediatric patients every year.

Up until August 2021, we recorded only one childhood death due to acute COVID-19 infection who succumbed due to complications of background co-morbidities. This was despite leading the Caribbean region with the highest number of PIMS cases at 60 patients, 16 of whom had documented neurologic involvement. With the emergence of the Delta variant in our country, we had one death due to presumed post-COVID-19 inflammatory response, with deleterious effects on the patient's central nervous system. After this study was completed, with the rising number of acute COVID-19 cases attributed to the Delta variant, two school-aged children unfortunately succumbed to the virus at the end of November 2021.

Since the beginning of the pandemic, approximately 7000 pediatric cases of COVID-19 were detected in Trinidad and Tobago during the time of this study [5]. Interestingly, as this paper reveals, over 15 months, we diagnosed and treated 20 children with either active or probable post-infectious inflammatory neurologic manifestations since June 2020.

### Objectives

1. To present cases of acute and post-infectious neuroinflammatory conditions in pediatric patients with no previous known medical conditions at Eric Williams Medical Sciences Complex (EWMSC), Trinidad and Tobago, during the COVID-19 pandemic.
2. To emphasize the radiological aspects of patients with central nervous system (CNS) neuroinflammatory manifestations – acute disseminated encephalomyelitis (ADEM)/acute demyelinating syndromes (ADS)/acute hemorrhagic necrotizing encephalopathy (AHNE) and CNS vasculitis/stroke.
3. To evaluate the involvement of other systems (cardiac, pancreas, cutaneous) and determine a link between ANA positivity and prognosis.
4. To discuss the treatment modalities and outcomes (development and neurologic symptoms).

## Methods

### Study design

This was an observational cross-sectional study.

### Setting

This was a single-center study based at EWMSC, NCRHA, Trinidad and Tobago, during the period June 2020–August 2021.

Ethical approval was granted by the institution and university on 28 June 2022 and 16 July 2020, respectively.

### Participants

Inclusion criteria:

- Children with no known previous medical conditions aged 0–16 years hospitalized at EWMSC, during the period June 2020–August 2021.
- Patients with an eventual diagnosis of a CNS/PNS inflammatory condition.

Exclusion criteria:

- Patients with prior diagnoses of neuroinflammatory conditions, e.g. AE, ADEM/ADS, stroke/vasculitis.
- Patients with a known diagnosis of neurogenetic conditions associated with epilepsy/movement disorders.

### Variables

Diagnoses fit into five main categories:

1. ADEM/ADS/AHNE
   - Diagnosis based on clinical and radiological features. ADEM should be suspected in a child who develops multifocal neurologic abnormalities with encephalopathy (e.g. confusion, excessive irritability, or an altered level of consciousness), especially if onset occurs one to two weeks after a viral infection or vaccination [6].
   - ADS/CNS inflammatory demyelinating diseases are a group of disorders that include multiple sclerosis (MS), ADEM, and neuromyelitis optica spectrum disorders (NMOSD) [7].

- AHNE is a rare neurologic complication secondary to viral infections, including para-infectious and hyperimmune response to SARS-CoV-2 infection. This clinicoradiological condition is characterized by rapidly progressive encephalopathy, with distinct neuroimaging features of multifocal diffusion restriction and microhemorrhages involving the cortex, subcortical and periventricular white matter, brain stem, and infratentorial regions [8].

2. AE [9]
   A diagnosis of pediatric AE should be considered in previously healthy children who present with acute or subacute (less than three months) onset of new focal or diffuse neurologic deficits, cognitive difficulties, developmental regression, movement abnormalities, psychiatric symptoms, and/or seizures.
   Children with a clinical presentation suggestive of AE should have serum and cerebrospinal fluid (CSF) examined for neuronal antibodies, undergo paraclinical testing for neuroinflammation, and have disease mimics excluded.
3. CNS Vasculitis/Ischemia [10]
   Clinical suspicion and recognition of CNS vasculitis (with laboratory/neuroimaging support) involving one of three distinct presentations:

   i. An acute or subacute encephalopathy, commonly presenting as an acute confusional state, progressing to drowsiness and coma.
   ii. A picture that superficially resembles MS but with atypical features ('MS-plus' or 'pseudo-MS'), a relapsing–remitting course including optic neuropathy and brainstem episodes, but also other features less common in MS, such as seizures, severe and persisting headaches, encephalopathic episodes, or hemispheric stroke-like episodes.
   iii. Intracranial mass lesions with headache, drowsiness, focal signs, and often raised intracranial pressure.

   Parenchymal changes (Neuroimaging) [11] – Involvement of small perforating arteries results in ischemic lesions localized in the deep or subcortical white and grey matter. When larger arteries are occluded, the resulting infarctions can be found in both cortex and white matter. Routine T2-weighted, FLAIR, and DW MR images all have a role in the detection of ischemic changes and infarction. Vasculitis may be associated with frank intracerebral hematoma, subarachnoid hemorrhage, and microbleeding.
4. Acute COVID-19 Encephalitis [12]
   The diagnosis of acute COVID-19 encephalitis is suspected in a febrile patient presenting with altered consciousness and signs of diffuse cerebral dysfunction plus evidence of SARS-CoV-2 polymerase chain reaction (PCR) positivity.
5. Guillain-Barré Syndrome (GBS) [13]
   Features required for diagnosis

   i. Progressive, ascending bilateral weakness of arms and legs.
   ii. Absent or decreased tendon reflexes in affected limbs (during clinical course).

   Features that strongly support diagnosis

   i. Progressive phase lasts from days to four weeks (usually less than two weeks)
   ii. Relative symmetry of symptoms and signs
   iii. Relatively mild sensory symptoms and signs (absent in pure motor variant)
   iv. Cranial nerve involvement, especially bilateral facial palsy
   v. Autonomic dysfunction
   vi. Muscular or radicular back or limb pain
   vii. Increased protein level in CSF; normal protein levels do not rule out the diagnosis
   viii. Electrodiagnostic features of motor or sensorimotor neuropathy (normal electrophysiology in the early stages does not rule out the diagnosis)

   Case Definition – PIMS [14]

   (a) A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal, or neurologic disorder) with additional features. This may include children fulfilling full or partial criteria for Kawasaki disease.
   (b) Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus.
   (c) SARS-CoV-2 PCR testing may be positive or negative.

