




## CASE STUDY

# Postvaccinal GABA-B receptor antibody encephalitis after ChAdOx1 nCoV-19 vaccination

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Received: 6 May 2022; Revised: 11 August  
2022; Accepted: 17 August 2022

doi: 10.1002/acn3.51659

## Abstract

Several cases of autoimmune encephalitis have been reported after ChAdOx1 nCoV-19 (AZD1222) vaccination. We encountered a male patient who presented with generalized tonic-clonic seizures, cognitive decline, and gait disturbance that occurred suddenly after the second dose of the ChAdOx1 nCoV-19 vaccine. Clinical presentation and magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) test results were compatible with limbic encephalitis. Synaptic autoantibody tests confirmed serum and CSF GABA B receptor antibodies were present. The patient was treated with immunotherapy with intravenous immunoglobulin and rituximab. This GABA-B receptor antibody encephalitis case occurred presumably due to transient autoantibody production following vaccine administration.

## Introduction

Due to the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), various types of vaccines have been developed and approved. As a result, unprecedented large-scale vaccination occurred worldwide. Although excellent safety data were obtained from clinical trials, unexpected side effects were also reported after vaccination, many of which occurred in the nervous system. Diverse neurological complications including demyelinating diseases, Guillain–Barre syndrome (GBS), seizure, and encephalopathy have been reported to date.<sup>1</sup>

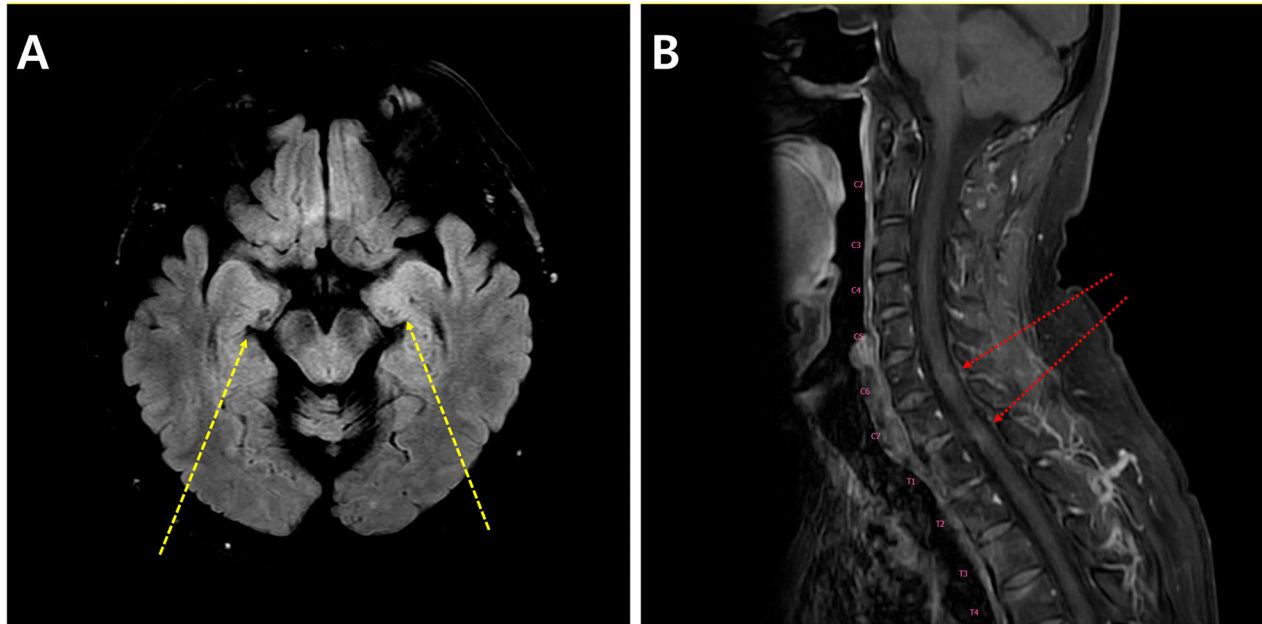
The ChAdOx1 nCoV-19 vaccine (AZD1222) consists of a replication-deficient chimpanzee adenoviral vector, ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene.<sup>2</sup> Similar to other coronavirus disease 2019 (COVID-19) vaccines, various adverse events, including autoimmune encephalitis have been reported after the injection of this vaccine worldwide. Here, we report another case of vaccination-induced autoimmune encephalitis, which was confirmed with the detection of the gamma-aminobutyric acid-B (GABA-B) receptor antibody.

