

Guillain-Barré Syndrome in the Placebo and Active Arms of a COVID-19 Vaccine Clinical Trial

Temporal Associations Do Not Imply Causality

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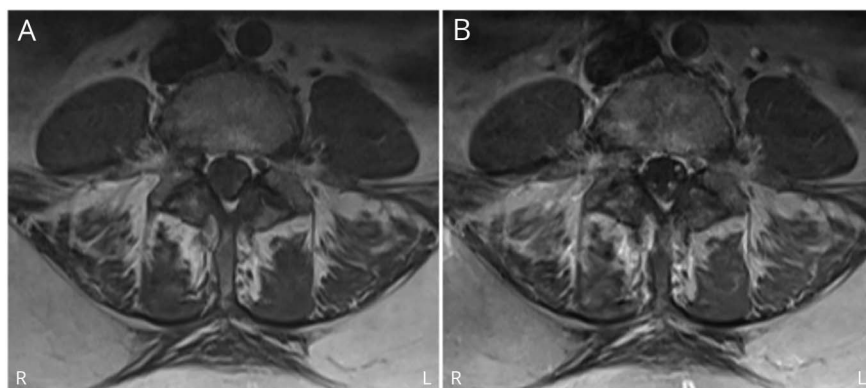
There are reports of Guillain-Barré syndrome (GBS) and cranial neuropathies occurring during or shortly after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.^{1,2} Some recent infections are known to trigger GBS. A recent epidemiologic cohort study found no evidence for causality between coronavirus disease 2019 (COVID-19) and GBS.³ There is a modest risk of GBS attributed to any vaccination (about 1 to 3 additional cases per million people vaccinated for seasonal influenza),⁴ and this has raised the possibility that the worldwide COVID-19 vaccination campaign may lead to some people developing GBS.⁵ Documents submitted to the Food and Drug Administration for Emergency Use Authorization of the Johnson & Johnson COVID-19 vaccine, d26.COV2.S, a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike protein, however, include reports of 2 patients, 1 in the placebo and 1 in the active arm of the trial, developing GBS within 2 weeks of receiving an injection.^{6,7} Here we report the clinical features of the participant who received the vaccine (5×10^{10} viral particles) at the intended dose for clinical practice and discuss why this case cannot be used to establish a causal association between vaccination and the onset of GBS.

Case Report

A 60-year-old woman with a history of migraines was in her usual state of health when she enrolled in the vaccine trial. Reverse transcriptase polymerase chain reaction (RT-PCR) assay for SARS-CoV-2 and antibody testing were negative at screening prior to vaccination. She received the vaccine on December 10, 2020. She remained well without any respiratory or gastrointestinal symptoms until 10 days after vaccination, when she started experiencing pain in her back and legs. She was seen for a study visit 4 days after symptom onset (December 24, 2020) and at that time the PCR assay for SARS-CoV-2 was negative. The next day, she awoke with a headache, nausea, vomiting, and diplopia, and she went to the hospital. The neurologic examination was normal, but she was treated for migraine overnight. The headache and diplopia persisted after discharge and on December 27, 2020, she was readmitted to the hospital, this time in the neurology service. Examination that day showed left eye esotropia on midline gaze and bilateral ocular abduction deficits but the strength, sensation, and reflexes in her limbs were normal. By the next day, her symptoms had progressed to bilateral facial weakness as well as numbness, areflexia, and 2/5 weakness of both legs. MRI of the lumbar spine demonstrated enhancement of the cauda equina (figure). Brain MRI was normal. Lumbar puncture revealed an increased opening pressure (29 cm H₂O) and the CSF had elevated protein (140 mg/dL), 9 nucleated cells, and normal

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Axial cuts T1 precontrast (A) and postcontrast (B) show cauda equina enhancement.

glucose (63 mg/dL). Electrophysiologic studies done 2 days after admission showed normal compound muscle and sensory nerve action potentials and absent late responses (peroneal and posterior tibialis F-waves and H-reflexes) in the legs. Needle EMG showed neurogenic recruitment (fast firing units) in leg muscles. These findings are the earliest electrophysiologic abnormalities seen in GBS. Anti-ganglioside antibodies were negative. RT-PCR for SARS-CoV-2 was repeated twice during admission and resulted negative. She was treated with IV immunoglobulin 2 g/kg over 2 days starting on December 29, 2020. Her strength slowly improved and she was discharged to rehabilitation 10 days after admission.

Discussion

Two patients in the Johnson & Johnson COVID-19 vaccine trial developed GBS 10 days after injection: 1 was in the placebo arm and 1 was in the active vaccine arm. The incidence of GBS was identical in both arms of the trial. Our patient in the vaccine arm did not have any clinical features differentiating her from patients with typical GBS. From the available evidence, it is not possible to draw causal inferences about the association of COVID-19 vaccination and the development of GBS. To avoid misattributing adverse events to the COVID-19 vaccine, and to clarify whether the risk of GBS is equal to or higher than the baseline rate in the population, or to the attributable risk reported for other vaccines such as the seasonal influenza A vaccine, large-scale epidemiologic studies and meta-analyses of data from several adverse event monitoring systems are needed, as was the case with prior pandemics and large-scale vaccination studies (e.g., for H1N1).⁴ In the setting of global vaccination efforts, it is impossible to conclude that any particular case is related to the vaccine. A large meta-analysis revealed the annual crude incidence of GBS among adults is about 8–19 per million⁸; we expect that among 1 billion people, around 8,000–19,000 will develop GBS each year. This means that as we advance toward the goal of vaccinating 1 billion people

against COVID-19 (and hopefully the number will be much higher), many people will develop GBS by coincidence within a few weeks of vaccination.⁹ By chance alone, we would expect to see 900–2,200 people develop GBS within 6 weeks of receiving a 1-dose vaccine (e.g., Johnson & Johnson) or 1,500–3,700 within a 10-week period from a 2-dose vaccination approach (e.g., Pfizer and Moderna). We must be careful to avoid misattributing adverse events to the vaccination program.⁹ Temporal associations do not imply causality. The fact that 1 other participant in the Johnson & Johnson vaccine trial also developed GBS 10 days after being injected with placebo supports the argument for a coincidental rather than a causal association. Neurologists must educate and reassure their patients, the public, and policy makers regarding the safety and rationale of COVID-19 vaccinations as more reports of GBS and other autoimmune diseases will likely emerge. Based on experience with other vaccination initiatives and the data in the adverse monitoring systems of the COVID-19 vaccines gathered so far, the benefits of vaccination outweigh the risks of COVID-19 infection and associated morbidity and mortality. We advise our patients with prior GBS that there is no contraindication to receiving any COVID-19 vaccination and that they should get vaccinated as soon as they can.

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Disclosure

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