**Data sources and measurement**

The records for hospitalized patients consulted by the Pediatric Neurology team during the specified period were obtained and the relevant information was collected by the researcher using a data collection form. Neuroimaging and reports for relevant cases were captured using the PACS system.

**Bias**

Sampling bias was addressed by the eligibility criteria defined by excluding patients with a pre-diagnosed inflammatory/neurologic condition.

Prevalence-incidence bias and interviewer bias was addressed by use of a formal data collection tool, with responders limited to one team (pediatric neurology).

**Study size**

The number of hospitalized cases with neuroinflammatory manifestations during the study period determined the sample size.

**Quantitative variables**

Quantitative variables included markers of inflammation/autoimmunity in blood (ESR, ANA titre), CSF (white cells and protein level), and COVID-19 IgM and IgG antibodies.

Normal values:

- ESR [15]: Male: ≤15 mm/h; Female: ≤20 mm/h
- ANA intensity of fluorescence, in international units per milliliter (IU/mL) [16]: >7 IU/mL
- CSF white cell [17]: $<5 \times 10^6$/L
- CSF protein [17]: <0.4 g/L
- COVID-19 IgM [18]: 0–1 AU/mL
- COVID-19 IgG [18]: 0–1 AU/mL

### Statistical methods

We report the frequency and type of neurologic conditions, pertinent blood/CSF investigations including COVID-19 status, treatment, and outcomes. Continuous variables were expressed as medians and interquartile ranges. Categorical variables were expressed as counts and percentages.

## Results (Table 1)

### Participants

Two patients were excluded from this study (one female with known epileptic encephalopathy/genetic etiology and one female with a history of recurrent CVST's/Sneddon syndrome).

Twenty patients were identified as meeting the inclusion criteria during the specified period (June 2020–August 2021).

### Descriptive data

### Age at presentation

The youngest patients (0–4 years) constituted 55% (11/20) of the total number of patients. Within this subset, 7/11 were diagnosed with ADEM/ADS/AHNE and 2/11 with AE. The other

**Table 1.** Neurologic manifestation during COVID-19 pandemic in 20 patients (aged <15 years), June 2020–August 2021

| | Neurologic conditions, no (%) | | | | | |
|---|---|---|---|---|---|---|
| **Variable** | **Overall** | **ADEM/ ADS/AHNE** | **Autoimmune encephalitis** | **Viral encephalitis** | **CNS vasculitis** | **GBS** |
| No. | 20 | 10 (50) | 3 (15) | 1 (5) | 3 (15) | 3 (15) |
| Age, median (IQR) | 0–4 years | 7 | 2 | 1 | 1 | 0 |
| | 5–9 years | 1 | 1 | 0 | 2 | 2 |
| | 10–15 years | 2 | 0 | 0 | 0 | 1 |
| | 4.9 (0.3–15) | | | | | |
| Male | 12 (60) | 7 (70) | 2 (67) | 1 (100) | 1 (33) | 1 (33) |
| Ethnicity | 14 (70) Afro-Caribbean | 6 (60) | 1 (33) | 1 (100) | 3 (100) | 3 (100) |
| | 2 (10) East Indian | 1 (10) | 1 (33) | | | |
| | 2 (10) Mixed | 1 (10) | 1 (33) | | | |
| | 1 (5) Chinese | 1 (10) | | | | |
| | 1 (5) Venezuelan | | | | | |
| COVID-19 status | 14/18 (78) | 8/9 (89) | 1/2 (50) | 1 (100) | 3 (100) | 1 (33) |
| *Positive PCR* | 2 | 0 | 0 | 1 | 1 | 0 |
| *Positive Ab* | 12 | 8 | 1 | 0 | 2 | 1 |
| *Not tested* | 2 | 1 | 1 | 0 | 0 | 0 |
| PIMS criteria met | 16 (80) | 10 (100) | 3 (100) | 1 (100) | 1 (33) | 1 (33) |
| Other systems involved | 10 (50) | | | | | |
| *Cardiac* | 5 (25) | 5 (50) | – | – | – | – |
| *Pancreas* | 3 (15) | 1 (10) | – | – | 1 (33) | 1 (33) |
| *Cutaneous* | 2 (10) | 2 (20) | – | – | – | – |
| Treatment | | | | | | |
| *No treatment* | 1 (5) | 1 (10) | – | – | – | – |
| *First line* | 10 (50) | 2 (20) | 1 (33) | 1 (100) | 3 (100) | 3 (100) |
| *Second line* | 5 (25) | 4 (40) | 1 (33) | – | – | – |
| *Third line* | 4 (20) | 3 (30) | 1 (33) | – | – | – |
| Outcome | | | | | | |
| *Recovered within three months* | 11 (55) | 4 (40) | 0 | 1 (100) | 3 (100) | 3 (100) |
| *Regression in skills* | 9 (45) | 6 (60) | 3 (100) | 0 | 0 | 0 |
| *Death* | 1 (5) | 1 (10) | 0 | 0 | 0 | 0 |

ADEM: acute disseminated encephalomyelitis; ADS: acute demyelinating syndrome; AHNE: acute hemorrhagic necrotizing encephalopathy; CNS: central nervous system; GBS: Guillain–Barre syndrome; IQR: interquartile range; PCR: polymerase chain reaction; Ab: antibodies; PIMS: pediatric inflammatory multisystem syndrome.

2/11 were diagnosed with CNS vasculitis (1/11) and viral encephalitis (1/11).

The 5–9-year age group constituted 30% (6/20) of the total number of patients. Within this subset, 2/6 were diagnosed with CNS vasculitis and another 2/6 were diagnosed with classic GBS. The remaining patients were diagnosed with ADEM/ADS (1/6) and AE (1/6).

The oldest patients (10–15 years) constituted the lowest percentage of patients 15% (3/20) – two patients were diagnosed with ADEM/ADS and 1 with Guillain Barré Syndrome variant.

### Gender

Of 20 patients, 12/20 were males (60%) and 8/20 were females (40%).