## Case Description

A 53-year-old male patient experienced first-onset generalized tonic-clonic seizures (GTCs). After GTCs, he

developed progressive neurologic symptoms including gait disturbance, dysarthria, and cognitive decline. One week prior to presentation, he received a second dose of the ChAdOx1 nCoV-19 vaccine. He was admitted to our hospital for these symptoms 9 days after vaccination.

In the first neurologic examination, severe attention deficit and memory decline were observed. The initial Mini-Mental State Examination (MMSE) score was 20/30. He showed impairment mainly in calculation and memory areas, and he could not remember the food he had just eaten. Spastic ataxic gait was observed with a hyper-reflexive deep tendon reflex (DTR), a positive Hoffman sign, and ankle clonus. Dysarthria and 10 Hz kinetic tremor in both hands were also found in the exam. The initial Clinical Assessment Scale in Autoimmune Encephalitis (CASE) score<sup>3</sup> was 8, and the modified Rankin scale (mRS) score was 3. Brain magnetic resonance imaging (MRI) showed slightly increased fluid-attenuated inversion recovery (FLAIR) signal intensity in the bilateral hippocampus (Fig. 1A). Whole-spine MRI revealed subtle fuzzy spinal cord enhancement at the C6 and C7/T1 levels (Fig. 1B). Cerebrospinal fluid (CSF) examination revealed lymphocytic pleocytosis of 60 leukocytes/ $\mu$ L (43 lymphocytes and 17 other cells) with elevated opening pressure (26 cmH<sub>2</sub>O). CSF protein was slightly elevated (53 mg/dL). The immunoglobulin G (IgG) index was 0.92, which was higher than the normal value. The CSF was positive for the oligoclonal band with a type 2 pattern. Interictal



**Figure 1.** Magnetic resonance imaging (MRI) scan of the patient. (A) Increased FLAIR signal intensity in the bilateral hippocampus (yellow arrows) on initial brain MRI. (B) Multiple enhanced lesions (red arrows) of the spinal cord (C6, T1 level) in the T1 enhanced image of spine MRI.

brain single-photon emission computed tomography (SPECT) revealed asymmetric hyperperfusion in the right medial temporal cortex and right striatum (Fig. 2A). Acute onset encephalitis was diagnosed on the basis of the clinical manifestations and MRI and CSF findings. For etiological diagnosis, extensive diagnostic workup was conducted (Table 1). Initial 24-hour video-EEG monitoring (VEM) showed no epileptiform discharge. With the suspected diagnosis of viral encephalitis or autoimmune encephalitis, he was initially treated with intravenous acyclovir and intravenous immunoglobulin (IVIg) simultaneously. After 1 week, viral encephalitis was ruled out, with negative results in PCR tests.

After that, the GABA-B receptor antibody was confirmed in the serum and CSF with immunohistochemistry. Other extensive diagnostic workups showed no significant results. Under the confirmed diagnosis of GABA-B receptor antibody encephalitis, further cancer screening workup was conducted. However, no suspicious malignancy was found on abdominal computed tomography (CT) or chest CT. Weekly intravenous rituximab (RTX) was administered to treat GABA-B receptor antibody autoimmune encephalitis. (Fig. 3).

