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Guillain-Barre Syndrome Associated with SARS-CoV-2 in Two Pediatric Patients

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Abstract

Guillain-Barre syndrome (GBS) is a recognized complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We report two children with GBS associated with SARS-CoV-2 presented to a tertiary center in Muscat, Oman in 2021: The first patient was a 3-month-old female infant who presented with bradypnea, encephalopathy, and generalized weakness that required mechanical ventilation. Polymerase chain reaction (PCR) testing of the nasopharyngeal swabs (NPS) was positive for SARS-CoV-2. She had axonal variant GBS based on a nerve conduction study, cerebrospinal fluid analysis, and neuroimaging findings. The second patient was a 6-year-old girl with fever, vomiting, and diarrhea followed by ascending weakness who presented with quadriplegia and facial weakness. Subsequently, she developed respiratory muscle weakness and required mechanical ventilation. PCR testing of NPS was negative for SARS-Cov-2, however IgG

serology analysis was positive. The clinical course of these two patients was rapidly progressive and both of them required mechanical ventilation. The patient with axonal variant GBS made an incomplete recovery.
Keywords: Acute Inflammatory Demyelinating Polyradiculoneuropathy, SARS-CoV-2, Oman.

Introduction

A wide array of neurological manifestations is linked to SARS-CoV-2 involving both the central and peripheral nervous systems.[1] These manifestations appear to be a combination of non-specific complications of systemic disease, the effects of direct viral infection, or inflammation of the nervous system and vasculature, which can be para-infectious or post-infectious.[2] Peripheral nervous system is less frequently involved and disorders that are described to be associated with COVID-19 include Guillain-Barre syndrome (GBS), Polyneuritis cranialis, myopathy and rhabdomyolysis.[1]

GBS is an immune-mediated disorder that can present in either a demyelinating or axonal form.[3] The demyelinating variant is characterized by autoantibodies that bind to the myelin sheath of Schwann cells and initiate complement activation, leading to a cascade of events resulting in focal destruction of the myelin sheath. In the axonal variant autoantibodies attack the nodal axolemma leading to the formation of membrane attack complex (MAC), which subsequently leads to axonal degeneration.[3]

Similar to adults, GBS is one of the most commonly reported neurological manifestations associated with COVID-19 in pediatric populations.[4] Most children developed GBS after COVID-19 but asymptomatic patients were also described. The clinical presentations and electrophysiologic findings are similar to the classic GBS with slight prevalence of acute inflammatory demyelinating polyneuropathy (AIDP) over acute motor axonal neuropathy (AMAN).[5] The prognosis is favorable with 70% of patients showing good response to intravenous immunoglobulins. The prognosis is worse in the older age groups which is also similar to the classic GBS.

We describe two pediatric patients with different variants of Guillain-Barre syndrome (GBS) associated with SARS-CoV-2 infection and their clinical course and outcome.

Case Reports

Patient One

A 3-month-old female infant born at 34 weeks gestation (corrected 8 weeks) had an uneventful antenatal and postnatal history and adequate growth and development. She presented to the emergency department (ED) with a two-day history of poor feeding, lethargy, shallow slow breathing, and decreased urine output. Ten days prior, she had one day of fever, vomiting, and diarrhea. Physical examination revealed an encephalopathic infant with a weak cry and Glasgow Coma Scale of E1V2M3. The patient was pale, tachycardic, hypertensive, poorly perfused; in compensated shock, bradypneic with intermittent episodes of apnea requiring intubation and mechanical ventilation. Further examination showed hypotonia with lower extremity weakness and absent deep tendon reflexes (DTR). She was resuscitated with fluid and covered with broad-spectrum antimicrobials (ceftriaxone, vancomycin and acyclovir) for the possibility of septic shock and meningoencephalitis. Initial testing showed that the nasopharyngeal aspirate (NPA) was positive for SARS-Cov-2, respiratory viral screen was positive for adenovirus and negative for the rest of viruses including parechoviruses, human bocavirus, influenza A & B, parainfluenza 1, 2, 3, 4, rhinovirus, respiratory syncytial virus (RSV), human metapneumovirus, enterovirus and H1N1. NPA for mycoplasma pneumoniae polymerase chain reaction (PCR) was negative. PCR for cytomegalovirus (CMV), and Epstein Barr virus (EBV) from the serum was negative. Computed tomography (CT) of the brain was normal; cerebrospinal fluid (CSF) analysis showed high protein 0.64 g/L (normal range: 0.15–0.45) and glucose 4.1 mmol/L(normal range: 3.3–4.4) with no leucocytes. CSF culture showed no growth, and viral PCR for herpes simplex virus (HSV), parechovirus, enterovirus, varicella zoster virus and mumps viruses.was negative.

