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Guillain–Barré Syndrome Variant Occurring after SARS-CoV-2 Vaccination

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Although SARS-CoV-2 vaccines are very safe, we report 4 cases of the bifacial weakness with paresthesias variant of Guillain–Barré syndrome (GBS) occurring within 3 weeks of vaccination with the Oxford–AstraZeneca SARS-CoV-2 vaccine. This rare neurological syndrome has previously been reported in association with SARS-CoV-2 infection itself. Our cases were given either intravenous immunoglobulin, oral steroids, or no treatment. We suggest vigilance for cases of bifacial weakness with paresthesias variant GBS following vaccination for SARS-CoV-2 and that postvaccination surveillance programs ensure robust data capture of this outcome, to assess for causality.

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The United Kingdom commenced a mass public immunization program against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2020. Cerebral venous sinus thrombosis with thrombocytopenia has been reported as a serious adverse effect after the AstraZeneca vaccine (AZV).[1]

Guillain–Barré syndrome (GBS) is an acute monophasic immune-mediated polyradiculoneuropathy that typically presents following an antecedent infective illness. The bifacial weakness with paresthesias variant of GBS is rare in general neurological practice and is characterized by facial diplegia being the only motor manifestation.[2,3] This syndrome has been described with SARS-CoV-2 infection.[4–7] Affected individuals report distal sensory symptoms, then facial diplegia, which is typically complete, and reaches a nadir after 48 hours. Deep tendon reflexes are normal, and it is rare for patients to have either objective sensorimotor signs in the limbs or involvement of other cranial nerves.[8] Where tested, SARS-CoV-2 has not been detected in the cerebrospinal fluid (CSF) of patients with GBS associated with the virus.[9]

We report 4 cases of bifacial weakness with paresthesias variant GBS occurring after administration of the first dose of AZV, all cases having presented within 10 days of each other. Symptom onset occurred 11 to 22 days postvaccination. As a postvaccination phenomenon, it has rarely been described in the literature.[10] The cases were reported to the Medicines and Healthcare products Regulatory Agency; all patients provided written consent for publication of their case histories, and collection of associated data was approved by Nottingham University Hospitals National Health Service Trust (audit number 20-158C).

All patients presented with profound bifacial weakness (facial diplegia) and normal facial sensation. Unless stated, the remainder of their neurological examination was normal. Deep tendon reflexes were normal, and there were no objective sensorimotor signs in the limbs. Cerebellar, bulbar, and respiratory function were normal, as were extraocular movements. No evidence of dysautonomia was observed during their inpatient stays. General examination was unremarkable.

They all tested negative for SARS-CoV-2 by reverse transcription polymerase chain reaction (PCR) of nasopharyngeal swabs. Routine blood tests were normal. There was normal CSF:serum glucose ratio, negative CSF microscopy and culture, and negative viral PCR for herpes simplex virus, varicella-zoster virus, enterovirus, parechovirus, and adenovirus. Serology for Epstein–Barr virus; cytomegalovirus; campylobacter; hepatitis A, B, C, and E; and *Mycoplasma pneumoniae* were negative for acute infection. Lyme, human immunodeficiency virus, and syphilis serology were negative, serum angiotensin-

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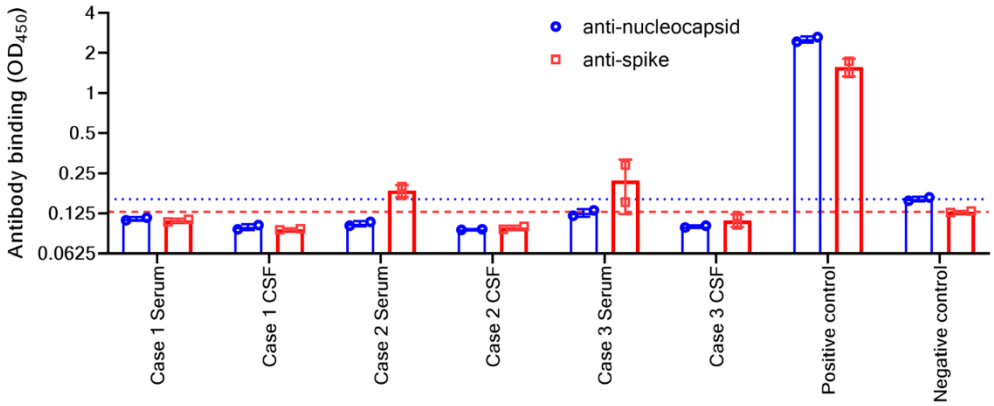

FIGURE: Serology results showing evolving vaccine response in Cases 2 and 3. Neither shows previous SARS-CoV-2 infection. CSF = cerebrospinal fluid. [Color figure can be viewed at www.annalsofneurology.org]

converting enzyme was normal, and chest radiographs showed no evidence of sarcoidosis or SARS-CoV-2 infection. Ganglioside antibodies GM1, GD1a, GD1b, GQ1b, and GM2 were negative.