Approximately 1 week after the first RTX injection, his neurologic symptoms, including dysarthria, started to improve. By the time of the third RTX injection, his cognitive function had partially improved. (MMSE 25/30, CASE 5). The detailed clinical course is described in Figure 3. Between the second and third RTX injections, he

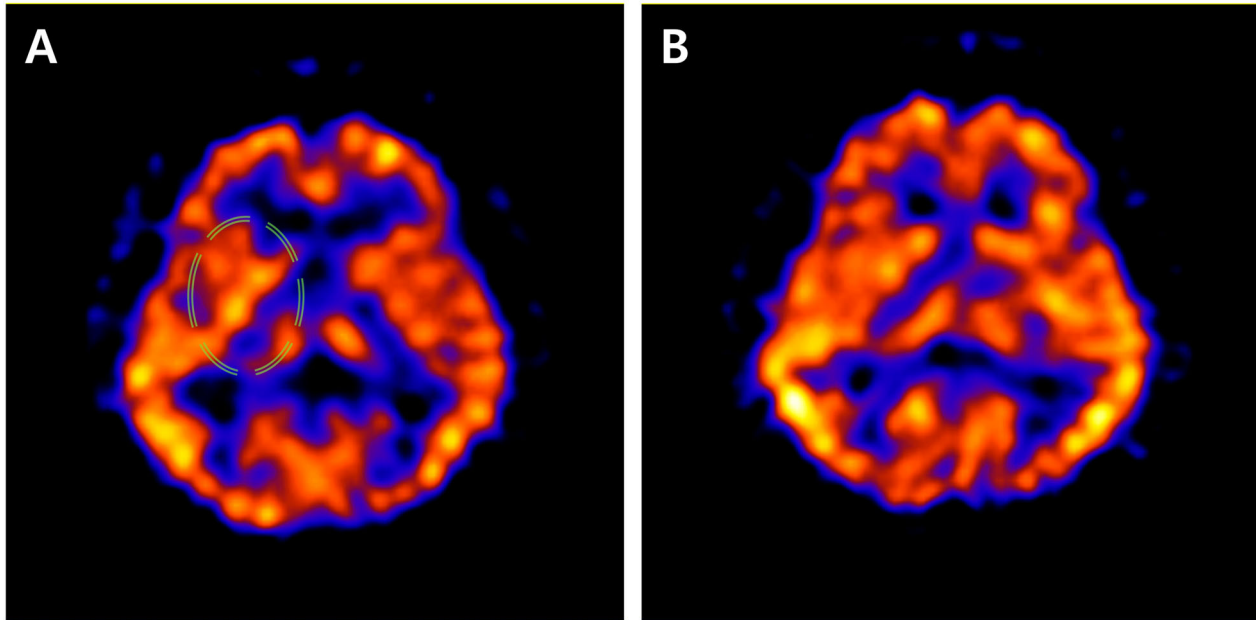
experienced GTCSs once again. Levetiracetam was added to previous lacosamide monotherapy. After that, no more seizures occurred.

Spastic, ataxic gait disturbance began to improve around the third injection of RTX. In the follow-up neurologic examination, the Hoffman sign and ankle clonus also disappeared. By the time of the 6<sup>th</sup> RTX injection (4 months after onset), he became neurologic symptom free. In the follow-up interictal brain SPECT, asymmetric hyperperfusion in the right medial temporal cortex had disappeared (Figure 2B). In the outpatient clinic, he will be regularly screened for cancer, which may occur in the future.

## Discussion

Unlike in previously reported cases of autoimmune encephalitis after the administration of the ChAdOx1 nCoV-19 vaccine,<sup>4,5</sup> the confirmation of the presence of autoantibodies against synaptic receptors resulted in a diagnosis of “definite autoimmune encephalitis” rather than “possible autoimmune encephalitis” in our case.<sup>6</sup> Moreover, the presence of GABA-B receptor antibodies was confirmed without systemic cancer involvement. These findings strongly support that autoimmune encephalitis was developed following vaccination.

Temporal correlation between vaccination and the onset of encephalitis itself is not enough for definite proof of casualty. Since no large-scale epidemiologic studies of



**Figure 2.** Interictal single-photon emission computed tomography (SPECT) image of the patient. (A) Asymmetric hyperperfusion in the right medial temporal cortex and right striatum (green mark) was found in the acute phase of GABA-B receptor antibody encephalitis. (B) After rituximab treatment, asymmetric hyperperfusion disappeared in the follow-up SPECT image.

