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LETTER TO THE EDITOR

Re: Guillain-Barré Syndrome Associated with SARS-CoV-2 in Two Paediatric Patients

Dear Editor,

We read with interest the article by Al Amrani *et al*. published in the August 2023 issue of SQUMJ on 2 paediatric patients, a 3 months-old female (patient 1) and a 6-year-old female (patient 2) with SARS-CoV-2 (SC2) associated Guillain Barre syndrome (GBS), subtype acute motor and sensory axonal neuropathy.[1] Both patients required mechanical ventilation and were additionally treated with intravenous immunoglobulins and plasma exchange. Patient 1 was discharged home for palliative care with nasogastric tube feeding and permanent BiPAP ventilation, while patient 2 fully recovered within four weeks of discharge. The study is impressive but has several limitations.

We disagree that patient 1 had only GBS involving cranial nerve 8. Encephalopathy was also described in patient 1, suggesting central nervous system involvement. In addition, contrast-enhanced cerebral magnetic resonance imaging (MRI) showed leptomeningeal enhancement, suggesting meningitis. It is unclear what the clinical manifestations of this encephalopathy were and what were the findings of electroencephalography (EEG). Since SC2 can be complicated by immune-encephalitis, it would have been crucial to also test the patient for specific antibodies associated with autoimmune encephalitis. A normal cell count in the cerebrospinal fluid (CSF) does not rule out encephalitis/meningitis.[2] Even in the absence of an enhancing lesion on MRI, a patient may have encephalitis. Since cerebral MRI showed leptomeningeal enhancement on the brainstem surface, Bickerstaff encephalitis should be suspected. We should also know if SC2 was found in CSF or not. According to Figure 1, the patient had an affection of cranial nerve VIII.[1] The reader should know whether patient 1 also suffered from hypoacusis or dizziness.

Left ventricular hypertrophy in patient 1 was explained by arterial hypertension due to dysautonomia. However, if dysautonomia were responsible for the arterial hypertension, left ventricular hypertrophy would not have developed within a few days from the onset of GBS. Left ventricular hypertrophy was more likely due to congenital hypertrophic cardiomyopathy than arterial hypertension. Was the family history positive for hypertrophic cardiomyopathy? Were patient 1's parents consanguineous? Was there evidence that axonal neuropathy existed prior to SC2 infection? Why was whole exome sequencing (WES) performed in a patient with an acute infection and a suspected immunological complication of that infection?

We disagree that patient 2 had an acute SC2 infection.[1] The SC2 infection in patient 2 was diagnosed solely based on the presence of IgG antibodies against SC2. Polymerase chain reaction (PCR) for SC2 was negative and no pneumonia was evident. Since IgG antibodies against SC2 can persist for months, it is more likely that patient 2 had a gastrointestinal infection due to an infectious agent other than SC2, such as *Campylobacter jejuni*, mycoplasma pneumoniae, cytomegalovirus, Epstein–Barr virus, influenza, hepatitis E or Zika.[3] Were these pathogens excluded as causes of the gastrointestinal infection that preceded GBS in patient 2?

We disagree that only GBS, polyneuritis cranialis, myopathy and rhabdomyolysis can be peripheral nervous system (PNS) complications of SARS-CoV-2 infection, as outlined in the introduction.[1] In addition, cervico-brachial plexitis (Parsonage Turner syndrome), polyneuropathy, new-onset myasthenia, flares of myasthenia, myasthenic syndrome and myositis have been reported as PNS complications of SC2 infections.[4]

Patient 1 and patient 2 required mechanical ventilation, which was attributed to respiratory muscle involvement in GBS.[1] However, it was reported that both patients also had COVID-19. How did the authors distinguish between respiratory failure due to COVID-19 and respiratory failure due to GBS?

We disagree that adenovirus is not a potential cause of GBS; although rare, adenovirus-associated GBS has occasionally been reported.[5]

In summary, this excellent study has limitations that call the conclusions into question. Patient 1 had GBS involving not only the cranial nerves but also meninges or the brain. In patient 2, GBS was not associated with acute SARS-CoV-2 infection.

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References

1. Al Amrani F, Al-Abdwani R, Al Rashdi F, Al-Ajmi E, Al Futaisi A. Guillain-Barré Syndrome Associated with SARS-CoV-2 in Two Pediatric Patients. Sultan Qaboos Univ Med J 2023; 23:400–4. https://doi.org/10.18295/squmj.5.2022.040.
2. Jarius S, Pache F, Körtvelyessy P, Jelčić I, Stettner M, Franciotta D, et al. Cerebrospinal fluid findings in COVID-19: A multicenter study of 150 lumbar punctures in 127 patients. J Neuroinflammation 2022; 19:19. https://doi.org/10.1186/s12974-021-02339-0.
3. Adeniyi OV, Durojaiye OC, Masilela C. Persistence of SARS-CoV-2 IgG Antibody Response among South African Adults: A prospective cohort study. Vaccines (Basel) 2023; 11:1068. https://doi.org/10.3390/vaccines11061068.
4. Perilli L, Fetta M, Capponi M, Guido CA, Grosso S, Iannetti P, Spalice A. Peripheral nervous system involvement in SARS-CoV-2 infection: A review of the current pediatric literature. Front Neurol 2023; 14:1134507. https://doi.org/10.3389/fneur.2023.1134507.
5. Pachas P, Donaires F, Gavilán RG, Quino W, Vidal M, Cabezas C, et al. Infectious agents in biological samples from patients with Guillain-Barré syndrome in Peru, 2018-2019. Rev Peru Med Exp Salud Publica 2020; 37:681–8. https://doi.org/10.17843/rpmesp.2020.374.5169.

