Sultan Qaboos University Med J, August 2023, Vol. 23, Iss. 3, pp. 400–404, Epub. 28 Aug 23
Submitted 19 Jan 22
Revision Req. 9 Mar 22; Revision Recd. 24 Apr 22
Accepted 17 May 22
https://doi.org/10.18295/squmj.5.2022.040

CASE REPORT

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

Fatema Al Amrani,[1] Raghad Al-Abdwani,[2] Fatma Al Rashdi,[3] Eiman Al-Ajmi,[4] *Amna Al Futaisi[5]

**ABSTRACT:** Guillain-Barré syndrome (GBS) is a recognised complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We report two children with GBS associated with SARS-CoV-2 who presented to a tertiary centre in Muscat, Oman in 2021: The first patient was a three-month-old female infant who presented with bradypnea, encephalopathy, and generalised 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 six-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; Case Report; Oman.

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-Barré 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 characterised 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 paediatric populations.[4] Most of such 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 favourable 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 paediatric patients with different variants of GBS associated with SARS-CoV-2 infection and their clinical course and outcome.

## Case Reports

### CASE ONE

A three-month-old female infant born at 34 weeks gestation (corrected eight 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.

*[1]Pediatric Neurology Unit and [2]Pediatric Intensive Care Unit, Department of Child Health and [3]Pediatric Emergency Unit, Emergency Medicine Department, Sultan Qaboos University Hospital, Sultan Qaboos University, Muscat, Oman; [4]Department of Radiology and Molecular Imaging, Sultan Qaboos University Hospital, Sultan Qaboos University, Muscat, Oman; [5]Pediatric Neurology Unit, Department of Child Health, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman*

**Corresponding Author's e-mail: amnaf@squ.edu.om*

**Table 1:** Clinical characteristics of reported paediatric patients with Guillian-Barré syndrome associated with SARS-CoV-2.[9–12]

| Author and publication year | Curtis *et al.*[9] (2021) | Khalifa *et al.*[11] (2020) | Frank *et al.*[12] (2021) | Akçay *et al.*[10] (2021) |
|---|---|---|---|---|
| Gender | Male | Male | Male | Male |
| Age at onset in years | 8 | 11 | 15 | 6 |
| Time to functional ability loss | Few days | Few days | Few days | 4 days |
| Invasive ventilation | + | - | - | + |
| Diagnosis from symptom onset in days | 12 | 2 | NA | 14 |
| Clinical features | Flaccid weakness | Distal weakness of the upper and lower extremities | Progressive upper and lower extremity weakness | Flaccid weakness |
| Cranial nerves involvement | - | - | - | - |
| Dysautonomia | - | - | - | - |
| Cerebrospinal fluid cytoalbumin dissociation | + | + | + | + |
| IVIG regimen | 2 g/kg over 2 days | 2 g/kg over 2 days | 0.4 g/kg over 5 days | 2 g/kg over 2 days |
| PLEX | - | - | - | + |
| Invasive ventilation period in days | 4 | - | - | 30 |
| Nasopharyngeal SARS-CoV-2 PCR | + | + | + | + |
| Cerebrospinal fluid SARS-CoV-2 PCR | - | NA | - | NA |
| Serum SARS-CoV-2 serology | NA | NA | + | NA |
| Anti-gangliosides antibodies | NA | NA | - | - |
| GBS-variant | AIDP | AIDP | AMAN | AMAN |

*NA = not available; IVIG = intravenous immunoglobulin; PLEX = plasma exchange; PCR = polymerase chain reaction; AIDP = acute inflammatory demyelinating polyradiculopathy; AMAN = acute motor axonal neuropathy; GBS = Guillian-Barré syndrome.*

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 the viruses including parechoviruses, human bocavirus, influenza A & B, parainfluenza 1–4, 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 leukocytes. CSF culture showed no growth, and viral PCR for herpes simplex virus (HSV), parechovirus, enterovirus, varicella zoster virus and mumps viruses were 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,

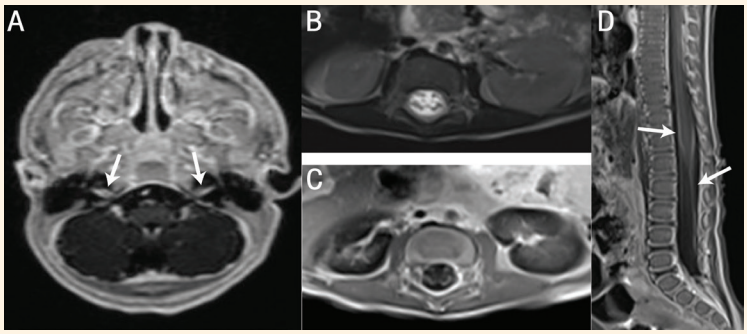


**Figure 1: A:** A gadolinium-enhanced axial T1-weighted image through the posterior fossa showing bilateral enhancement in the internal auditory canals (arrows). **B:** An axial T2-weighted image of the lumbar spine doesn't show abnormal thickening of the cauda equina nerve roots. **C:** Gadolinium-enhanced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

neonatal metabolic screen and createnine kinase were normal. Furthermore, the patient had whole exome sequencing 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 course of IVIG. The patient was successfully extubated to bilevel positive airway pressure (BiPAP) but could not be weaned off due to generalised muscle weakness and bradypnea so a tracheostomy and home ventilation were planned. 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.