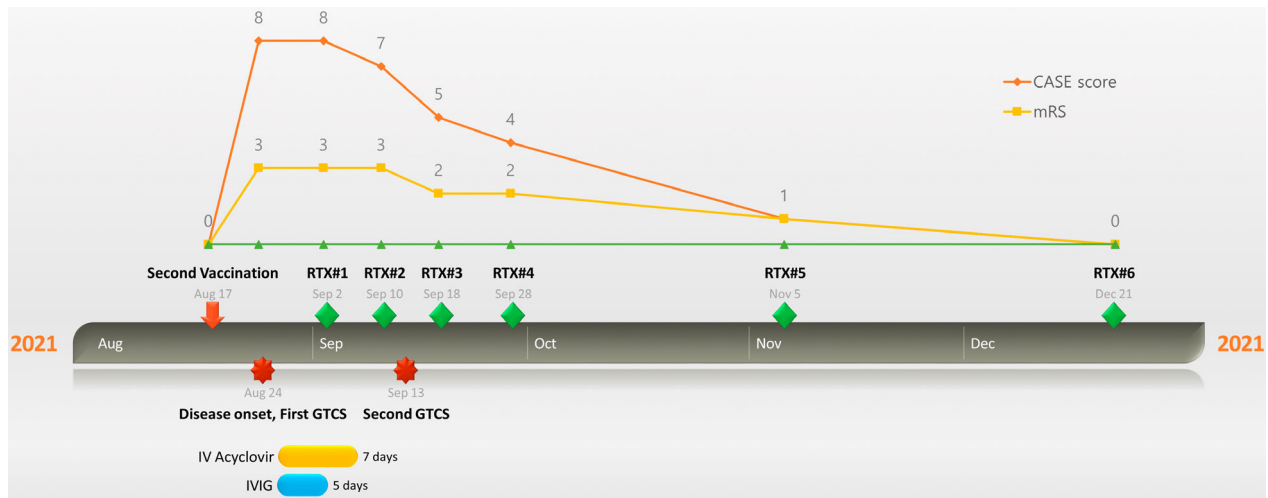
**Table 1.** Extensive laboratory tests in blood and cerebrospinal fluid (CSF).

Infection tests in serum	HIV, Rickettsia Tsutsugamushi Ab, Japanese B encephalitis, Mycoplasma Ab, Measles IgM Ab, VZV IgG Ab
Infection tests in CSF	DNA-PCR of HSV1, HSV2, EBV, CMV, VZV, Enterovirus, respiratory virus, HHV6, HHV8, JC virus, Mycoplasma, TB/NTM
Vasculitis, SLE, SREAT screening in serum	VZV IgG Ab, Cryptococcus Ag, ANCA (MPO Ab, PR III Ab), ANA, RF, anti-ds DNA, anti-Ro/La Ab, anti-TPO Ab
Autoantibody test of serum and CSF	GAD65, NMDAR, GABA-B-R, AMPAR, DPPX, LGI1, CASPR2, Amphiphysin, CV2/CRMP5, Ma2/Ta, Hu, Ri, Yo, Recoverin, Sox1, Titin

HIV, human immunodeficiency virus; VZV, Varicella Zoster Virus; HSV, herpes simplex virus; EBV, Epstein-Barr Virus; HHV, Human Herpesvirus; JC, John Cunningham; TB/NTM, tuberculosis/non-tuberculous mycobacterium; ANCA, antineutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase-3; ANA, antinuclear antibody; RF, rheumatoid factor; TPO, thyroid peroxidase; GAD, Glutamic acid decarboxylase; NMDAR, N-methyl-D-aspartate receptor; GABA, gamma-aminobutyric acid; AMPAR,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; DPPX, dipeptidyl-peptidase-like protein 6; LGI1, Leucine-rich glioma-inactivated 1; CASPR2, Contactin-associated protein-like 2; CRMP5, collapsin response mediator protein 5.

