Post COVID-19 Vaccination GBS—Association or Causation?

Sir,

The Coronavirus Disease - 2019 (COVID-19)pandemic is more than a year old, and yet, we have more questions than answers as of today. Neurotropism of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)virus has been amply reported.[1] Post-vaccinal Guillain-Barré syndrome (GBS) has been previously reported following the administration of influenza and H1N1 vaccines.[2,3] The debate on whether GBS is triggered or is association with these vaccines has been raging for more than four decades. We, herein, report two cases of GBS temporally associated with the administration of COVID-19 vaccination.

A healthy 22-year-old male (case 1) presented with 4 days history of acute onset difficulty in walking. The weakness in both the legs was progressive and he required one person's support to ambulate at admission (Hughes grade 3). There was no difficulty in the overhead abduction but he noticed a mild grip weakness in the right hand. He had no history suggestive

of facial, bulbar weakness, or dysautonomia. He had received his first dose of the Covishield vaccine 2 weeks before the symptom onset. The patient did not recollect any recent upper respiratory tract or gastrointestinal illness. On examination, he had sensorimotor weakness in both the lower limbs (power Medical Research Council (MRC) 2/5 in both the lower limbs proximally and 3/5 distally, impaired joint position at toes) and a mild grip weakness of the right hand without facial or bulbar involvement. There was areflexia in both the lower limbs (absent knee and ankle jerk bilaterally) with diminished right biceps and triceps reflex. The COVID-19 Reverse Transcriptase - Polymerase Chain Reaction (RT-PCR) was negative. The routine hematological and biochemical parameters were normal. The cerebrospinal fluid (CSF) analysis performed on day 5 showed albumino-cytological dissociation (cells <5/cu.mm, protein: 59 mg/dL, sugar: 50 mg/dL, chloride: 118 mEq/L). The CSF viral panel was negative and the culture was sterile. The nerve conduction studies (NCS) showed increased distal motor latencies with reduced compound muscle action potential of both peroneal nerves and right ulnar nerve, absent F waves, and prolonged onset latency with reduced sensory nerve action potential (SNAP) amplitude of the right ulnar nerve [Table 1]. He was treated with intravenous immunoglobulin (400 mg/kg daily for 5 days). A brisk recovery was noted with improvement to Hughes grade 2. He was uneventfully discharged.

A 75-year-old female (case 2), hypertensive, obese with coronary artery disease presented with 3 days history of backache followed by weakness of both the lower limbs. Her symptoms began 3 days after receiving the first dose of the Covishield vaccine. On examination, she had pure motor areflexic lower motor neuron (LMN) quadriparesis without facial, bulbar, or bowel and bladder involvement (Hughes grade 4). The MRC power was 2/5 in both the lower limbs and 3/5 in both the upper limbs. The COVID-19 RT-PCR was negative. She had unremarkable baseline hematological and biochemical parameters, including viral serology (Hepatitis-B, Hepatitis-C, and HIV) except for hyponatremia (Na^+: 132 mEq/L). The CSF analysis done on day 7 after the symptom onset showed albumino-cytological dissociation (cells <5/cu.mm, protein: 177 mg/dL, sugar: 60 mg/dL, chloride: 112 mEq/L). CSF COVID-19 PCR and CSF viral panel were negative (Japanese encephalitis antibody, herpes simple × 1 and 2 antibodies, cytomegalovirus antibody). The stool routine microscopy was normal and the culture showed no growth. The neurophysiology showed reduced compound muscle action potential (CMAP) with absent F waves of both tibial, left peroneal, and right ulnar nerve and conduction block in the left tibial nerve [Table 1]. She was treated with intravenous immunoglobulin (400 mg/kg daily for 5 days) and hyponatremia was corrected. The improvement in the lower limb power was noticed and the sodium normalized. On day 7 of admission, she developed sudden bradycardia and asystole, consequent to dysautonomia of GBS versus arrhythmia triggered by an underlying cardiac disease. She was revived with cardiopulmonary resuscitation and mechanical ventilation. Subsequently, she developed acute respiratory distress syndrome and succumbed.

GBS is an acute immune-mediated peripheral nervous system inflammatory disease. The strongest reports of a causal association between GBS and immunization emerged after the use of the swine influenza vaccine in 1976–1977.[2] In contrast, the meta-analysis and recent studies ascribe only a small risk of GBS post-immunization (one to two cases per one million vaccinated individuals).[2,3] Grave and Stowe *et al*.[4,5] in two separate studies published in 2020 refuted an increased risk of GBS following influenza vaccination and stated the risk of developing GBS following natural influenza infection to be higher than post-immunization GBS.

Currently, two vaccines against COVID-19 are in mass rollout in India, one is the Covaxin containing killed coronavirus and the other is the Covishield ChAdOx1 vaccine containing recombinant replication-deficient chimpanzee adenovirus encoding SARS-CoV-2 spike glycoprotein.

Brighton criteria have been previously used for diagnosing post-immunization GBS.[6] Both patients met the criteria comprising of the presence of bilateral flaccid paralysis with reduced deep tendon reflexes of the involved limbs, monophasic symptom progression, albumino-cytological dissociation in CSF, electrophysiology consistent with GBS, and the absence of other probable causes.[7] In April 2021, Patel *et al*.[8] from the UK reported a single case of GBS following the ChAdOx1 vaccine. Further, the United Kingdom

Table 1: Neurophysiological parameters of the affected nerves

	Nerve	Distal latency (ms)	Velocity (m/s)	Distal Amplitude (mV)	F wave (ms)
Case 1					
Right	Peroneal	9.38	45.96	1.3	Absent
Left	Peroneal	11.98	42.80	1.2	Absent
Right	Ulnar: Motor	5.00	60.12	3.0	Absent
	Sensory	3.90	47.27	9.4	
Case 2					
Right	Ulnar	2.60	58.82	2.3	Absent
Left	Peroneal	3.44	45.40	2.0	Absent
Right	Tibial	4.79	42.64	1.6	Absent
Left	Tibial	4.90	43.15	1.6 with conduction block	Absent

Medicines and Healthcare Products Regulatory Agency (UK MHRA) stated that 6 patients out of the 42,917 immunized with the ChAdOx1 vaccine developed GBS.[9]

In case 1, the symptoms of GBS appeared 2 weeks after vaccination, suggesting a molecular mimicry between self and coronavirus antigen mediating an immune attack on the peripheral nerves, similar to the established model in GBS with other pathogens.[10] However, post-vaccination GBS has been reported as early as 2 days after immunization.[6] The mechanisms of post-vaccination GBS are, therefore, likely to be heterogeneous and further data may help in better understanding.[6] A follow-up NCS was not done by us. An electrophysiological follow-up would have helped in delineating the subtype of GBS, especially in detecting the reversible conduction failure.[6]

One-third of the patients with GBS present without a preceding gastrointestinal or respiratory infection in the previous 4 weeks before the symptom onset.[9] The possibility of GBS occurring in both our cases following an asymptomatic infection cannot be completely excluded, and hence, a chance association with vaccination is possible. However, previous reports of GBS post-vaccination and the absence of any evidence of infection or systemic inflammation (ESR 8 and 21 mm/h and C- Reactive protein (CRP) <6 mg/L in both patients) lend weight to a likely vaccine-induced trigger for GBS in both patients.[2,3,6]

Undoubtedly, the benefits of vaccination outweigh the risk. Nevertheless, close surveillance and awareness of all the potential adverse effects of any vaccination are warranted.

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Conflicts of interest

There are no conflicts of interest.

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