Case 1

A 54-year-old Caucasian male with no relevant past medical history was taking no regular medications. Four days before presentation, he noted distal dysesthesia in his feet and hands, which ascended over 2 days, but had begun to recede as facial weakness developed. He had received his first dose of the AZV 16 days prior to presentation.

CSF analysis revealed mild lymphocytosis (19 cells/microlitre, normal range ≤ 5) and elevated protein (1,626mg/l, normal range = 150–450). Contrast enhanced magnetic resonance imaging (MRI) of the brain demonstrated subtle enhancement bilaterally in the distal facial nerves at the internal auditory canal. There was symmetric enhancement of the labyrinthine, tympanic, and descending portions of the facial nerves. This was considered within the normal limits of contrast enhanced MRI by the reporting neuroradiologist.

He was commenced on oral prednisolone 60mg for 5 days. There was no progression of his neurological symptoms. Electrophysiological assessment was performed 16 days after presentation. Facial nerve conduction studies (NCS) showed severely reduced compound muscle action potential amplitude responses (0.6–1.7mV) and normal terminal latencies bilaterally (2.92–3.85 milliseconds). The right orbicularis oris and oculi showed active denervation with no volitional motor activity. The left orbicularis oris and oculi showed active denervation with occasional fast firing, long duration polyphasic units, and severely reduced recruitment. Sensory and motor NCS were normal in the upper and lower limbs.

Case 2

A 20-year-old male of British Iranian origin with a past medical history of ulcerative colitis since 2018 completed a course of prednisolone in February 2021, and was maintained on mesalamine 1.5g twice daily. Five days before presentation he complained of an occipital headache without photophobia or neck stiffness. One day later, he developed dysesthesia in his distal lower limbs, and 3 days before admission he developed facial diplegia, which reached its nadir over <24 hours. He had received his first dose of the AZV 26 days prior to presentation.

On examination, passive movement of the neck was uncomfortable but without nuchal rigidity. Non-contrast MRI of the brain was normal. CSF analysis revealed mild lymphocytosis (14 cells/microlitre) and elevated protein (1,232mg/l).

He was started on oral prednisolone 60mg for 5 days. There was no progression of his neurological symptoms. Electrophysiological assessment was performed 13 days after presentation. Facial NCS showed borderline normal amplitude responses (3.2–3.3mV) and normal terminal latencies bilaterally (2.71–3.65 milliseconds). Bilaterally, orbicularis oculi and oris showed active denervation in addition to early recruited fast firing polyphasic units of small duration and low amplitude. Sensory and motor NCS were normal in the upper and lower limbs. Minimum F-wave latencies were 28 milliseconds in the right ulnar nerve and 49 to 50 milliseconds in the tibial nerves.

Case 3

A 57-year-old Caucasian male had a past medical history of asthma and osteoarthritis requiring bilateral knee replacements. His regular medications were steroid and salbutamol inhalers, loratadine, omeprazole, and tamsulosin. Ten days before presentation, he noted a dull lumbar back pain that radiated into his flanks. Four days

later he noticed dysarthria and facial weakness. The facial weakness reached a nadir within 48 hours. He also noted distal dysesthesia in his feet and proximal leg weakness that continued to progress until admission. He reported a fall 2 days before presentation. He had received his first dose of the AZV 21 days prior to presentation.

On examination, there was subjective diplopia on extreme left gaze, but a full range of extraocular eye movements. There was symmetric weakness proximally in the legs (4/5 on Medical Research Council [MRC] scale). Deep tendon reflexes were absent at the knees but normal elsewhere. Noncontrast MRI of the brain was normal. CSF analysis revealed mild lymphocytosis (8 cells/microlitre) and elevated protein (2,471mg/l).

Two days postadmission, his weakness had worsened; MRC scale scores in his legs where 3/5 proximally and 4/5 distally and in his arms 4/5 proximally and 5/5 distally. Intravenous immunoglobulin was commenced. There was no further progression of his neurological symptoms. Electrophysiological assessment was performed 13 days after presentation. Facial NCS and electromyography were not performed. Sensory and motor NCS were normal in the upper and lower limbs. Minimum F-wave latencies were 26 to 33 milliseconds in the median nerves.

Case 4

A 55-year-old Caucasian male with a past medical history of hypertension. His regular medications were amlodipine and lisinopril. Seven days before presentation, he noted bilateral thigh paresthesias. One day later, he reported numbness in the sacral and lumbar regions. Two days prior to admission, he developed facial diplegia, which reached a nadir within 96 hours. He had received his first dose of AZV 29 days prior to presentation.