encephalitis after vaccination have been conducted, indirect estimation based on existing data is the alternative. In a survey of encephalitis occurring after vaccination in United States, the onset of encephalitis was found to be within 2 weeks after vaccination in most cases (50.7%).<sup>7</sup> Three previously reported case series of postvaccinal encephalitis after the administration of the ChAdOx1 nCoV-19 vaccine were developed at approximately 7 days (5 days, 6 days, 8 days) after vaccination.<sup>4</sup> In this paper, Zuhorn et al discussed that the estimated incidence of encephalitis after vaccination with ChAdOx1 nCoV-19 was 8 per 10 million, which is a higher rate than what is expected in spontaneously occurring encephalitis cases. In addition, significantly more cases were reported after administration of the ChAdOx1 nCoV-19 vaccination than after administration of the Pfizer-Biontech mRNA vaccine (79 cases in 99.3 million doses vs. 20 cases in 110.6 million doses, Pearson's  $\chi^2 = 41.923$ ,  $p < 0.001$ ).<sup>4</sup> In our case, the patient's neurologic symptoms developed 9 days after the second dose of the ChAdOx1 nCoV-19 vaccine. We believe that this temporal relationship (occurrence within 2 weeks) strongly supports the fact that this case was caused by a vaccine.

In this case, autoimmune encephalitis developed after the second dose of a vaccine was administered. Additionally, another case of autoimmune encephalitis that was observed after the second dose of the ChAdOx1 nCoV-19 vaccine was administered has been reported.<sup>5</sup> The second



**Figure 3.** Timeline of clinical events and treatments for a patient with GABA-B receptor antibody encephalitis. CASE, Clinical Assessment Scale in Autoimmune Encephalitis; mRS, modified Rankin scale; RTX, rituximab; GTCS, generalized tonic-clonic seizure; IVIg, intravenous immunoglobulin.

dose of the ChAdOx1 nCoV-19 vaccine also appeared to cause solicited adverse events during the phase 3 clinical trial of the ChAdOx1 nCoV-19 vaccine although in fewer numbers than those observed following the first dose.<sup>2</sup> Assessments of the immunogenicity of the ChAdOx1 nCoV-19 vaccine showed boosted humoral response against the SARS-CoV-2 spike protein.<sup>8</sup> In addition, human bodies can develop immunity to the adenoviral vector itself. Possible cross-reactivity with the adenoviral vector could contribute to the production of GABA-B receptor antibodies.

GABA-B receptor antibody encephalitis is an autoimmune encephalitis caused by synaptic autoantibodies to the central nervous system. Typical clinical characteristics of GABA-B receptor antibody encephalitis include epilepsy, cognitive dysfunction, and mental behavioral abnormalities, which are classified as limbic encephalitis.<sup>9</sup> In a recent study with 14 patients in China, GABA B receptor antibody encephalitis tended to occur in middle-aged elderly men. All of these patients (100%) experienced epilepsy, 78% (11/14) developed cognitive impairments, and 64% (9/14) showed behavioral abnormalities.<sup>10</sup> In our case, recurrent GTCSs, cognitive decline, and behavior change were observed in a middle-aged elderly male patient. These are typical presentations of GABA-B receptor antibody encephalitis. In addition, atypical neurologic presentation was also observed in our case. Ataxia and spasticity were prominent with ankle clonus. These findings are suggestive of myelopathy, and fuzzy enhancement at the cervical cord (C6-T1) in spine MRI confirmed this diagnosis. Not only the limbic encephalitis symptoms but also the ankle clonus and spastic ataxia disappeared after immunotherapy. In a previous clinical study with 20

patients with GABA-B receptor antibody encephalitis, only one patient (5%) showed cerebellar ataxia and limb spasticity.<sup>11</sup> Ataxia and spasticity seemed to be rare manifestations of GABA-B receptor antibody encephalitis.

A close relationship with malignancy, especially lung cancer, is well known for GABA-B receptor autoantibodies. In five case series reported by Kim et al., 80% (4/5) of patients had small-cell lung cancer and showed complete or partial response to immunotherapy.<sup>12</sup> In a case series with 20 patients, 10 (50%) patients had small-cell lung cancer, and 78% (15/19) showed complete or partial improvement. In our case, no underlying malignancy was detected in the cancer screening work-up. We believe that vaccination with ChAdOx1 nCoV-19 provokes transient production of GABA-B receptor antibody. In addition, our patient showed complete response to immunotherapy by the time of 6<sup>th</sup> RTX injection. Excellent treatment outcomes might also result from transient antibody production rather than continuous antibody production due to the underlying malignancy. Even if cancer was not detected at the time, cancer can be diagnosed later in cases of the presence of paraneoplastic antibodies. These antibodies associated with cancers can be a predictive indicator of cancer.<sup>13</sup> Therefore, this patient will also be periodically screened for the possibility of developing cancer in the future.

