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APLAR GRAND ROUND CASE

Case report of acute encephalitis following the AstraZeneca COVID-19 vaccine

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Abstract

Coronavirus disease 2019 (COVID-19) vaccines have proven to be safe, effective and life-saving. However, little information is available on the neurological complications of COVID-19 vaccine. Here, we report a case who developed acute encephalomyelitis 1 week after being vaccinated with AstraZeneca COVID-19 vaccine (AZ vaccine). Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was also suspected. After intravenous dexamethasone and subcutaneous fondaparinux therapy, he returned to normal life without neurological sequelae. Four months later, he received Moderna COVID-19 vaccine without any sequelae.

KEYWORDS
COVID-19, encephalitis, vaccine

1 | INTRODUCTION

In December 2019, a novel coronavirus, SARS-CoV-2, first reported in the Wuhan city of China, soon spread around the world and caused substantial impact on health. As of March 2022, SARS-CoV-2 has infected ~400 million people worldwide and caused 6.07 million deaths. During the global COVID-19 pandemic, people in Taiwan maintained normal lives due to longstanding strategies of masking, personal hygiene, social distancing, quarantine measures and contact tracing. Unfortunately, the community outbreak of COVID-19 in Taiwan began in May 2021. To stop virus transmission, Taiwan Centers for Disease Control made an effort to increase COVID-19 vaccination coverage. Four types of vaccines, including Moderna, AstraZeneca (AZ), Pfizer-Biontech (BNT) and MVC COVID-19 Vaccine, are available in Taiwan. Headache is the most common neurological side effect after COVID-19 vaccination. In phase 3 clinical trials, the incidence of headache was 24%-35% and 46%-63% after first and second doses of Moderna vaccination;[1] 50.2% after first and second doses of AZ vaccination;[2] and 25%-42% and 39%-52% after first and second doses of BNT vaccination.[3] In s phase 2 clinical trial, the incidence of headache was 15.1% and 13.2% after first and second doses of MVC COVID-19 vaccination, respectively.[4] However, some rare neurological disorders post-COVID-19 vaccine, like Bell's palsy, encephalomyelitis, Guillain-Barré syndrome, and transverse myelitis have been reported.[5–8] Here, we report a case of new-onset acute encephalomyelitis after receiving the first dose of AZ vaccine.

2 | CASE REPORT

A 55-year-old man was admitted to hospital with fever and consciousness disturbance. The patient received the first dose of AZ vaccine 1 week before admission. Mild injection site pain was observed and subsided in the following 2 days. Two days before admission, the patient suffered from fever up to 39°C, nonproductive cough, general malaise and muscle soreness. One day before admission, progressive weakness and lowered consciousness and drowsiness developed. He had difficulty in sitting up from bed and changing clothes due to weakness. Due to progressive disorientation to people and place and slow response, he was referred to our hospital for help.

The patient had a history of hypertension, hyperlipidemia and sleep apnea and was currently under medication. He did not smoke tobacco, use illicit drugs, or drink alcohol. He lived in an urban area with his wife. He did not have a pet.

At the emergency department, body temperature was 37.9°C, blood pressure was 135/74 mm Hg, pulse rate was 108 beats per minute, respiratory rate was 18 breaths per minute, and oxygen saturation was 97% on room air. Neurological examination disclosed Glasgow Coma Scale was 10 (E3V2M5), normal pupils with intact light reflex (3+/3+), intact blink reflex, symmetric muscle power (UE 3/3 and LE 3/3), down-going bilateral plantar reflex, impaired verbal expression (only could say simple words) and positive Kerning's sign and Brudzinski's sign.

Lumbar puncture was performed and cerebrospinal fluid (CSF) testing showed the white cell count was 16/μL (reference range, 0–5), with a neutrophil/lymphocyte/monocyte count 3/4/7, red cell count was 1/μL (reference value, 0), the protein level was 97.3 mg/dL (reference range, 15 to 45) and positive antinuclear antibody (ANA; 1:2). Serum white cell count, platelet count and C-reactive protein were within normal range, and elevated D-dimer (1.19 mg/L fibrinogen equivalent units [FEU]) was noted. Other laboratory and serial CSF findings are shown in Tables 1 and 2.

Serology survey showed positive serum ANA (1:640), slightly elevated ferritin (351.02 ng/dL) and D-dimer (1.19 mg/1 FEU). Antiplatelet factor 4 (PF4) antibody was negative. Other autoimmune profiles are showed in Table 3. CSF bacterial, fungal and tuberculosis culture, CSF viral culture, BIOFIRE® FILMARRAY® Meningitis/Encephalitis Panel test and antibodies of paraneoplastic neurologic syndrome and limbic encephalitis were all negative findings. In addition, CSF and nasopharyngeal SARS-CoV2 polymerase chain reaction were negative. Magnetic resonance angiography of brain was done on day 4 after admission and showed pachymeningeal enhancement without definite abnormal signal intensity over brain parenchyma.

