


**CASE REPORT**

# Recombinant protein subunit COVID-19 vaccine-induced Guillain-Barré Syndrome in an adolescent: A case report

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Guillain-Barré Syndrome (GBS), an autoimmune neurological disease of peripheral nerves, has been causally associated with COVID-19 vaccination in adults. However, no such report has been published so far in children. We describe a 13-year-old female child who presented to the emergency department with complaints of bilateral upper limb, lower limb and truncal weakness over 3 days following first dose of recombinant protein subunit COVID-19 vaccine (*Corbevax*). Clinical examination and nerve conduction studies showed pure motor axonal polyneuropathy with absent compound muscle action potential (CMAP) in all sampled nerves of upper and lower limbs which was consistent with the diagnosis of GBS after ruling out possible alternative aetiologies. A temporal association between first dose of protein subunit COVID-19 vaccine administered a day prior and symptom onset was noted. The causality assessment using the World Health Organization (WHO) tool for adverse event following immunization (AEFI) assessment indicated vaccine product-related reaction categorized as A1. The patient's clinical condition improved after seven sessions of plasmapheresis. The purpose of this report is to create awareness among health care professionals about COVID-19 vaccine-induced GBS in children as early diagnosis and management can be critical in avoiding complications and improving patient outcomes.

**KEYWORDS**

acute flaccid paralysis, acute inflammatory demyelinating polyneuropathy (AIDP), adolescent, *Corbevax*, Guillain-Barré Syndrome (GBS), protein subunit COVID-19 vaccine

## 1 | INTRODUCTION

The COVID-19 pandemic has severely impacted not only health services but also the economy in both the developed as well as the developing world.<sup>1</sup> COVID-19 vaccination has emerged as a necessary measure to alleviate the burden of the disease and to enable relaxation of COVID-19 lockdown measures, allowing resumption of normal everyday life and economic activities. Since the vaccine rollout, more than five billion people worldwide, including elderly and those with comorbid conditions including diabetes, hypertension, heart diseases,

autoimmune diseases, cancer patients, among others, have received COVID-19 vaccines, with ~2 billion doses administered in India as of 23 May 2022.<sup>2</sup> Despite reported high efficacy and satisfactory safety of COVID-19 vaccines in clinical trials, there is a possibility of rare side effects going undetected in the clinical trials given their inherent limitations. GBS, or acute inflammatory demyelinating polyneuropathy (AIDP), is a neurological autoimmune condition that has been reported as a rare adverse event following COVID-19 vaccination in adults.<sup>3-7</sup> On 22 July 2021, the European Medicines Agency (EMA) issued a statement that GBS should be listed as a very rare adverse effect of adenovirus COVID-19 vaccine and that a warning should be included in the vaccine information to raise awareness among concerned

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health care professionals and individuals receiving the recombinant adenovirus COVID-19 vaccine.<sup>8</sup> Subsequently, the Global Advisory Committee on Vaccine Safety (GACVS) COVID-19 subcommittee recommended that health care professionals and individuals receiving COVID-19 vaccines from Janssen or AstraZeneca should be alerted and if clinical signs and symptoms suggestive of GBS develop, they should seek immediate medical care.<sup>9</sup>

Corbevax is a recombinant protein subunit vaccine, developed by Biological E. Ltd by using a protein antigen (spike receptor-binding domain) adjuvanted with dynavax CpG 1018 and alum. The advantage over the recombinant mRNA vaccines is that it is relatively inexpensive and can be produced on a much larger scale in a shorter timespan. Another advantage is that the vaccine can be stored in a regular refrigerator for storage and distribution to even remote places.

The most common adverse effects of COVID-19 vaccines are injection site pain, tenderness, nausea, fever and chills, malaise, fatigue, headache, myalgia and arthralgia. The rare adverse events include anaphylaxis, rash, abdominal pain and back pain.<sup>10</sup> Recently, there had been growing concerns regarding very rare but life-threatening adverse events like vaccine-induced thrombotic thrombocytopenia (TTP), thromboembolic events and GBS following adenovirus-based COVID-19 vaccines (Oxford/AstraZeneca, Pfizer and BioNTech, Johnson & Johnson adenovirus vaccines). Recent analysis of data by the Centers for Disease Control and Prevention (CDC) from the Vaccine Safety Datalink found the rate of occurrence of GBS within the first 3 weeks of receiving COVID-19 vaccination to be 21 times higher with Johnson & Johnson vaccine when compared to Pfizer-BioNTech or Moderna mRNA vaccines.<sup>11</sup> To the best of our knowledge, no such incident has been reported so far in children with recombinant subunit COVID-19 vaccines. We herein present a case report of a recombinant protein subunit COVID-19 vaccine, Corbevax, which induced GBS in a 13-year-old adolescent child.