The patient remained persistently tachycardic and hypertensive despite hydration and sedation but was controlled with propranolol. Renal ultrasound and magnetic resonance

angiography of the aorta and renal arteries were normal. Echocardiography revealed left ventricular hypertrophy with moderate outflow obstruction. In view of this clinical presentation, magnetic resonance imaging (MRI) of the brain was performed which showed leptomeningeal enhancement on the surface of the brainstem and within the internal auditory canals. MRI of the spine showed diffuse enhancement of the spinal nerve roots, which was more conspicuous along the cauda equina nerve roots, with surface enhancement of the cord at the conus (Figure 1). Nerve conduction studies (NCS) showed sensorimotor axonal polyneuropathy. Moreover metabolic screen including lactate, ammonia, lactase dehydrogenase, thyroid function test, neonatal metabolic screen and createnine kinase (CK) were normal. Furthermore patient had whole exome sequencing (WES) that came negative with no pathogenic variants or variants of unknown significance.

The patient was diagnosed with GBS based on the results of CSF analysis, NCS, and neuroimaging. She was treated with intravenous immunoglobulin (IVIG; 2g/kg) followed by plasma exchange (PLEX; five cycles) and a second dose of IVIG. The patient was successfully extubated to bilevel positive airway pressure (BiPAP) but could not be weaned off due to generalized muscle weakness and bradypnea so we planned for a tracheostomy and home ventilation. However, because of her difficult socioeconomic status, the parents refused tracheostomy, and the patient was eventually discharged home and palliated on continuous BiPAP and exclusive nasogastric tube feeding.

Patient Two

A 6-year-old previously healthy girl presented to a community hospital with one week history of fever, vomiting, constipation, and abdominal pain followed by lower extremity weakness on day 7 of illness. The weakness progressed to involve the upper extremities and respiratory muscles requiring intubation and mechanical ventilation. CSF analysis revealed cytoalbuminologic dissociation with protein of 0.94 g/L (normal range: 0.15–0.45), glucose of 3.93 mmol/L (normal range: 3.3–4.4), WBC of 0 and RBCs of 512. The patient was treated with IVIG but showed no major improvement so was transferred to our institution for further management. Here, she was found to have bilateral facial weakness as well as axial and appendicular hypotonia with a strength of 1/5 on the right and 0/5 on the

left side. DTR were absent, and the plantar flexors showed no clonus. No signs of autonomic involvement were observed. The NPA was negative for SARS-Cov-2, however IgG serology testing was positive. Poliovirus PCR in the stool was negative.

The NCS showed a sensorimotor demyelinating polyneuropathy with conduction blocks. The patient underwent PLEX followed by IVIG, and was eventually extubated and discharged home with follow up at four weeks showing normalization to her baseline functional status.

Consents were taken from patients' parents for these case reports publication.

Discussion

GBS is classified as either acute inflammatory demyelinating polyradiculoneuropathy (AIDP) or acute axonal neuropathy which is further classified as acute motor axonal neuropathy (AMAN) or acute motor sensory axonal neuropathy (AMSAN).[3] Other GBS variants include Miller-Fisher syndrome, Bickerstaff encephalitis, pharyngeal-cervical-brachial variant, and pandysautonomia variant.[3] This autoimmune-mediated disorder can be triggered by viruses such as cytomegalovirus, Epstein-Barr virus (EBV), influenza, hepatitis E, and Zika, or by bacteria such as *Campylobacter jejuni* or *Mycoplasma pneumoniae.*[5,65] SARS-Cov-2 has been reported to be a potential trigger that could be associated with GBS. The first case of GBS associated with SARS-Cov-2 was reported in early 2020 in an adult.[2] Since this initial report, there have been multiple case reports, case series, and systemic reviews demonstrating this association including in the pediatric population.[5,7-12] Table 1 summarizes GBS cases associated with SARS-Cov-2 in pediatric population.

Here, we report two pediatric patients who were diagnosed with GBS and tested positive for SARS-Cov-2. The first patient is of particular interest because of the age at presentation of 8 weeks. GBS usually occurs after the age of 3 years; onset in infancy is extremely rare. There are reported cases of congenital GBS but the youngest patient reported was 11 months old.[13, 14] Our patient had symptoms of infection such as fever, vomiting, and