The youngest male patient was four months old, diagnosed with COVID-19 encephalitis. The youngest female patient was one year old and diagnosed with AE (anti-NMDA antibody receptor positive).

Of the 11 patients who were less than five years old, 9/11 were males and 2/11 were females. Of the two female patients in this age group, one was diagnosed with ADEM/ADS and the other was the youngest female patient with NMDA receptor positive AE. Of the males, the majority were diagnosed with ADEM/ADS/AI encephalitis 7/9, the other two were diagnosed with COVID-19 encephalitis (1/9) and CNS vasculitis (1/9).

In contrast, all patients who were more than 10 years old were females (3/3) – two diagnosed with ADEM/ADS and one with GBS variant.

The middle age group (five to nine years) was equally split—3/6 males and 3/6 females. The males in this subgroup were diagnosed with ADEM/ADS (1/3), AI encephalitis (1/3), and CNS vasculitis (1/3). The females in this subgroup were diagnosed with CNS vasculitis (2/3) and classic GBS (1/3).

### Ethnicity

Most of our patients, 70% (14/20), were of African descent, with 2/20 of mixed African/East Indian ethnicity, 2/20 of East Indian descent, 1/20 of Chinese ancestry, and 1/20 of South American (Venezuelan) ethnicity.

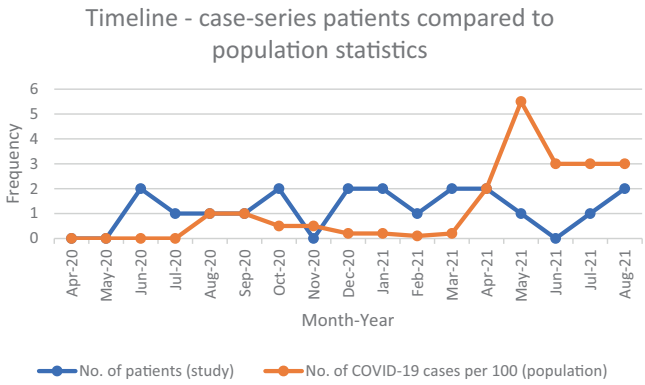
### Outcome data

#### SARS-CoV-2/COVID-19 testing (Figure 1)

At the beginning of the pandemic, testing was limited due to lack of PCR kits; therefore, only persons with respiratory symptoms and a travel history were tested.

Our initial four patients during the June to August 2020 period presented with viral GE symptoms (4/4) prior to developing neurologic concerns and did not have a travel history; therefore, they were not eligible for PCR testing. COVID-19 antibody testing was made available in mid-August 2020. On testing the severe ADEM cases (2/2) two to three months post treatment, both tested positive for COVID-19 IgM antibodies (IgM 1.123, 1.5). Of note, one of these patients had RCA ectasia on post-treatment ECHO study.

**Figure 1.** Timeline demonstrating frequency of cases over specified period (June 2020–August 2021).




During the next period September–November 2020, when a population surge of COVID-19 cases was noted (possibly compounded by non-discriminate testing), our first two CNS vasculitis cases were identified (both COVID-19 antibody positive). Due to the increase in cases of PIMS, one of the patients who was initially treated as such with IVIG (dilated coronary arteries, mild MR, small pericardial effusion) was also assessed by pediatric neurology as he had generalized weakness and regression in speech/language. His SARS-CoV-2 PCR was negative, but his COVID-19 Ig M was positive at 1.2 and his neurologic symptoms improved with additional steroid treatment.

The post-Christmas season end December–February 2021 also had a small rise in cases and during this time, we had our final two (2/3) cases of AE (1 COVID-19 Ab positive), and an additional three cases of ADEM/ADS (3/3 COVID-19 Ab positive), two of whom also had cardiac manifestations (dilated coronary arteries).

Our worst COVID-19 crisis occurred during March–May 2021 with the emergence of the Gamma variant. This was when our first two cases of GBS (one COVID-19 Ab positive), and our severe, lone case of brainstem encephalitis/transverse myelitis presented (COVID-19 Ab positive).

The number of cases continued despite extreme lockdown measures and vaccination with the arrival of the Delta variant in mid-August 2021. During the final four-month period, we had two acute COVID-19 cases (SARS-CoV-2 PCR positive) with neurologic manifestations (CNS vasculitis, COVID-19 encephalitis) and two of our most severe CNS inflammatory cases of AHNE (2/2 COVID-19 Ab positive).

#### Neurologic conditions, course, and treatment modalities (Figures 2–4)

Of the 20 patients in our pediatric cohort, 50% (10/20) were diagnosed with ADEM/ADS/AHNE. Children with a diagnosis of AE (3/20), CNS Vasculitis (3/20), and GBS (3/20) accounted for another 45% of cases. The remaining 5% were diagnosed with viral encephalitis (1/20).

The most severe presentation was diagnosed with acute hemorrhagic necrotizing leukoencephalopathy; he unfortunately passed on *(see Supplemental Data 1).*

**Figure 2.** Bar chart – frequency of diagnoses by age group (0–4, 5–9, 10–15 years). AHNE: acute hemorrhagic necrotizing encephalopathy; ADEM: acute disseminated encephalomyelitis; ADS: acute demyelinating syndrome.

