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RESEARCH

Seronegative acute encephalitis following COVID-19 vaccines: a case series of an overlooked diagnosis with literature review

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Abstract

Purpose Autoimmune encephalitis is a neurological emergency of new-onset altered mental status, caused by an exaggerated immune-mediated response that targets the central nervous system. Autoimmune encephalitis has become an emerging differential diagnosis, when a classical infection cannot explain neurological symptoms. Displaying overlapping clinical presentations, ranging from the insidious onset of cognitive deficiency to more severe forms of encephalopathy with refractory seizures, autoimmune encephalitis can be challenging for clinicians. When evidence of malignancy is absent and pathogenic autoantibodies are undetected, with typical clinical and imaging features of autoimmune encephalitis, seronegative autoimmune encephalitis may be considered. Recently, vaccination-related autoimmune encephalitis and acute encephalitis after COVID-19 vaccination have attracted attention.

Methods and results We report a case series consisting of three patients with autoimmune encephalitis occurring shortly after COVID-19 vaccination and a current review of all previous reported autoimmune encephalitis related to COVID-19 vaccines.

Conclusion We emphasise on the prompt diagnosis of autoimmune encephalitis induced by Covid-19 vaccines and its timely treatment to improve the clinical outcome of this severe neurological condition. Post-licencing vaccine safety surveillance for potential adverse events is essential for vaccine safety and public confidence.

Keywords COVID-19 vaccines · Autoimmune encephalitis · Adverse drug reaction · Neurological complications · Neuroinflammation

Introduction

Two years after its emergence and despite being developed at an unprecedented speed, COVID-19 vaccines had demonstrated a well-established safety and efficacy in controlling the COVID-19 pandemic [1]. Common, expected, and self-limited adverse drug reactions (ADRs) have been related to COVID-19 vaccines, including site injection reactions, fever with chills, fatigue, and swollen lymph nodes [2]. However, the occurrence of serious vaccination-associated ADRs such as neurological complications has been described, including transverse myelitis, facial palsy, Guillain–Barre syndrome (GBS), ischemic stroke, and cerebral venous thrombosis [3]. Autoimmune encephalitis (AIE), accounting for 20% of all acute encephalitis, is a severe immune-mediated inflammatory disorder of the brain and one of the most common causes of noninfectious encephalitis [4]. It is characterised by a myriad of clinical manifestations, including behavioural and psychiatric symptoms, autonomic disturbances, movement disorders, and seizures [5]. Triggered mostly by tumour or infections, AIE has drawn attention as one of the potential causes of acute encephalitis that may be induced by vaccines, which includes the COVID-19 vaccine. However, the causal relationship is not yet established, and the pathophysiology of those complications is still being speculative. Herein, we describe a case series consisting of three patients with AIE that occurred following COVID-19 vaccination. All the reported cases had been notified to the national COVID-19 vaccine adverse event reporting system. A current review of all previous reported AIE related to COVID-19 vaccines aims to shed light on this potential ADR.