diarrhea 10 days prior to her presentation to the ED. PCR testing of the nasopharyngeal and throat swabs were positive for SARS-Cov-2 and adenovirus. PCR testing of the CSF for SARS-Cov-2 was not performed. GBS in our patient was likely triggered by SARS-Cov-2 infection, as this association has been previously reported and adenovirus infection is not among the reported potential infectious triggers of GBS. [5, 7] However, there is a question regarding the possible association between the adenovirus vaccine and GBS as a possible complication.[15] SARS-Cov-2 is likely the potential trigger for GBS, due to either surface epitope mimicry of SARS-Cov-2 to the antigens on Schwann cell myelin sheaths in the demyelinating variant or to the nodal axolemma in the axonal variant.[3] This molecular mimicry has been reported with other viruses, such as varicella zoster virus (VZV), EBV and CMV in patients infected with human immunodeficiency virus.[16] Both patients had cytoalbuminologic dissociation, which has been well documented in previous reports.[5, 7] The neurophysiological evaluation of our first patient showed a picture suggestive of AMSAN. The AMSAN variant has been reported in association with SARS-Cov-2. In a recent systematic review of different GBS variants, there were seven cases of AMSAN reported, with an age range of 23–77 years and no cases in the pediatric age group.[17] Recently, Akçay et al. reported the first pediatric patient with axonal variant GBS associated with SARS-Cov-2.[10] Our patient is the youngest reported pediatric patient with AMSAN associated with SARS-Cov-2. The AMSAN variant of GBS has been reported in children but is mainly associated with C. jejuni gastroenteritis.[18] Our patient's diagnosis was based on the presence of sensorimotor axonal polyneuropathy, cytoalbuminologic dissociation in the CSF, and cauda equina root enhancement on neuroimaging. Furthermore, she had features of dysautonomia, including persistent hypertension that was initially refractory to medical treatment and pupillary abnormalities. The persistent hypertension likely led to a hypertrophic left ventricle. Autonomic disturbances are among the clinical features of GBS, especially during the acute clinical presentation. These clinical features may include blood pressure and heart rate instability, sweating disturbances, bowel and bladder retention, incontinence, and vasomotor instability.[19] In addition, the presence of dysautonomia correlates with illness severity, and this is particularly true for hypertension and tachycardia.[20] Moreover, this patient had rapid progression of the disease requiring intubation and mechanical ventilation at the time of presentation, indicating a

rapidly progressive course of her illness and a short peak to disability. She required a prolonged period of mechanical ventilation in the PICU before weaning to non-invasive ventilation was possible. This course is similar to that of a previously reported pediatric patient with axonal GBS associated with SARS-Cov-2.[10] This patient had multiple poor prognostic factors, including the rapid deterioration of her clinical status requiring mechanical ventilation on presentation, the axonal variant of GBS and the presence of dysautonomia.[22, 23] Peak disability has been reported as an independent risk factor for outcomes.[22] Although the combination of GBS and encephalopathy in this patient seems unusal, the early resolution of encephalopathy and longer-persisting neuropathy may permit the consideration of GBS as a possible diagnosis.

In the second patient, PCR testing of the NPS and throat swab were negative for SARS-Cov-2, but IgG serology was positive. Hence, GBS was likely part of a parainfectious process associated with SARS-Cov-2. Her clinical course was similar to a previously reported case of the demyelinating variant of GBS associated with SARS-Cov-2.[24] Her outcome was more favorable than that of the first patient, although her initial presentation was rapidly progressive, and she had a short peak to disability. Prognosis was more favorable in the demyelinating variant than in the axonal variant, which is well documented in the literature.[25] In addition, this patient did not have dysautonomia, and her period of mechanical ventilation was shorter. Given that SARS-Cov-2 diagnosis in this patient was based on IgG serology and that other antimicrobial causes were not excluded, GBS may not be related to SARS-Cov-2.

In both cases, the clinical course was severe with rapid progression, which is likely related to the severe autoimmune response that is mounted by the body in response to SARS-Cov-2 infection.[26]

Conclusion

GBS should be considered in the differential diagnosis of any child presenting with acute flaccid paralysis even in patients less than one year of age. There is growing evidence that there is association between SARS-Cov-2 infection and GBS.

Authors' Contribution

AAF conceptualized the idea. FAA and AAF drafted the manuscript. FAR and RA-A drafted the case history. EAA prepared the images, annotation and description. FAA, RA-A and AAF revised the manuscript. All authors approved the final version of the manuscript.