Under the impression of encephalomyelitis, empiric intravenous ceftriaxone and acyclovir were administered.

TABLE 1 Serial cerebrospinal fluid (CSF) findings

	Reference range	25 June (admission d 1)	28 June (admission d 4)	5 July (admission d 11)
Opening/closing pressure, cmH_2O	-	16.2/7.4	16/10	3/2.5
Appearance	-	Colorless, clear	Colorless, clear	Colorless, clear
Red cell count per μL	0	1	4	6
White cell count per μL, differential count (neutrophil/lymphocyte/monocyte), %	0-5	16 (N/L/M 3/4/7)	73 (N/L/M 9/62/2)	2 (N/L/M 0/1/1)
Protein, mg/dL	15-45	97.3	172.6	102.4
Lactate, mg/dL	10-25	19.9	14.7	16.2
CSF glucose, mg/dL	40-70	69	55	60
Serum glucose, mg/dL	70-200	-	97	-
Adenosine deaminase, U/L	<9	0	1	-
Antinuclear antibodies	-	1:2 (fine speckled)	-	1:8 (fine speckled)
Venereal disease research laboratory test	-	Non-reactive	-	-
Immunoglobulin G index	0.34-0.58	0.404	-	-
Oligoclonal bands	-	Negative	-	-
Bacterial culture	-	Negative	Negative	-
CSF polymerase chain reaction, VZV/Parvovirus B-19/HSV-1/HSV-II/EBV/CMV/HIV/SARS-CoV2	-	Negative	-	-

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; VZV, varicella zoster virus.

Vaccine-induced immune thrombocytopenia and thrombosis (VITT) could not be excluded at that time due to post-vaccine and elevated D-dimer, so subcutaneous fondaparinux was administered. Due to suspected non-infectious causes of meningoencephalitis (negative work up of infectious etiology and positive CSF/serum ANA). New-onset or flare of immune-mediated disease (IMD) following COVID-19 vaccine injection was of concern and intravenous dexamethasone 5 mg once daily was initiated on day 3 after admission. The fever subsided and consciousness level gradually improved. Treatment course and CSF protein change are summarized in Figure 1. He returned to normal life without neurological sequelae and was discharged on day 14 after admission. Four months later, he received BNT COVID-19 vaccine without any sequelae.

TABLE 2 Serum laboratory data

Variable	Reference range, adult	25 June admission d 1
White cell count, per μL	3900-10 600	7670
Differential count (%)		
Neutrophils	40–74	82.1%
Lymphocytes	19-48	12.1%
Monocytes	3.4-9	5.6%
Eosinophils	0–7	0.1%
Hemoglobin, g/dL	13.5-17.5	14.7
Platelet count, per μL	150000-400000	240000
Alanine aminotransferase, U/L	10-50	18
Aspartate aminotransferase, U/L	8–38	17
Alkaline phosphatase, U/L	50-190	68
Total bilirubin, mg/dL	0.2-1.2	0.8
Prothrombin time, s	9.5-11.7	10.8
Prothrombin time international normalization ratio	0.85-1.15	1.02
D-dimer, mg/L fibrinogen equivalent units	<0.55	1.19
Ferritin, ng/mL	21.81-274.66	360.18
Lactate dehydrogenase, U/L	120-240	208
C-reactive protein, mg/dL	<0.3	0.1
Erythrocyte sedimentation rate, mm/h	0-20	7
Urea nitrogen, mg/dL	5-25	13
Creatinine, mg/dL	0.7-1.4	1.30
Sodium, mEq/L	137-153	140
Potassium, mEq/L	3.5-5.3	4.2
Calcium, mg/dL	8.4-10.2	8.1
Lactic acid, mg/dL	3-12	20.3

3 | DISCUSSION

AZ vaccine, developed at Oxford University, is a replication-deficient chimpanzee adenoviral vector vaccine containing the SARS-CoV-2 structural surface glycoprotein antigen gene. The phase 1 clinical trial in the UK was started in April, 2020.[9] Since then, several randomized controlled trials were initiated to evaluate the safety and efficacy of AZ vaccine.[10–12] The interim analysis showed 62.1% vaccine efficacy in 2 standard doses-vaccinated participants and 90.0% vaccine efficacy in a low dose followed by a standard dose-vaccinated group.[13] Common adverse events reported in clinical trials included injection site reactions, fatigue, headache, muscle ache and feeling feverish.[9–12]