MRI of the brain and whole spine with contrast showed enhancement of the facial nerve within the right internal auditory canal. CSF analysis revealed normal cell count (4 lymphocytes/μl) and elevated protein (890mg/l).

He did not receive any treatment. There was improvement of his subjective numbness 2 days postadmission. Electrophysiological assessment was not performed.

No Previous Exposure to SARS-CoV-2

None of these patients reported previous infection with SARS-CoV-2. Paired serum and CSF samples were taken at the time of clinical presentation from Cases 1 to 3. They were tested by enzyme-linked immunosorbent assays for the presence of antibodies to SARS-CoV-2 nucleocapsid protein (baculovirus-expressed recombinant SARS-CoV-2 His_6-tagged nucleocapsid; Sino Biological, Beijing, China) and spike protein (recombinant, HEK293-expressed His_6-tagged SARS-CoV-2 Spike S1 [B.1 variant]). All 3 CSF samples were negative, at a dilution of 1 in 10 (Fig).[11] Two of the 3 serum samples (from Cases 2 and 3), were negative for antinucleocapsid but positive for the presence of low-level antispike, at a dilution of 1 in 120, consistent with an evolving immune response to vaccination. Although Case 1 was negative for both antibodies on their admission sample, they had the shortest duration between vaccination and presentation, 16 days. None of Cases 1 to 3 had a previous SARS-CoV-2 infection.

Discussion

Cerebrovascular disorders associated with SARS-CoV-2 are well described, as are postinfectious encephalopathies, transverse myelitis, and acute disseminated encephalomyelitis.[12] Peripheral neurological manifestations, typically GBS and its variants, have also been described, but causality is debated.[13–16] GBS associated with SARS-CoV-2 typically has a median onset of 11 days following initial manifestation of infection.[15] In our cases, there was an interval of 11 to 22 days between vaccination and symptom onset. This would coincide with the period that the maximal immune response to the vaccine would be anticipated.

Although these patients had neurological symptoms temporally associated with vaccination, causality cannot be assumed. It certainly warrants robust postvaccination surveillance, which requires both accurate clinical diagnosis and robust national reporting mechanisms. Surveillance mechanisms linked to the prescription of intravenous immunoglobulin would not have recorded 3 of our cases. We felt secure in the diagnosis, despite the mild CSF pleocytosis in 3 cases, having considered alternative causes for isolated facial diplegia and screened for several common infectious triggers of GBS. Alternative explanations include coincidental idiopathic cases occurring in our large catchment area and all 4 cases having subclinical infections with a known causative pathogen, which was not detected. Over the 4 months prior to our cases presenting, 320,160 first doses of AZV and 187,145 first doses of the Pfizer SARS-CoV-2 vaccine had been administered to a population of 1,018,611 where Cases 1 to 3 lived. In Case 4's region, the figures were 391,890 AZV first doses and 164,643 Pfizer first doses to a total population of 914,648. From the latest epidemiological data, we expect less than 4 GBS cases per month in the total population described.[13] A systematic review of SARS-CoV-2–associated GBS found 3 of 42 cases (7.1%) were bifacial weakness with paresthesias variant, which is higher than previous estimates.[5] The largest case series of this variant

to date showed it was more likely to be associated with upper respiratory tract infections than "typical" GBS.[2]

The development of a postvaccination neurological syndrome, as we describe, could result from the generation of host antibodies that cross-react with proteins present in peripheral myelin. These antibodies may be generated in direct response to the SARS-CoV-2 spike protein, but a less specific immune response, for example, to components of the adenovirus vector, is also plausible. However, the report of a similar syndrome in the setting of SARS-CoV-2 infection suggests an immunologic response to the spike protein. There is evidence that the SARS-CoV-2 spike protein can bind to sialic acid–containing glycoprotein and gangliosides on cell surfaces, increasing its viral transmissibility.[17] Antibody cross-reactivity between the SARS-CoV-2 spike protein and peripheral nerve glycolipids may be involved in the pathogenesis of GBS associated with SARS-CoV-2 infection or immunization. The specific genetic background of the host, the human leukocyte antigen haplotype profile, may also play a role, as it does in SARS-CoV-2–associated GBS and other autoimmune neurological disorders.[18]

In conclusion, we suggest vigilance for cases of bifacial weakness with paresthesias variant GBS following vaccination for SARS-CoV-2 and that postvaccination surveillance programs ensure robust data capture of this outcome, to assess for causality.

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Author Contributions

C.M.A., A.W.T., P.J.T., W.L.I., R.T., and J.R.E. contributed to the conception and design of the study; C.M.A., S.R., A.W.T., P.J.T., and J.R.E. contributed to the acquisition and analysis of data; C.M.A., S.R., A.W.T., P.J.T., R.T., and J.R.E. contributed to drafting the text or preparing the figure.

Potential Conflicts of Interest

Nothing to report.

Data Availability

All data have been shared with the relevant regulatory agency.

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