In this case, the use of high-dose corticosteroids, which is the most common immunosuppressive agent used in the treatment of autoimmune encephalitis, was skipped. We chose to give IVIg alone as a first-line therapy since the possibility of viral encephalitis was not initially ruled out. Since the diagnosis of antibody-mediated autoimmune encephalitis was confirmed, we directly moved on

to a second-line therapy rather than treating with corticosteroids. In the Autoimmune Encephalitis Alliance Clinicians Network (AEACN) survey,<sup>14</sup> IVIg was the most chosen acute immunotherapy when corticosteroids were contraindicated. If antibody-mediated autoimmune encephalitis, such as N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis, was suspected, 40% of responders chose the use of IVIg alone or in combination therapy.<sup>14</sup> In our institution, a prospective clinical trial of IVIg for functional recovery in autoimmune encephalitis was conducted.<sup>15</sup> The study revealed favorable efficacy of IVIg regarding functional outcomes of autoimmune encephalitis. As supported by this case, when it is difficult to administer high-dose corticosteroids, the use of IVIg alone seems to be sufficiently effective as a first-line therapy for autoimmune encephalitis treatment.

Several autoantibodies related to COVID-19 vaccination have been reported. In transient thrombocytopenia, glycoprotein-specific platelet autoantibodies were detected after vaccination with the COVID-19 adenoviral vector vaccine (Ad26.COVS. S; Johnson & Johnson).<sup>16</sup> Adenoviral vaccines are not the only vaccines that induce autoantibodies. Anti-GPIIb $\alpha$  autoantibodies were detected in immune thrombocytopenia patients 5 days after vaccination with the BNT16B2b2 mRNA COVID-19 vaccine.<sup>17</sup> Antineutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis after vaccination with the Pfizer-BioNTech COVID-19 vaccine was also reported.<sup>18</sup> Myeloperoxidase (MPO)-ANCA was positive in a young female patient 16 days after vaccination.

The relationship between vaccination and autoimmune encephalitis has mostly been studied in the context of NMDAR antibody encephalitis. A few cases of NMDAR antibody encephalitis were reported after vaccination with the H1N1 vaccine, tetanus/diphtheria/pertussis vaccine, polio vaccines, and Japanese encephalitis vaccine.<sup>19</sup> Recently, a case of NMDAR antibody encephalitis following COVID-19 vaccination was reported (Pfizer-BioNTech).<sup>20</sup> In a recent review paper of COVID-19 and NMDAR antibody encephalitis, the possible effect of microRNA in triggering the disease was discussed.<sup>21</sup> Although the risk is not high, a small risk of triggering NMDAR antibody encephalitis following SARS-CoV-2 infection or COVID-19 vaccination exists.

## Conclusions

Likewise, GABA-B receptor antibody encephalitis and other autoimmune encephalitis could be related to SARS-CoV-2 infection or COVID-19 vaccination. Although the COVID-19 pandemic is coming to an end, large-scale infections and large-scale vaccination programs around the world have allowed several rare neurological manifestations related to vaccination to be reported. This case

may serve as a clue as to the cause of autoimmune encephalitis and GABA-B receptor antibody encephalitis in the future.

## Authors' Contributions

SJA contributed to data acquisition and analysis and drafted a significant portion of the manuscript. STL contributed to data acquisition and analysis and supervised the study. KC contributed to the design and conception of the study and supervised the study. All authors performed a critical review of the manuscript.

## Acknowledgment

The authors are grateful to the patient who participated in this study. This publication was supported by SK Chemicals, Co. (0620213640).

## Conflict of Interest

The authors declare that they have no conflict of interest.

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