After emergency approval of AZ COVID-19 vaccine in several countries, a wide spectrum of post-vaccination neurological adverse events were reported. Guillain-Barré syndrome (GBS) was reported in India (n = 7) and Britain (n = 1).[5,14] GBS occurred mostly within 3 weeks of the first vaccination dose. The incidence was extremely low at about 5.8 per million.[5] Most patients recovered well after intravenous immunoglobulin (IVIg) therapy. Other complications, including new-onset refractory status epilepticus[15] and acute transverse myelitis[6,16] were also reported. The recurrent seizures occurred 10 days after vaccination and were refractory to conventional antiepileptic drug therapy, which dramatically improved after steroid pulse therapy and plasma exchange.[15] Vaccination-associated myelitis developed within 2 weeks after vaccination and symptoms were rapidly improved after initiation of high-dose corticoid therapy.[6,16]

TABLE 3 Autoimmune profile

Antinuclear antibody	1:640, fine speckled
Anti-double-stranded DNA antibody	Negative
Anti-Smith/ribonucleoprotein antibodies	Negative
Anti-Sjögren's syndrome A/B antibodies	Negative
Anti-neutrophil cytoplasmic antibodies/myeloperoxidase antibodies/anti-proteinase-3 antibodies	Negative
Anti-cardiolipin IgM/IgG, anti-β2 glycoprotein I IgM/IgG, lupus anticoagulant	Negative
Complement 3, 87-200 mg/dL	116.6 mg/dL
Complement 4, 19-52 mg/dL	37.6 mg/dL
Anti-parietal cell antibody	Positive, 1:160