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Table 1: Clinical Characteristics of reported pediatric patients with Guillian-Barre syndrome –associated with SARS-Cov-2

	Author	Sex	Age at onset (yr)	Time to loss functional ability	IV	Dx from symp onset (D)	Clinical Features	CN involvement	Dysautonomia	CSF cytoalbumin dissociation	IVIG regimen	PLEX	Invasive ventilation period (D)	Nasopharyngeal SARS-Cov-2 PCR	CSF SARS-Cov-2 PCR	Serum SARS-Cov-2 serology	Anti-gangliosides Abs	GBS-variant
1	Curtis et al [9]	M	8	Few days	+	12	Flaccid weakness	-	-	+	2 g/kg over 2D	-	4	+	-	NA	NA	AIDP
2	Khalifa et al [11]	M	11	Few days	-	2	Distal weakness of the U & LE	-	-	+	2 g/kg over 2D	-	-	+	NA	NA	NA	AIDP
3	Frank CHM et al [12]	M	15	Few days	-	NA	Progressive U and LE weakness	-	-	+	0.4 g/kg x 5D	-	-	+	-	+	-	AMAN
4	Akçay et al [10]	M	6	4D	+	14	Flaccid weakness	-	-	+	2 g/kg over 2D	+	30	+	NA	NA	-	AMAN

Abbreviations: yr: age in years, **IV:** invasive ventilation**, D:** days, **CN:** cranial nerves, **Dx from symp onset**: diagnosis from symptom onset**, CSF:** cerebrospinal fluid, **IVIG**: intravenous immunoglobulin, **PLEX:** Plasma Exchange, **PCR:** polymerase chain reaction, **Abs:** Antibodies, **AIDP:** acute inflammatory demyelinating polyradiculopathy, **AMAN:** acute motor axonal neuropathy, **NA:** not available

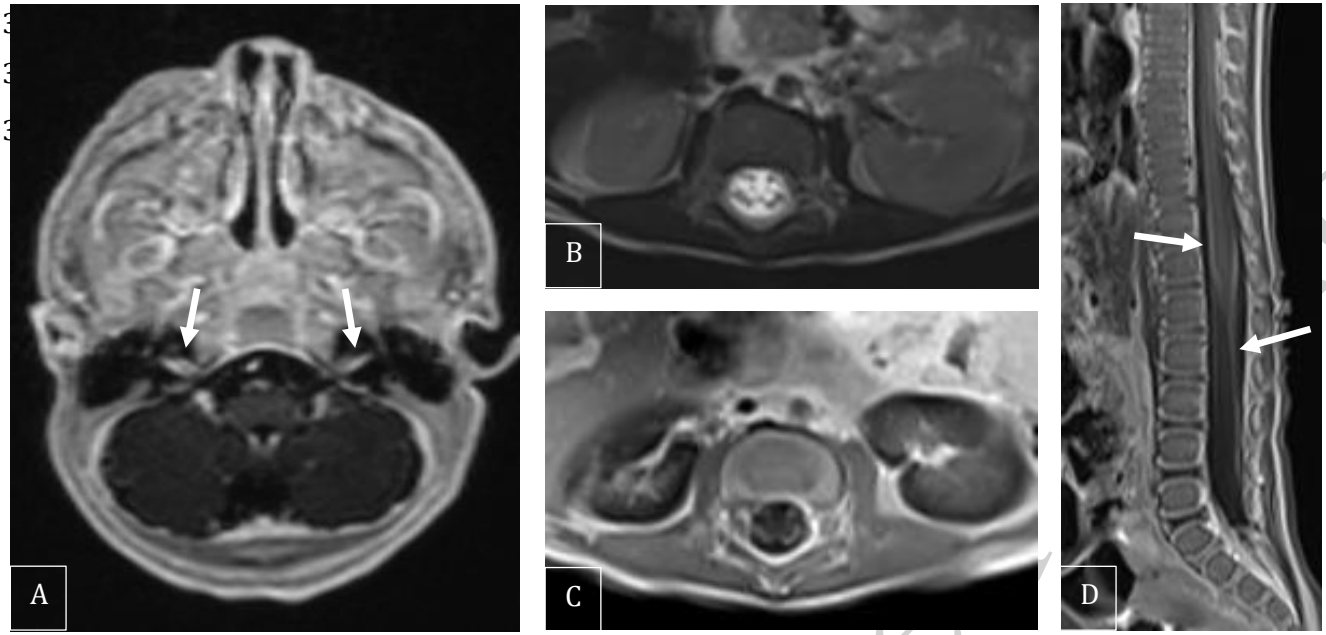

Figure 1. (A) A gadolinium-enhanced axial T1-weighted image through the posterior fossa shows bilateral enhancement in the internal auditory canals (arrows). **(B)** An axial T2-weighted image of the lumbar spine doesn't show abnormal thickening of the cauda equina nerve roots. There is however uniform enhancement of the spinal nerve roots on gadolinium-enhanced axial T1-weighted image **(C)**. **(D)** The enhancement on the surface of the disatal cord and cauda equina nerve roots is also shown on sagittal post-contrast T1 weighted image (arrows).