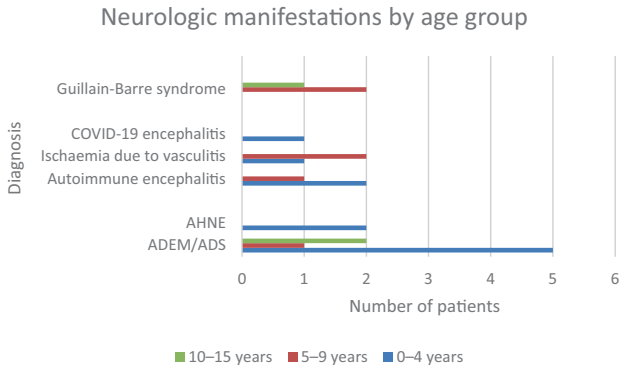
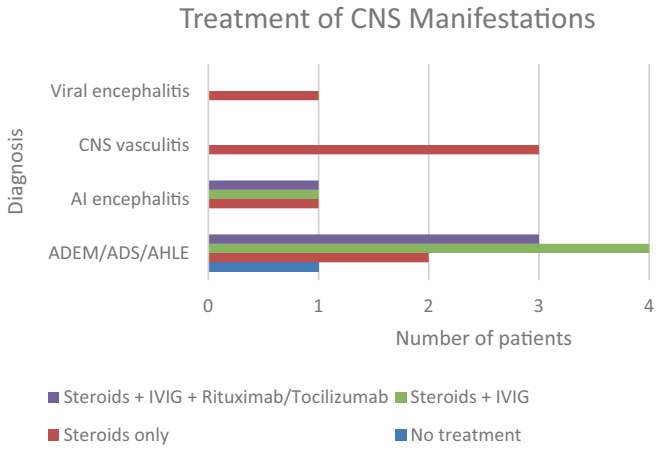



**Figure 3.** Bar chart – frequency of patients with CNS manifestations in relation to treatment. AHNE: acute hemorrhagic necrotizing encephalopathy; ADEM: acute disseminated encephalomyelitis; ADS: acute demyelinating syndrome.




Of the three initial presentations of ADEM in June 2020 two male patients were less than two years old *(see Supplemental Data 2)*. They responded gradually but successfully to steroids followed by IVIG. However, resolution of motor function delay lagged by approximately three to six months.

The oldest patients who were diagnosed with ADEM/ADS in January/February 2021 also presented with severe symptoms, requiring additional third-line immunomodulatory treatment (rituximab) – one met the criteria for a diagnosis of seronegative NMOSD *(see Supplemental Data 3)*. In addition, both females had a longer motor function recovery time compared to the younger males – six months for the 13-year-old and one year for the 15-year-old.

All patients with CNS vasculitis responded well to steroid treatment only, with complete resolution of symptoms within one month. All patients with GBS responded well to IVIG treatment, with complete resolution of symptoms within two months.

Of the three patients diagnosed with AE, the youngest two (12 and 18 months old) are unfortunately still developmentally regressed. The 12-month-old female presented with a Reye-like encephalopathy and then progressed to exhibiting dystonia and choreo-athetoid movements. Although her abnormal movements improved with immunomodulation (currently on third-line rituximab and NMDA receptor positive), her developmental milestones did not recover. The 18-month-old male presented with encephalopathy, differing seizure types (focal motor, absence, facio-brachial dystonic seizures), and eye movement abnormalities. Seizure control improved (post IVIGx2 and steroids; anti-TPO Ab positive, LGI-1 Ab negative); however, his developmental milestones (mainly speech, language) did not recover. The oldest patient with AE presented with encephalopathy, status dystonicus, seizures, and choreo-athetoid movements. He recovered quickly with steroid treatment despite his initial severe presentation; however he had a relapsing course with focal seizures and developmental regression.

The lone patient with a diagnosis of COVID-19 viral encephalitis was our youngest, a four-month-old male who

**Figure 4.** ECHO and neuroimaging findings.
**Figure 4a.** Parasternal short axis echocardiographic image in one patient demonstrating left main coronary artery dilation (Z score 4.6) and left anterior descending artery dilation (Z score 4.2) prior to treatment with rituximab.

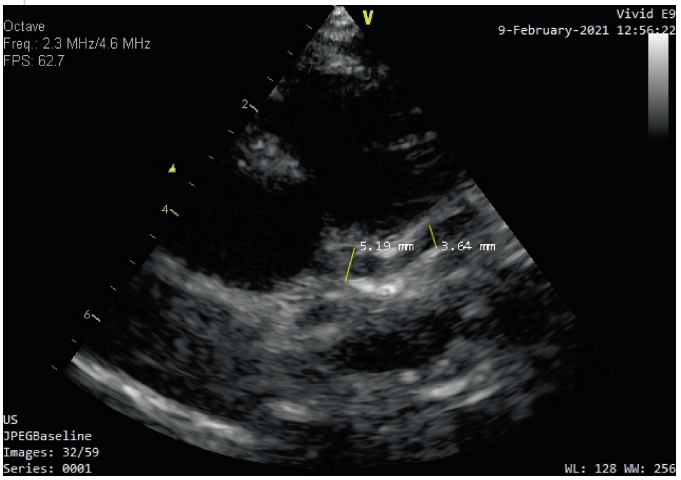



**Figure 4b.** Post-treatment with rituximab demonstrating improvement in left main coronary artery dilation.

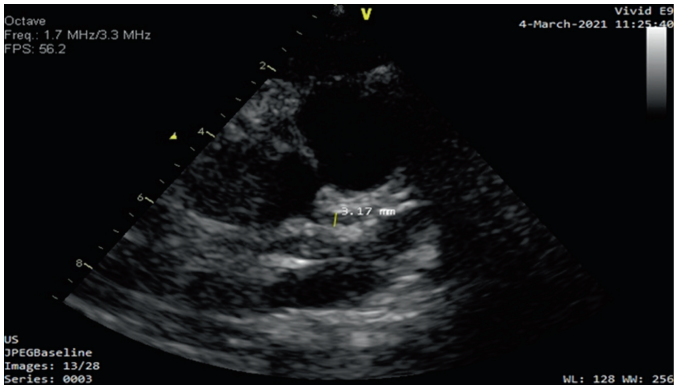
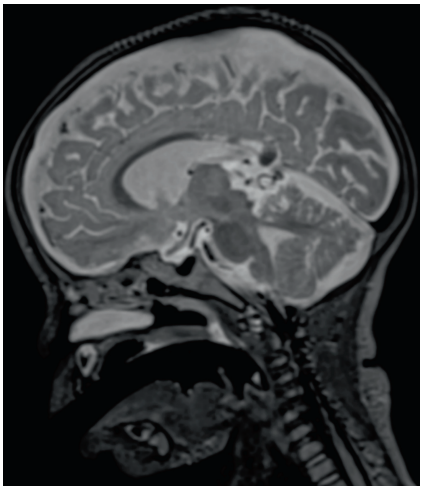
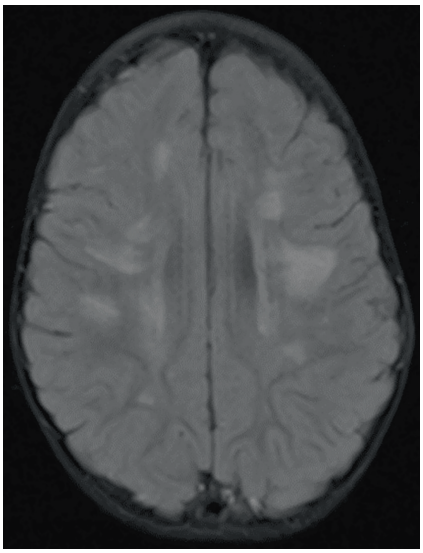