## 2 | CASE PRESENTATION

A 13-year-old female presented to the emergency department of a tertiary care academic centre in north India with 4 days' history of bilateral upper limb and lower limb weakness following the first dose of recombinant protein subunit COVID-19 vaccination (Corbevax, BECOV2D). The child was apparently well prior to vaccination. On the evening of the day of vaccination, the patient began complaining of a tingling sensation followed by weakness in her bilateral upper limb in the form of difficulty breaking *chapatti* (bread) and holding a glass of water. The following day, she started experiencing bilateral lower limb distal weakness presenting as difficulty in wearing footwear, which progressed rapidly to bilateral proximal lower limb weakness in the form of difficulty walking by herself and frequent falls while attempting to walk. The weakness gradually progressed to involve the trunk by the third day post vaccination with inability to turn over in bed. However, there was no sensory loss or bowel/bladder involvement. She did not complain of shortness of breath, diplopia, dysphagia or nasal regurgitation of food. The episode was not associated with

### What is already known about this subject

- COVID-19 vaccines have been reported to rarely cause GBS in adults.
- The WHO Global Advisory Committee on Vaccine Safety (GACVS) COVID-19 subcommittee, after reviewing US Food and Drug Administration (FDA) and European Medicines Agency (EMA) data on GBS induced by COVID-19 vaccines, warned health care professionals and individuals receiving adenoviral vector COVID-19 vaccine to be alert to clinical signs and symptoms of GBS and seek immediate medical advice in case of weakness, tingling or paralysis in the extremities occurring post-COVID-19 vaccination.

### What this study adds

- Through this case report the authors wish to highlight that GBS can be induced by COVID-19 vaccination not only in adults but also in the paediatric age group, which could be life threatening if not managed early.
- To the best of our knowledge, no case reports of recombinant protein subunit COVID-19 vaccine-induced GBS has been reported so far in adults or in children.

fever, cough, chest pain, rash, joint pain, headache, vomiting, seizures, neck stiffness or loose stools. There was no history of any preceding respiratory illness or gastrointestinal infection or intake of any medicine.

On clinical examination at admission, her vital signs were normal with a pulse rate of 100/min, blood pressure of 120/76 mm Hg, respiratory rate of 18/min, SpO<sub>2</sub> 98% on room air, and she was afebrile. Higher mental functions were normal measuring 15/15 on the Glasgow Coma Scale (GCS). The patient was alert, conscious, cooperative and oriented to time, place and person. There were no signs of meningeal irritation. Cranial nerve examination was normal. Single breath count and breath holding time was significantly reduced, but gag reflex and cough reflex was intact. Bilateral upper limb and lower limb power was 1/5 with reduced tone, absent superficial as well as deep tendon reflexes and truncal weakness. Sensory examination for touch, pain, vibration and proprioception was normal in all the four extremities.

Laboratory investigations on admission showed haemoglobin 13.1 g/dl, total leucocyte count of 14.1 \* 10<sup>9</sup>/L with normal differentials and platelet count 402 \* 10<sup>9</sup>/L. The renal, hepatic function tests, serum electrolytes and coagulation profile were normal. Cerebrospinal fluid biochemistry was normal and Gram stain, culture, acid-fast bacillus (AFB), India Ink staining was negative. Urine for porphobilinogen was negative. HbsAg, HIV and HCV screening tests were negative.