Response from the Authors

Dear Reader,

We appreciate our colleagues' response to our article. The clinical presentation, nerve conduction studies, cytoalbuminologic dissociation and nerve root enhancement support a diagnosis of GBS in both patients. During the initial presentation of patient 1, the child displayed symptoms of lethargy, poor oral intake and poor sucking, which are non-specific and can indicate infection and sepsis in this age group. However, the child did not exhibit any signs of seizures, including abnormal movements. Unlike her flaccid weakness, her consciousness level improved significantly over a few days. The EEG showed diffuse slowing without epileptic activity. The SC2 PCR test for the CSF was not available at our institute and, therefore, not conducted, as shown in Table 1. According to the literature, CSF PCR was performed in 2 paediatric patients with GBS associated with SC2 and it was negative in both cases.[1]

We agree that SC2 has the potential to cause autoimmune encephalitis. However, in this case, an autoimmune work-up was not performed due to the patient's improved clinical presentation within a few days of their initial symptoms, and the absence of seizures, movement disorders and CSF pleocytosis. It is worth noting that brain MRI revealed leptomeningeal enhancement, which can be a typical feature of GBS, including the leptomeningeal enhancement seen around the brainstem.[2] Unfortunately, as the patient was only 3 months old, it was difficult to determine if they had any symptoms of hypoacusis or dizziness as they are non-verbal at this age.

Patient's blood pressure was consistently high at presentation. Mild left ventricular hypertrophy detected, possibly due to an underlying genetic cause or persistent high blood pressure. Primary hypertrophic cardiomyopathy usually shows both left and right ventricular hypertrophy, so seeing only left ventricular hypertrophy is uncommon. The parents were consanguineous but there was no history of hypertrophic cardiomyopathy in the family.

The patient had a normal birth and development. During an infection, she experienced flaccid paralysis, indicating an acquired weakness. WES was conducted to investigate the possibility of inherited diseases due to congenital CMT and multiple symptoms at presentation.

It is highly probable that the GBS of patient 2 was triggered by SC2 infection. The patient was tested 2 weeks after experiencing symptoms of fever, vomiting, constipation and abdominal pain. It should be noted that the SC2 PCR test can yield negative results within a week of the initial infection, depending on the severity of the case. Antibodies, on the other hand, can persist for weeks after the initial infection.[3] Other respiratory virus tests were negative and no DNA was detected for *Mycoplasma pneumoniae*. Therefore, we believe that patient symptoms were likely associated with SC2.

The authors provided examples of peripheral nervous system complications associated with SC2 infection, rather than an exhaustive list, as this is not a review article.

Acute respiratory distress associated with SC2 typically shows infiltrate of the lungs however, the 2 patients had normal chest X-rays throughout their intensive care unit stay.[4] It is unlikely that their respiratory distress was due to SC2 infection, but rather neuromuscular weakness from GBS. GBS is rarely caused by adenovirus and the association with SC2 is stronger. Therefore, it's probable that the patients' GBS was associated with SC2.[5]

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References

1. Al Amrani F, Al-Abdwani R, Al Rashdi F, Al-Ajmi E, Al Futaisi A. Guillain-Barré Syndrome Associated with SARS-CoV-2 in Two Pediatric Patients. Sultan Qaboos Univ Med J 2023; 23:400–4. https://doi.org/10.18295/squmj.5.2022.040.
2. Sancho-Saldaña A, Lambea-Gil Á, Liesa JLC, Caballo MRB, Garay MH, Celada DR, et al. Guillain-Barré syndrome associated with leptomeningeal enhancement following SARS-CoV-2 infection. Clin Med (Lond) 2020; 20:e93–4. https://doi.org/10.7861/clinmed.2020-0213.
3. Güner R, Hasanoğlu I, Aktaş F. COVID-19: Prevention and control measures in community. Turk J Med Sci 2020; 50:571–7. https://doi.org/10.3906/sag-2004-146.
4. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology 2020; 296:E32–40. https://doi.org/10.1148/radiol.2020200642.
5. Bentley SA, Ahmad S, Kobeissy FH, Toklu HZ. Concomitant Guillain-Barré Syndrome and COVID-19: A Meta-Analysis of Cases. Medicina (Kaunas) 2022; 58:1835. https://doi.org/10.3390/medicina58121835.