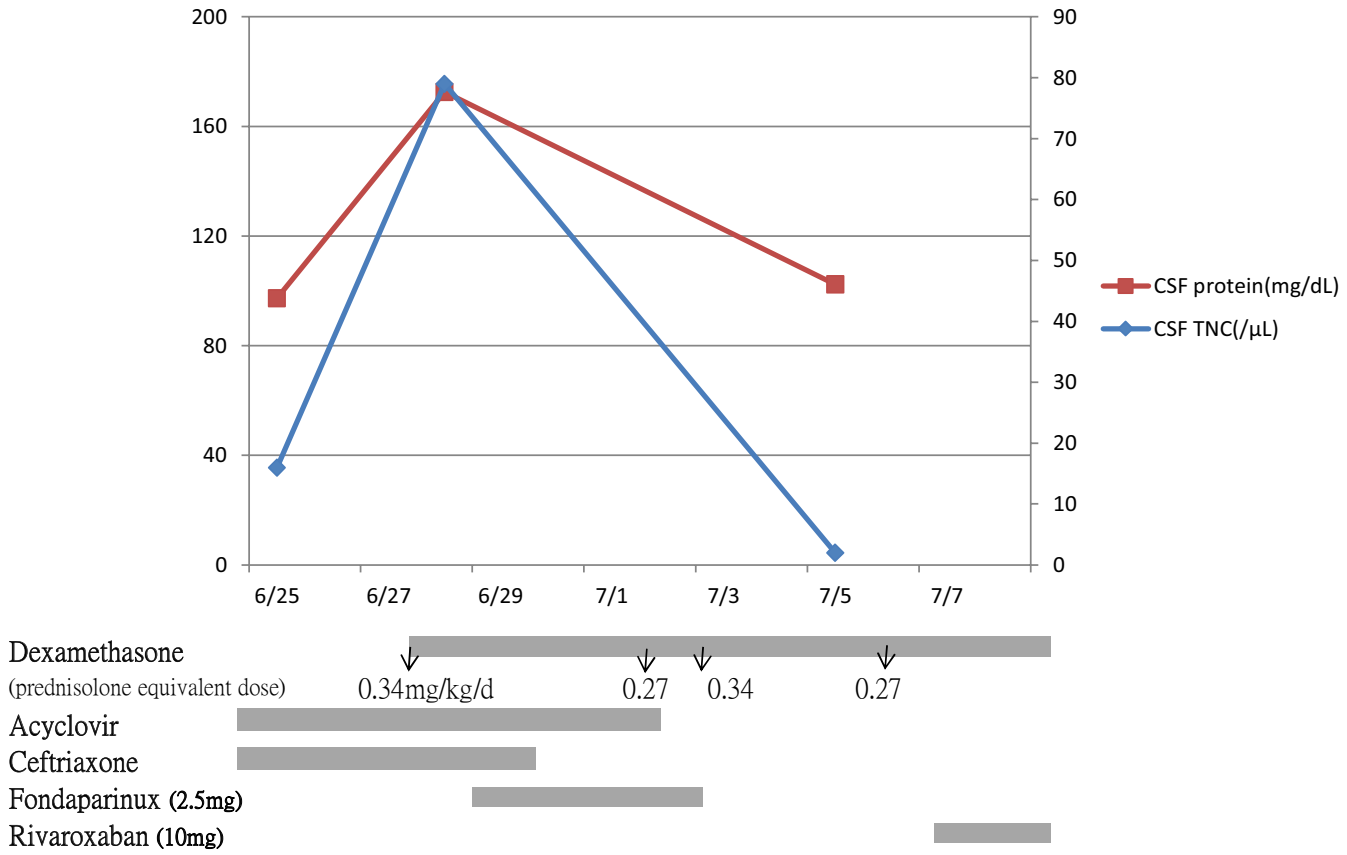

FIGURE 1 Serial cerebrospinal fluid (CSF) protein and total nucleated cell (TNC) changes and treatment course

In Taiwan, severe adverse events are reported to Taiwan Vaccine Adverse Event Reporting System (Taiwan VAERS). Till September 2021, neurological adverse events according to Taiwan VAERS included facial palsy, seizure, transverse myelitis, acute disseminated encephalomyelitis, GBS, myelitis, encephalitis and optic neuritis. A total of 116 cases in 13.6 million doses with a resulting incidence of almost 0.85 per 100 000 for post-vaccination neurological adverse effects has been recorded in Taiwan.

In our case, the symptoms of post-vaccination encephalitis onset occurred at day 7 after vaccination. Brain magnetic resonance imaging was performed with normal status of parenchyma. Significant improvement of the symptomatology was noted after steroid therapy. A first case of post-vaccination encephalitis was reported in Italy.[17] Zuhorn et al.[18] also reported 3 cases of acute encephalitis after AZ vaccine injection. We also summarize case reports of COVID-19 vaccine-related encephalomyelitis in Table 4.[8,19–26] Similar to our case, the symptoms of encephalitis developed within 30 days after vaccination. After excluding alternative causes, vaccination-related autoimmune encephalitis was suspected and symptoms rapidly recovered after the initiation of immunosuppressive therapy. Case reports of COVID-19 vaccine-related encephalomyelitis were mostly in AZ vaccine. According to public databases, the incidence of post-vaccination encephalitis is extremely rare, about 0.08 per 100 000 in AZ COVID-19 vaccine, 0.02 per 100 000 in Pfizer-Biontech messenger RNA vaccine.[18]

A new syndrome, VITT, with clinical features of thrombosis at unusual sites, elevated D-dimer, thrombocytopenia, coagulation abnormalities and positive antibodies to PF4, has emerged after wide vaccination.[27] VITT is caused by antibodies that recognize PF4 bound to platelets. Anticoagulation therapy is primary therapy for VITT.

Our patient presented with neurological symptoms 1 week after vaccination and elevated D-dimer so VITT could not initially be excluded. Therefore, subcutaneous fondaparinux was initially administered. However, normal platelet count and absent evidence of thrombosis over brain imaging and negative anti-PF4 did not support the diagnosis of VITT. In this case, we gradually discontinued anticoagulation agents after neurological conditions improved.

Another possible mechanism of meningoencephalitis post-vaccination is autoimmune/inflammatory syndrome induced by adjuvants (ASIA). ASIA was proposed by Shoenfeld et al. in 2011. ASIA presents with a heterogeneous clinical picture including multiple system involvement.[28] Around 13% severe ASIA cases harbored nervous system involvement.[29] Watad et al.[30] reported 27 cases of new-onset or flare of IMDs following COVID-19 vaccine injection. Among those IMDs cases, 78% had at least 1 underlying autoimmune disease prior the vaccination, and 80% of cases had excellent response after the use of steroid therapy. Connolly et al.[31] conducted a prospective observational study to evaluate disease