**TABLE 1** Nerve conduction study (NCS) test report

Panel A: Sensory NCS							
Nerve/sites	Rec. site	Onset Lat (ms)	NP amp ( $\mu$ V)	Segments	Distance (mm)	Velocity (m/s)	
<b>R Median - digit II (antidromic)</b>							
Wrist	Digit II	1.98	36.9	Wrist–digit II	120	61	
<b>L Median - digit II (antidromic)</b>							
Wrist	Digit II	1.98	35	Wrist–digit II	120	61	
<b>R Ulnar - digit V (antidromic)</b>							
Wrist	Digit V	1.82	35.1	Wrist–digit V	100	55	
<b>L Ulnar - digit V (antidromic)</b>							
Wrist	Digit V	1.82	26.1	Wrist–digit V	100	55	
<b>R Sural - ankle (calf)</b>							
Calf	Ankle	2.5	16.8	Calf–ankle	120	48	
<b>L Sural - ankle (calf)</b>							
Calf	Ankle	1.67	13.9	Calf–ankle	120	72	
Panel B: Motor NCS							
Nerve/sites	Muscle	Latency (ms)	Amplitude (mV)	Amp (%)	Duration (ms)	Segments	Lat diff (ms)
<b>R Median - APB</b>							
Wrist	APB	NR	NR	NR	NR	APB - wrist	
Elbow	APB	NR	NR	NR	NR	Wrist - elbow	NR
<b>L Median - APB</b>							
Wrist	APB	NR	NR	NR	NR	APB - wrist	
Elbow	APB	NR	NR	NR	NR	Wrist - elbow	NR
<b>R Ulnar - ADM</b>							
Wrist	ADM	NR	NR	NR	NR	Wrist - ADM	
Elbow I	ADM	NR	NR	NR	NR	Elbow - wrist	NR
<b>L Ulnar - ADM</b>							
Wrist	ADM	NR	NR	NR	NR	Wrist - ADM	
Elbow	ADM	NR	NR	NR	NR	Elbow - wrist	NR
<b>R Peroneal - EDB</b>							
Ankle	EDB	NR	NR	NR	NR	Ankle - EDB	
Fib head	EDB	NR	NR	NR	NR	Fip Head - ankle	NR
<b>L Peroneal - EDB</b>							
Ankle	EDB	NR	NR	NR	NR	Ankle - EDB	
Fib head	EDB	NR	NR	NR	NR	Fip Head - ankle	NR
<b>R Tibial - AH</b>							
Ankle	AH	NR	NR	NR	NR	Ankle - AH	
Pop fossa	AH	NR	NR	NR	NR	Pop fossa - ankle	NR
<b>L Tibial - AH</b>							
Ankle	AH	NR	NR	NR	NR	Ankle - AH	
Pop fossa	AH	NR	NR	NR	NR	Pop fossa - ankle	NR

Abbreviations: ABP, Abductor pollicis brevis; ADM, Abductor digiti minimi; AH, Abductor hallucis; EDB, Extensor digitorum brevis; NCS, Nerve conduction study; NP amp, Nerve potential amplitude.

Autoimmune workup including complement levels, antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA) were within normal limits. No evidence of myopathy or myositis was noted with creatine kinase (CK-Nac) being normal. Nerve conduction tests

were suggestive of pure motor axonal polyneuropathy with absent compound muscle action potential (CMAP) in all sampled nerves of both upper and lower limbs (Table 1). Contrast enhanced magnetic resonance imaging (CE-MRI) of the spine was performed to rule out

possible transverse myelitis and was grossly normal. Based on these clinical findings and diagnostic results, the patient was fitting into level 1 diagnostic certainty of GBS as per the Brighton criteria and was started on plasmapheresis therapy.

## 2.1 | Progress

After 14 days of therapy and seven sessions of plasmapheresis, the patient improved clinically with power of 4/5 in bilateral upper limbs and 3/5 in bilateral lower limbs at the time of discharge. Single breath count and breath holding time had also improved significantly. The patient was advised to continue physiotherapy and rehabilitation.

## 3 | DISCUSSION

The World Health Organization (WHO) causality assessment of an AEFI tool was applied to evaluate causal relationship.<sup>12</sup> There was a positive temporal association between onset of symptoms and vaccine administration. There was no other strong evidence of either any drug or infection being related to the event. Also, there is evidence of GBS post COVID-19 vaccination in published literature. Therefore, as per the causality assessment criteria, the adverse event can be adjudicated as a vaccine product-related reaction (categorized as A1) (Figure S1 in the Supporting Information).