**Figure 4c.** Range of neuroimaging findings (top left to bottom right): (i) Corpus callosal lesions and petechial microhemorrhages within cerebellum; (ii) Deep white matter T2-weighted hyperintensities; (iii) Enhancing foci cerebellum left and right; (iv) and (v) sulcal thickening/edema enhancement in the right fronto-temporal, right parieto-occipital lobes, and area postrema enhancement (vi) Bilateral symmetric high T2-weighted signal in medulla; Cervical spine expansion over long segment (cervical spine) C2 to C7 with symmetrical high T2 signal involving central gray matter and dorsal columns (vii) Long segment of cord enlargement with heterogenous appearance from (cervical spine) C1 to C6 (viii) High T2/low T1-weighted signal changes subcortical white matter lesions (ix) wedge-shaped low T1-weighted, high T2-weighted areas within the left frontal and posterior parietal regions (T2 shine through) (x) Multiple necrotic, hemorrhagic lesions of a peripheral nature involving cortical and subcortical regions (xi) diffuse leptomeningeal enhancement and communicating hydrocephalus with centrally located infarcts.

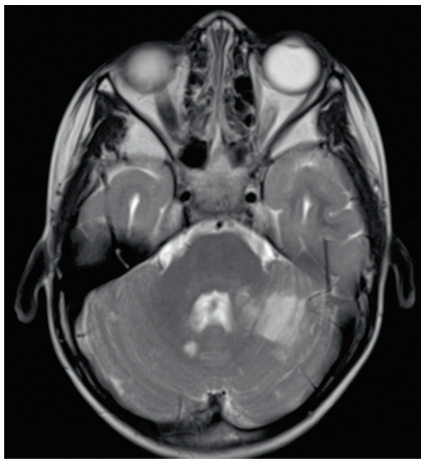


(i)

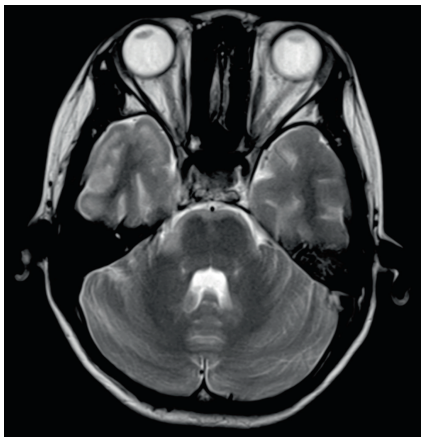


(ii)

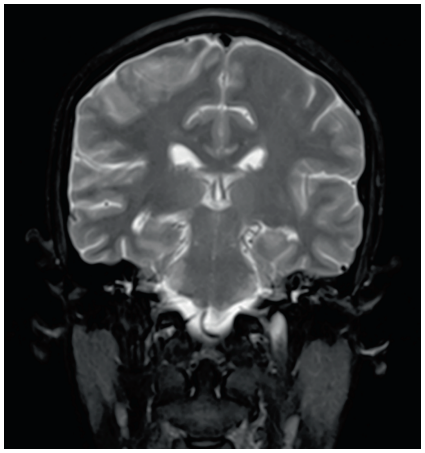
**Figure 4c.** Continued



(iii)

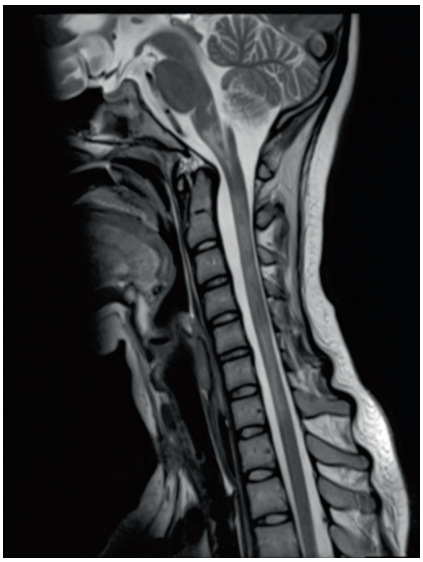


(iv)

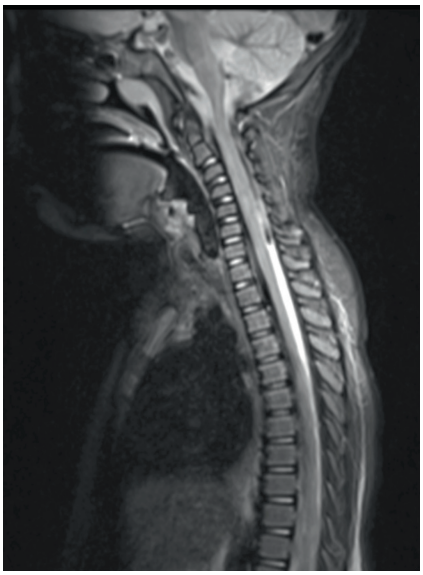


(v)

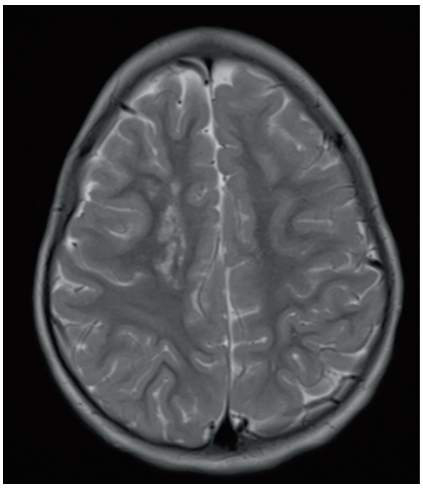
**Figure 4c.** Continued



(vi)