### CASE TWO

A six-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 seven 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. There was no clonus, absent DTR and the plantars were flexors. 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 a follow-up at four weeks showing normalisation to her baseline functional status.

Consents were taken from both patients' parents for the publication of these reports.

## Discussion

GBS is classified as either AIDP or acute axonal neuropathy which is further classified as 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, EBV, influenza, hepatitis E and Zika, or by bacteria such as *Campylobacter jejuni* or *Mycoplasma pneumoniae*.[5,6] 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 paediatric population [Table 1].[5,7–12]

Here, we report two paediatric 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 eight weeks. GBS usually occurs after the age of three 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] The patient in case one 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 the first patient was likely triggered by a 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, 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 the first patient was 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 paediatric age group.[17] Recently, Akçay *et al.* reported the first paediatric patient with axonal variant GBS associated with SARS-CoV-2.[10] The patient in case one is the youngest reported paediatric 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] The first 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 paediatric 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 unusual, 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 favourable than that of the first patient, although her initial presentation was rapidly progressive, and she had a short peak to disability. Prognosis was more favourable 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 younger than one year. There is growing evidence that there is association between SARS-CoV-2 infection and GBS.

### AUTHORS' CONTRIBUTION

AAF conceptualised 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.

## References


1. Guerrero JI, Barragán LA, Martínez JD, Montoya JP, Peña A, Sobrino FE, et al. Central and peripheral nervous system involvement by COVID-19: A systematic review of the pathophysiology, clinical manifestations, neuropathology, neuroimaging, electrophysiology, and cerebrospinal fluid findings. BMC Infect Dis 2021; 21:515. https://doi.org/10.1186/s12879-021-06185-6.
2. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré - syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 2020; 19:383–4. https://doi.org/10.1016/S1474-4422(20)30109-5.
3. Yuki N, Hartung H-P. Guillain-Barré syndrome. N Engl J Med 2012; 366:2294–304. https://doi.org/10.1056/NEJMra1114525.
4. Sánchez-Morales AE, Urrutia-Osorio M, Camacho-Mendoza E, Rosales-Pedraza G, Dávila-Maldonado L, González-Duarte A, et al. Neurological manifestations temporally associated with SARS-CoV-2 infection in pediatric patients in Mexico. Childs Nerv Syst 2021; 37:2305–12. https://doi: 10.1007/s00381-021-05104-z5.
5. Abu-Rumeileh S, Abdelhak A, Foschi M, Tumani H, Otto M. Guillain-Barré syndrome spectrum associated with COVID-19: An up-to-date systematic review of 73 cases. J Neurol 2021; 268:1133–70. https://doi.org/10.1007/s00415-020-10124-x.
6. Grygorczuk S, Zajkowska J, Kondrusik M, Pancewicz S, Hermanowska-Szpakowicz T. [Guillain-Barré Syndrome and its association with infectious factors]. Neurol Neurochir Pol 2005; 39:230–6.
7. Sansone P, Giaccari LG, Aurilio C, Coppolino F, Esposito V, Fiore M, et al. Post-Infectious Guillain-Barrrr its association to SARS-CoV-2 Infection: A Systematic Review. Life (Basel) 2021; 11:167. https://doi.org/10.3390/life11020167.
8. Al-Zadjali MM, Shibli EA, Maskari MA, Gujjar AR, Asmi AA. Post COVID-19 Guillain-Barré-Syndrome (GBS): A case report from Oman. Sultan Qaboos Univ Med J 2022; 3:409–12. https://doi.org/10.18295/squmj.6.2021.090.