TABLE 4 Case reports of COVID-19 vaccine-related encephalomyelitis

Age/gender	Dose/vaccine	Onset post-vaccination	Past history	Symptoms	Treatment	Outcome	Ref
77/M	1/AZ	2 d	1. Sarcoidosis and polymyalgia rheumatica 2. COVID-19 5 mo ago	Agitation and confusion	Methylprednisolone for 4 d and taper to oral prednisolone	Complete remission	17
21/F	1/AZ	5 d	Obesity	Attention and concentration difficulties	Dexamethasone	Improved, with mild cognitive slowing	18
63/F	1/AZ	6 d	Not available	Immobilizing opsoclonus myoclonus syndrome	Methylprednisolone for 5 d	Improved, with low-grade tremor	18
63/M	1/AZ	8 d	Not available	Aphasia	Steroid was rejected by patient	Improved	18
56/F	1/BNT	2 wk	Recurrent cutaneous herpes zoster	Hemi-ataxia and dysmetria	Corticosteroid 2 wk	Improved, with mild dysmetria and intention tremor	19
63/M	1/AZ	12 d	Diabetes, ischemic heart disease, and atrial fibrillation	Declining cognition, emerging disorientation and impaired attention	Corticosteroids and plasmapheresis	Expired	20
34/M	2/Sputnik V	3 wk	Previously healthy	Acute confusional state and imbalance	Plasmapheresis	Improved	21
88/F	2/BNT	29 d	Diabetes and Alzheimer's disease	Impaired consciousness and gaze-evoked nystagmus	Steroid pulse therapy	Improved	22
56/F	1/AZ	10 d	Not available	Weakness of the lower limbs and slurred speech	Steroid pulse therapy	Marked improvement	23
19/F	1/Moderna	2 wk	Atopic dermatitis and depression	Headache, fever, back and neck pain with nausea, vomiting and urinary retention	Corticosteroids and plasmapheresis	Complete remission	24
36/F	1/AZ	14 d	Not available	Bilateral optic neuritis	Corticosteroid	Improved	25
64/M	1/AZ	10 d	Not available	Fever and drowsiness	Corticosteroids, plasmapheresis, and rituximab	Complete remission	26
65/M	2/AZ	10 d	Not available	Behavioral changes and jerky movements	Corticosteroids and IVIG	Marked improvement	26
64/ M	2/AZ	20 d	Not available	Ascending paresthesias in the legs and hand	Corticosteroids, IVIG, and rituximab	Marked improvement	26
46/M	1/AZ	4 d	Not available	Progressive lower limb weakness and numbness	Corticosteroids and plasmapheresis	Marked improvement	26
42/F	1/AZ	5 d	Not available	Headache and photophobia	Corticosteroid	Marked improvement	26
37/M	1/Sinopharm	1 mo	Previously healthy	Progressive muscle weakness in all limbs with dysphagia	Corticosteroids, plasmapheresis, and IVIG	Marked improvement	27

Abbreviations: AZ, AstraZeneca; BNT, Pfizer-Biontech; IVIG, intravenous immunoglobulin.

flare-up and post-vaccination reaction among 1377 patients with rheumatic and musculoskeletal disease. The incidence of disease flares requiring treatment after 2-dose COVID-19 vaccination was 11%, with no reports of severe flares. Age-associated B cells (ABCs)-mediated autoimmunity (new-onset or flares) was thought to explain this autoimmune phenomena following COVID-19 vaccination.[32] ABCs subset are known as double negative B cells in humans, which are hyperresponsive to Toll-like receptor 7 (TLR7) signaling.[33] The use of TLR7/8 and TLR9 agonists, as adjuvants of COVID-19 vaccine, may trigger this post-vaccination autoimmune phenomena. Our patient fitted some features of ASIA: exposure to external stimuli prior to clinical manifestations and typical clinical manifestations (neurological manifestations and cognitive impairment). The patient receiving another COVID-19 vaccine (BNT) without adverse events might imply that special immune system activation resulting in neurological adverse events was triggered by AZ vaccine in our patient.

4 | CONCLUSION

We present a case of meningoencephalitis after AZ vaccine in Taiwan. Rational temporal association of COVID-19 vaccination, negative diagnostic work up of other meningoencephalitis etiologies and rapid clinical response after steroid treatment supported the possibility of CNS inflammation triggered by vaccination. Due to the COVID-19 pandemic, COVID-19 vaccine was quickly developed and put into clinical use. Safety of COVID-19 vaccination should be closely monitored and the benefit–risk balance should be reassessed. Further research is needed to study the mechanism of vaccine-related neurological adverse events.

AUTHOR CONTRIBUTIONS

Drs S-P Lin, S-Y Li, and H-H Chen were involved in the clinical care of the patient and planned the case report. Drs S-P Lin and S-Y Li wrote the first draft and created the tables and figures. Drs P-Y Liu, Z-Y Shi, Y-H Lin and C-A Tsai were responsible for clinical consultation. All authors reviewed and revised the manuscript and approved the final manuscript as submitted.

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CONFLICT OF INTEREST

The authors declare they have no conflicts of interest.

ETHICS STATEMENT

No investigations or interventions were performed outside routine clinical care for this patient. The patient signed an approval for the publication of the case.

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