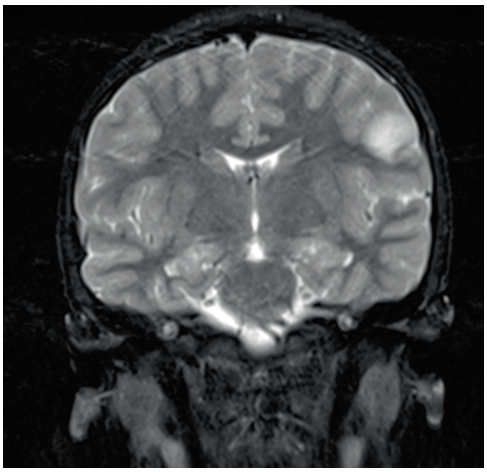


(vii)

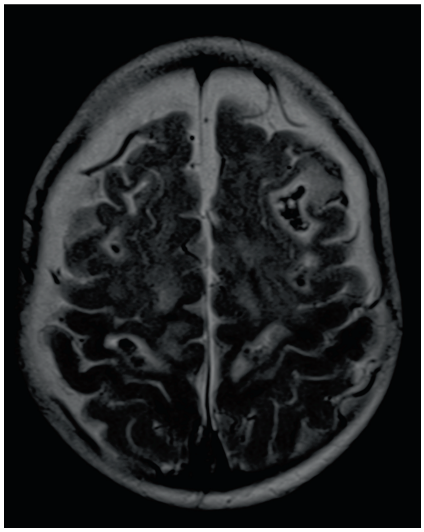


(viii)

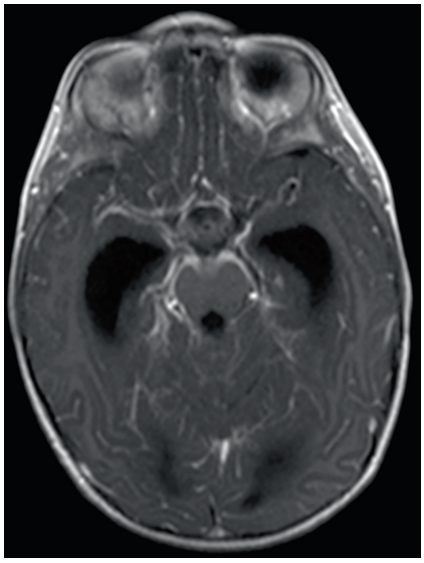
**Figure 4c.** Continued



(ix)



(x)



(xi)

presented with infrequent seizures, then two weeks later developed encephalopathy, intractable seizures, and developmental regression. His SARS-CoV-2 PCR was positive in the second presentation. He was treated with prednisolone and recovered. His neurologic outcome was excellent – no further seizures, developmentally appropriate for age (up until follow-up at 16 months of age), with no focal deficits.

### Systemic involvement

### Cardiac involvement (Figure 4)

Of the patients diagnosed with ADEM/ADS, 50% (5/10) had cardiac manifestations. The spectrum of cardiac involvement included, more commonly, coronary artery dilation and mitral regurgitation and, less commonly, pericardial effusion. Coronary artery dilation was noted in the acute phase in the setting of a robust inflammatory response. Fortunately, all instances of coronary artery dilation were marked by resolution in the convalescent phase concordant with improved clinical status and reducing inflammatory markers. Mitral regurgitation was graded as mild in most cases. This was believed to be due to mitral valvulitis, which also resolved as clinical status improved. Pericardial effusions, when observed, were small and localized. There were no cases of cardiac tamponade. Upon clinical resolution of these patients, comprehensive cardiac evaluation including structure and function was normal in all cases.

Electrocardiographic assessment in the patients presenting with ADEM was notable for sinus tachycardia and non-specific T wave abnormalities in the inferior leads. There were no cases of arrhythmia. Troponin estimation was conducted in two of five of the patients with ADEM, with elevation documented in both patients.

### Other manifestations (cutaneous, liver, muscle, kidneys, pancreas)

Two patients less than two years old also had cutaneous manifestations – one with severe ADEM (erythema nodosum at presentation) and one with AHNE (maculopapular rash of trunk and limbs during the second week of hospitalization). This case also had multisystem involvement, including myocarditis and acute kidney injury secondary to rhabdomyolysis.

All patients with ADEM/ADS/AHNE (10/10) had transaminitis and myositis of differing severities.

The patient diagnosed with brainstem encephalitis/transverse myelitis developed autoimmune pancreatitis, whereas two patients (GBS variant, CNS vasculitis) were diagnosed with type 1 diabetes mellitus, initially presenting with severe diabetic ketoacidosis.

### Blood and CSF findings

Of the patients diagnosed with ADEM/ADS/AHNE and AE, 100% (13/13) met the criteria for PIMS according to the RCPCH guidance. Within this same patient cohort, CSF studies (biochemistry, cell count, M/C/S) were performed in 12/13 (nine diagnosed with ADEM/ADS/AHNE; three diagnosed with AI encephalitis). Out of nine, five patients diagnosed with ADEM/ADS/AHNE had CSF pleocytosis and elevated CSF protein, whereas all three patients diagnosed with AI encephalitis had normal CSF findings.

The two younger patients with AE (anti-TPO positive, anti-NMDAR positive) were ANA positive with elevated ESR. Of the seven ADEM/ADS/AHNE patients tested for ANA, four were positive – both patients with AHNE and both adolescent females with seronegative NMOSD and brainstem encephalitis.

## Discussion

### Key results

Our case series of pediatric patients with no prior medical conditions during the stipulated period June 2020–August 2021 presented with varying severities of acute and post-infectious inflammatory conditions – ADEM/ADS/AHNE, AE, GBS, CNS vasculitis, and COVID-19 encephalitis.