9. Curtis M, Bhumbra S, Felker MV, Jordan BL, Kim J, Weber M, et al. Guillain-Barré Syndrome in a Child With COVID-19 Infection. Siatrics 2021; 147:e2020015115. https://doi.org/10.1542/peds.2020-015115.
10. Akçay N, Menentoğlu ME, Bektaş G, Şevketoğlu E. Axonal Guillain-Barre syndrome associated with SARS-CoV-2 infection in a child. J Med Virol 2021; 93:5599–602. https://doi.org/10.1002/jmv.27018.
11. Khalifa M, Zakaria F, Ragab Y, Saad A, Bamaga A, Emad Y, et al. Guillain-Barré-Syndrome (GBS): Severe Acute Respiratory Syndrome Coronavirus 2 Detection and Coronavirus Disease 2019 in a Child. J Pediatric Infect Dis Soc 2020; 9:510–13. https://doi.org/10.1093/jpids/piaa086.
12. Frank CHM, Almeida TVR, Marques EA, de Sousa Monteiro Q, Feitoza PVS, Borba MGS, et al. Guillain-Barré Syndrome Associated with SARS-CoV-2 Infection in a Pediatric Patient. J Trop Pediatr 2021; 67:fmaa044. https://doi.org/10.1093/tropej/fmaa044.
13. Luijckx GJ, Vles J, Baets M de, Buchwald B, Tmost J. Guillain-Barré syndrome in mother and newborn child. The Lancet 1997; 349:27. https://doi.org/10.1016/s0140-6736(97)24001-8.
14. Kannan MA, Ch RK, Jabeen SA, Mridula KR, Rao P, Borgohain R. Clinical, electrophysiological subtypes and antiganglioside antibodies in childhood Guillain-Barré syndrome. Neurology India 2011; 59:727. https://doi.org/10.4103/0028-3886.86549.
15. McNeil MM, Paradowska-Stankiewicz I, Miller ER, Marquez PL, Seshadri S, Collins LC, et al. Adverse events following adenovirus type 4 and type 7 vaccine, live, oral in the Vaccine Adverse Event Reporting System (VAERS), United States, October 2011-July 2018. Vaccine 2019; 37:6760–7. https://doi.org/10.1016/j.vaccine.2019.08.087.
16. Gnann JW. Varicella-zoster virus: atypical presentations and unusual complications. J Infect Dis 2002; 186:S91–8. https://doi.org/10.1086/342963.
17. Robinson-Papp J, Simpson DM. Neuromuscular diseases associated with HIV-1 infection. Muscle Nerve 2009; 40:1043–53. https://doi.org/10.1002/mus.21465.
18. Sriwastava S, Kataria S, Tandon M, Patel J, Patel R, Jowkar A, et al. Guillain Barré Syndrome and its variants as a manifestation of COVID-19: A systematic review of case reports and case series. J Neurol Sci 2021; 420:117263. https://doi.org/10.1016/j.jns.2020.117263.
19. Heikema AP, Islam Z, Horst-Kreft D, Huizinga R, Jacobs BC, Wagenaar JA, et al. Campylobacter jejuni capsular genotypes are related to Guillainin vaccine, lme. Clin Microbiol Infect 2015; 21:852.e1-9. https://doi.org/10.1016/j.cmi.2015.05.031.
20. Zaeem Z, Siddiqi ZA, Zochodne DW. Autonomic involvement in Guillain–Barré syndrome: An update. Clin Auton Res 2019; 29:289–99. https://doi.org/10.1007/s10286-018-0542-y.
21. Dimario FJ, Edwards C. Autonomic dysfunction in childhood Guillain-Barré syndrome. J Child Neurol 2012; 27:581–6. https://doi.org/10.1177/0883073811420872.
22. Kalita J, Kumar M, Misra UK. Prospective comparison of acute motor axonal neuropathy and acute inflammatory demyelinating polyradiculoneuropathy in 140 children with Guillain-Barré syndrome in India. Muscle Nerve 2018; 57:761–5. https://doi.org/10.1002/mus.25992.
23. Chakraborty T, Kramer CL, Wijdicks EFM, Rabinstein AA. Dysautonomia in Guillain-Barré Syndrome: Prevalence, Clinical Spectrum, and Outcomes. Neurocrit Care 2020; 32:113–20. https://doi.org/10.1007/s12028-019-00781-w.
24. Hasan I, Saif-Ur-Rahman KM, Hayat S, Papri N, Jahan I, Azam R, et al. Guillain-Barré syndrome associated with SARS-CoV-2 infection: A systematic review and individual participant data meta-analysis. J Peripher Nerv Syst 2020; 25:335–43. https://doi.org/ 10.1111/jns.12419.
25. Estrade S, Guiomard C, Fabry V, Baudou E, Cances C, Chaix Y, et al. Prognostic factors for the sequelae and severity of Guillain-Barré syndrome in children. Muscle Nerve 2019; 60:716–23. https://doi.org/10.1002/mus.26706.
26. Garcrc/mus.26706.rd C, Fae, Inflammation, and the Clinical Spectrum of COVID-19. Front Immunol 2020; 11:1441. https://doi.org/10.3389/fimmu.2020.01441.