Guillain-Barré Syndrome, an autoimmune condition that affects the peripheral nerves and nerve roots, is triggered by certain infections like *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, hepatitis E virus and *Mycoplasma pneumoniae*.<sup>13</sup> Vaccines are very rarely implicated in the occurrence of GBS. Vaccines reported to cause GBS include influenza, tetanus toxoid, rabies, BCG, mumps rubella (MMR), oral poliovirus, hepatitis B and diphtheria vaccine.<sup>14</sup> According to the International Guillain Barré Syndrome Outcome study, around 76% of GBS patients have history of a triggering event preceding onset of weakness within 4 weeks, and this is either infection or vaccination.<sup>15</sup> However, post-vaccination GBS has a shorter time interval, with over half of the studied population having symptom onset within 2 days of vaccination. This shorter interval was more pronounced in the younger population (<20 years of age) where the median time to symptom onset post vaccination was 1 day (IQR 1–3 days) as compared to those over 20 years of age, where the median time to symptom onset was 10 days (IQR 3–15 days).<sup>16</sup> Waheed et al. were the first to report a case of post COVID vaccination GBS after the first dose of the Pfizer-BioNTech COVID-19 vaccine in 2021.<sup>17</sup> Several case reports have been published in the past year showing a possible link between GBS and adenoviral COVID-19 vaccines.<sup>3–7</sup> In the cohort study of surveillance data from the Vaccine Safety Data-link, which included data on 15.1 million doses of COVID-19 vaccines from nine United States integrated healthcare systems and the CDC, the occurrence of GBS within 3 weeks of receiving the Janssen adenoviral COVID-19 vaccine was 32.4 per 100 000 person-years, which

was significantly higher than the background incidence of 1–2 per 100 000 person-years in adults. In contrast, the incidence of GBS following mRNA-based vaccines was 1.3 per 100 000 person-years. In the adjusted head-to-head evaluation, incidence of GBS after the adenoviral vector vaccines was 20.6 times higher than after mRNA vaccines within 21 days' post vaccination.<sup>18</sup> Although the exact mechanism of post-COVID-19 vaccination GBS is not known, it has been hypothesized that, by inducing immunization against SARS-CoV-2 spike proteins, COVID-19 vaccines can lead to antibody cross-reaction. These antibodies directed against viral spike protein can bind to sialic acid containing glycoproteins and gangliosides on the cell surfaces of nerves causing an acute immune-mediated disease of peripheral nerves, resulting in demyelination or axonal degradation.<sup>19</sup>

Corbevax is currently licensed patent free by the Serum Institute of India to Biological E. Ltd, so that low- to middle-income countries can produce and distribute the vaccine locally, thus addressing vaccine inequity. The vaccine has been found to be safe in the Phase II/III trial (BECT069) conducted in 1268 subjects aged 18–80 years with the majority of adverse effects being of mild–moderate intensity and no severe adverse events. The common adverse events seen were injection site pain, fatigue, pyrexia, chills, headache, myalgia and arthralgia. The rare adverse events seen were lethargy, back pain, pharyngitis, decreased appetite and urticaria. A similar safety profile was seen in the Phase II/III study (BECT072) conducted in 624 subjects aged ≥5 to <18 years.<sup>10</sup> No serious adverse events were reported in these studies.

## 4 | CONCLUSION

Through this case report, the authors wish to highlight that GBS can possibly occur with receptor binding domain (RBD) protein subunit COVID-19 vaccine (Corbevax) in children and could be life-threatening in the absence of immediate management measures. While the benefits of COVID-19 vaccination substantially outweigh the risk of GBS, health care professionals should be vigilant to this possible adverse event, as early recognition and management is crucial to avoid possible adverse clinical consequences.

### ACKNOWLEDGEMENTS

No specific grant or funding was taken from any funding agencies.

### COMPETING INTERESTS

None.

### CONTRIBUTORS

A.K.K. and R.M. conceptualized the study. R.R. was responsible for the consent documentation and the data curation, and A.K.K. was responsible for project administration. R.R., A.K.K. and R.M. came up with the methodology. R.R. and D.K. carried out the investigations, and D.K., R.M. and V.S. looked after patient management. The study was supervised by R.M. and V.S. The original draft of the manuscript

was written by R.R. and A.K.K. All author reviewed and edited the manuscript for intellectual content

## DATA AVAILABILITY STATEMENT

Research data are not shared.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Rohilla R, Kakkar AK, Divyashree K, Mohindra R, Suri V. Recombinant protein subunit COVID-19 vaccine-induced Guillain-Barré Syndrome in an adolescent: A case report. *Br J Clin Pharmacol.* 2022;1-5. doi:10.1111/bcp.15466