Prior to 2020, the incidence of pediatric ADEM/ADS diagnosed in T&T was at most one case per year, and there has never been a pediatric patient diagnosed with AHNE nor acute necrotizing encephalopathy of childhood. The incidence of the acute demyelinating syndromes (ADEM/ADS/AHNE) during the study period year (2020–2021) significantly increased ninefold in the pediatric population of Trinidad and Tobago. Our toddler/school-age patients responded well to first- and second-line treatments, whereas our adolescent patients required additional third-line treatments (rituximab). Additionally, the recovery of our adolescent patients was slower despite receiving rituximab. Regarding the severe cases of AHNE, we attributed a positive response due to early immunosuppressive therapy and early presentation.

Of the patients diagnosed with AE, those with autoimmune antibodies (anti-NMDA, anti-TPO) were still developmentally/cognitively regressed more than one year post presentation, and still exhibit abnormal movements and seizures, albeit at a lesser frequency and intensity, despite immunomodulation.

Patients diagnosed with CNS vasculitis and viral encephalitis responded well to first-line treatment and recovered within four to six weeks. Albuminocytologic dissociation was a hallmark finding for all GBS cases and they responded well to IVIG treatment.

An element of autoimmunity was also found in our severe cases including all patients diagnosed with AE and both patients diagnosed with AHNE.

Neuroimaging findings were corpus callosal lesions, deep white matter T2 hyperintensities, cerebellar involvement, area postrema and brainstem/C-spine involvement, microhemorrhages and necrotizing/hemorrhagic lesions (peripheral/central).

The ethnic population of Trinidad and Tobago is diverse; however, dominated by two main ethnic groups by descent [19] – East Indians 40.3% and Africans 40%. Due to the political unrest in neighboring Venezuela, we have had a recent increase in

Venezuelan migrants. The increase in severe neurologic inflammatory conditions during the COVID-19 pandemic can therefore be accounted for by our population statistics.

All patients diagnosed with ADEM/ADS/AHNE and AE met the criteria for PIMS-UK, with cardiac, pancreatic, cutaneous, liver, and muscle involvement of varying severities.

SARS-CoV-2 is a neurotropic virus that can reach the CNS either directly or indirectly. Both adaptive and innate immune responses against SARS-CoV-2 infection and virus itself may cause damage within the CNS or PNS [20]. Most patients described in this paper seem to be affected by the alteration of neuroinflammatory mechanisms.

The punctate enhancement pattern has been reported to be characteristic of disease processes that progress from endoluminal, vessel wall, or perivascular cellular proliferation [21]. SARS-CoV-2 infects the host through its CoV spike glycoprotein, which binds to the angiotensin converting enzyme 2 (ACE2) receptor, which is also expressed in the endothelial cells [22]. The expression of the ACE2 receptor in neurons and cerebral endothelial cells indicates a high level of invasiveness for the SARS-CoV-2.

Auto-antibodies have been described in many adult patients with COVID-19; however, the outcome of ANA positive patients was notably worse than that of the auto-antibody negative patients [23]. It is possible, therefore, that the poor neurologic outcome of our patients diagnosed with AE could be linked to a level of autoimmunity.

Animal models and clinicopathological evidence support an autoimmune mechanism and potential molecular mimicry between antibodies against myelin and gangliosides in the nervous system and recent infectious agents, now including COVID-19 infection [24, 25].

Imaging features of diffuse abnormal T2 hyperintensities and reduced diffusivity involving the white matter and genu or splenium of the corpus callosum on MRI have been ascribed to COVID-19 in adults [26] and in children with PIMS [27–29]. Additionally, three patterns of CNS white matter changes have been described: medial temporal lobe signal abnormalities, and microhemorrhages either in the context of multifocal white matter hyperintense lesions or as separate features respectively [30]. Cytotoxic lesions in the corpus callosum are thought to be associated with increased numbers of glutamate and cytokine receptors in the corpus callosum, particularly the splenium [27, 31, 32].

Acute fulminant cerebral oedema has been previously reported in a child with COVID-19 [33] and is a recognized phenotype with high mortality in adults [34, 35] and children [27, 36] associated with other viral causes.

In comparison to other studies [37, 38], severe inflammatory manifestations have been found to be more prevalent in our patients of Afro-Caribbean/East Indian ethnicity. A study done in the United States particularly in children and adolescents diagnosed with PIMS revealed that 60% of the cohort with life-threatening neurologic conditions (severe encephalopathy, stroke, CNS infection/demyelination, GBS/variants and acute fulminant cerebral oedema) were categorized as Hispanic/non-Hispanic blacks [39].

### Limitations

Limitations were mainly due to its observational cross-sectional research design, emerging information on a novel disease, and our cognizant low-resource setting during a pandemic.

1. Results of certain key investigations (e.g. ANA) were not always available.
2. The supply of reagents for biochemical and inflammatory investigations was not consistent.
3. PCR testing for SARS-CoV-2 was limited in our country at the start of the pandemic (only patients with a travel history and respiratory symptoms were approved for testing) due to insufficient testing kits. Antibodies testing for COVID-19 IgG and IgM became available after four of our patients had presented and were treated.
4. During the first three to four months due to restricted testing and new guidance on PIMS, patients with unusual neuroinflammatory diagnoses were not fully investigated (D-dimers, troponin, ferritin testing).
5. Anti-MOG and Aquaprin-4 antibodies testing are not available in public healthcare setting. They could not be performed at presentation. When funding was finally approved, patients had already recovered.

## Conclusion

There has been an upsurge in neuroinflammatory cases since the COVID-19 pandemic began. The range of neuroradiological diagnoses and other systemic involvement alludes to a neuroinflammatory mechanism. Effects on long-term sequelae are concerning in some cases; however, at this early stage, are still unknown. Further studies are suggested – (1) longer term follow-up of these patients (with a focus on developmental scales) and (2) an additional cross-sectional study with the emergence of Omicron variants.

## Acknowledgement

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## Supplemental Data 1 – Clinical Summary of Patients With AHNE

Patient 1, 18-month-old male of African descent; presented with a three-week history of fever, irritability, and initially managed as partially treated meningitis. However, fever persisted and one week post admission, he became encephalopathic and developed a movement disorder. He was treated as a presumed AE with steroids and his GCS improved. However, lumbar puncture was repeated due to persistent fever, and his antibiotic coverage switched. Two weeks post admission, he developed signs of raised ICP. Due to CSF findings, radiology findings and clinical course, he was managed as Acute Hemorrhagic/Necrotizing Leukoencephalitis with escalation of immunomodulation (steroids, IVIG, tocilizumab). However, he was declared brainstem dead 23 days post admission. COVID-19 IgG positive.

Patient 2, seven-month-old male of Venezuelan descent; presented with a three-day history of fever, irritability, and resolved non-purposeful movements. Treatment for PIMS was instituted due to positive COVID-19 antibodies, elevated inflammatory markers, and evidence of myocardial dysfunction. However, he quickly deteriorated five days post admission—acute kidney injury and rhabdomyolysis. He was treated with IVIG followed by pulse methylprednisolone. On day 7 post admission, he developed subclinical seizures. His inflammatory markers, kidney function, myocarditis, and conscious level continue to improve despite the severity of his neuroimaging findings.

Results: MRI Head.

Patient 1 – Infarcts/cerebritis including bilateral thalami and left basal ganglia; diffuse leptomeningeal enhancement and communicating hydrocephalus with transependymal edema.

Patient 2 – Atypical acute necrotizing (hemorrhagic) encephalopathy due to the peripheral nature of lesions.

## Supplemental Data 2 – Comparison Summary of Initial Cases With Severe ADEM

| | **Case 1, 20-month-old male African descent** | **Case 2, 22-month-old male mixed (African/East Indian descent)** |
|---|---|---|
| History | Preceding GE symptoms (within past two weeks)<br>Main issues: focal motor seizures, fever, drowsiness, regression in skills | Preceding GE symptoms (within past two weeks)<br>Main issues: fever, drowsiness, regression in skills |
| Examination | Fluctuating GCS<br>Unable to fix and follow to light, pupils dilated<br>No head/trunk control<br>Generalized limbs spasticity, UMN signs<br>Erythema nodosum | Fluctuating GCS<br>Unable to fix and follow on faces, pupils dilated<br>No head/trunk control<br>Generalized limbs spasticity – UMN signs |
| EEG | Cerebral slowing right > left | Diffuse cerebral slowing; more over frontal regions |
| Blood/CSF | WCC 3.18, lymphopenia<br>Transaminitis<br>CSF white cells – 28; protein – 143 mg/dL | WCC 19.26, lymphocytosis<br>Transaminitis<br>CSF white cells – 0; protein – 23 mg/dL |
| Neuroimaging | Petechial hemorrhages cerebellum<br>Transient lesions corpus callosum<br>Bilateral frontal lobes atrophy | Bilateral fronto-parietal asymmetric deep white matter hyperintensity |
| Treatment | Steroids<br>IVIG | Steroids<br>IVIG |
| Outcome | Improved gradually within three months albeit with a gross motor lag for three to six months | Improved gradually within three months albeit with a gross motor lag for three to six months |

## Supplemental Data 3 – Clinical Summary of Patient Meeting Criteria for Seronegative NMOSD

13-year-old female; Chinese descent met the diagnostic criteria for sero-negative NMOSD:

1. Optic neuritis (presented initially with decreased vision right eye, progressed to complete blindness involving both eyes; optic discs swelling bilaterally) + enhancing focus in left parieto-occipital region.
2. Area postrema syndrome (intractable vomiting) + enhancing lesion in the left aspect of the dorsal medulla.
3. Acute brainstem syndrome (autonomic dysfunction, respiratory distress with new-onset squint) + enhancing foci in medulla.
4. Symptomatic cerebral syndrome (left arm weakness, headache, behavior change) + several enhancing foci within the cerebral hemisphere and sulcal thickening/edema enhancement in the right fronto-temporal lobe.

She presented initially with headache and behavior change x8 days; weakness left arm x6 days; loss of vision right eye x6 days; facial numbness x6 days; vomiting x2 days but no preceding viral illness/vaccine. She was initially managed as ADEM/ADS with steroids (imaging at this time revealed cerebral lesions). However, a protracted illness persisted with intractable nausea/vomiting, and development of new symptoms (squint, autonomic dysfunction, respiratory distress). Repeat imaging showed new involvement of the dorsal and ventral medulla. IVIG and rituximab treatment were then commenced.

Investigations:

- CSF pleocytosis (22 white cells) and elevated protein concentration (131 mg/dL)
- Anti-MOG and Aquaporin-4 antibodies testing post steroids were negative
- ESR increased to 82 mm/h and ANA titre was elevated
- Infectious screen negative (hepatitis studies, HIV, HSV, ASOT)
- Neoplastic workup negative (antineuronal antibodies, CEA, CA-125, AFP, blood film). MRI pelvis was normal
- Anticardiolipin and lupus anticoagulant antibodies negative

ECHO done post steroids, IVIG and during rituximab treatment showed moderately dilated left middle coronary artery and severely dilated left anterior descending artery. She was started on low-dose aspirin.

Her neurologic function improved by six months post IVIG and rituximab. She had a minor regression in left arm function post exposure to Pfizer BioNTech COVID-19 vaccine (dose 1), managed by increasing dose of steroids.

Due to the evidence of inflammation and neurologic and cardiac dysfunction – probable post SARS-COV-2 related presentation of PIMS.

**Unusual Neurologic Manifestations in Children with COVID-19**

**Data Collection Form**

**Patient Name** _____ **Date of Birth**

**Hospital Number** **Female / Male**

**Recruitment number**

**Neurologic Manifestations (please list)**

**Neurologic Findings**

**Overall Diagnosis**

**Electroencephalogram report (if done)**

**Immune therapy** **YES / NO** **(if YES) Clinical Response** **YES / NO**

**Viral prodrome elicited?** **YES / NO**

**SARS-COV-2 Testing**

| Test | Positive | Negative | Not Done |
|---|---|---|---|
| Viral Swab | | | |
| Ig M | | | |
| Ig G | | | |

**Inflammatory Markers**

**Other tests**

**ECHOCARDIOGRAM Findings (if done)**

**Outcome**