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Case reports

Case no. 1

A 40-year-old female patient with a medical history of rheumatoid arthritis treated with steroid and methotrexate had received her first dose of the BNT162b2 Comirnaty®, BioNTech and Pfizer vaccine. Three days later, she complained of headache and nausea complicated by four episodes of generalised tonic–clonic seizures and disorientation, for which she was admitted to the emergency room. On physical examination, the patient had a fever (40 °C) with no signs of meningeal irritation. However, she had significant word-finding difficulties, memory disturbance, and tachycardia. Magnetic resonance imaging (MRI) brain ruled out a vascular aetiology and revealed bilateral hyperintense FLAIR and diffusion signals in the temporal lobes and limbic systems predominant in the right side suggestive of limbic encephalitis (Fig. 1). The results of biological tests were within normal limits. Cerebrospinal fluid (CSF) showed normal protein and glucose levels without pleocytosis. Given concern for infectious encephalitis, acyclovir, amikacin, and ciprofloxacin were started empirically along with levetiracetam for 21 days. Nevertheless, cognitive deficit and memory impairment deteriorated further during subsequent days, with a calculated Montreal Cognitive Assessment (MoCA) score of 12/30 (normal range 26–30): short-term memory loss, severe dysexecutive syndrome, transcortical sensory aphasia, constructional apraxia, dysarthria, and reduced voluntary movement were observed. No sensory or cranial nerve affection was objected. Contemporarily, the patient developed signs of dysautonomia: hypersalivation with weak spontaneous breathing and decreased oxygen saturation at 74%, increased blood pressure at 180–100, and loss of consciousness (Glasgow Coma Scale (GCS) score of 7/15). She was transferred to the intensive care unit, where she was intubated and mechanically ventilated. A second MRI scan revealed extended hyperintensities to occipital and frontal lobes (Fig. 2). Extensive workup for encephalitis excluded other competing diagnoses, such as infective encephalitis, systemic, neoplastic, metabolic, or vascular causes (Table 1 summarises the laboratory workup). As differential diagnoses were ruled out, the patient met clinical diagnostic criteria for autoimmune encephalitis. Intravenous immunoglobulin 0.4 g/kg/day was started with drastic clinical improvement on day 2. She was discharged from the hospital 1 month later on oral levetiracetam and prednisone. At follow-up, she was fully oriented, but neuropsychological assessments revealed short-term memory and language impairment. Her MoCA score improved, reaching 21/30 with 2 weeks of ongoing corticotherapy treatment. Another MRI scan, performed 4 months later, showed a clear improvement of cerebral FLAIR hyperintensities, but with the appearance of atrophy next to lesions (Fig. 3).

Case no. 2

A 35-year-old female with a history of hypothyroidism, palpitations, and eczema had been vaccinated against COVID-19 with mRNA-1273 Spikevax® vaccine (first dose). Twenty days later, she started to show behavioural changes with gradual onset of confusion, prosopagnosia, apraxia, unsteady shuffling gait, and slurred with nonfluent speech. She presented to the emergency room, the following day, with status epilepticus refractory to levetiracetam and valproic acid. MRI brain showed diffuse brain oedema with a hyperintense

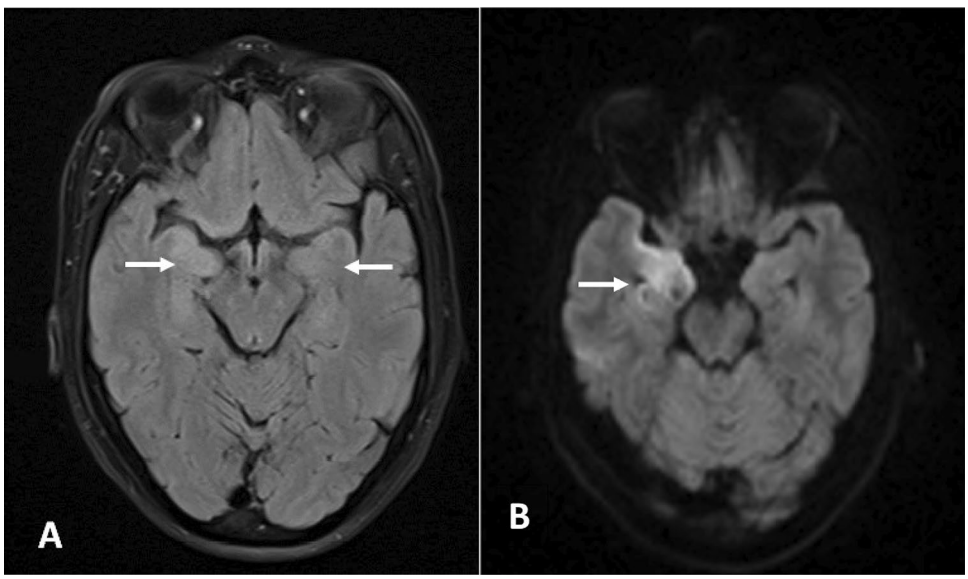

Fig. 1 MRI axial FLAIR (**A**) and diffusion (**B**) sequence revealed bilateral hyperintense signals in the temporal lobes and limbic systems predominant in the right side suggestive of limbic encephalitis in case no. 1, 3 days after COVID-19 vaccination

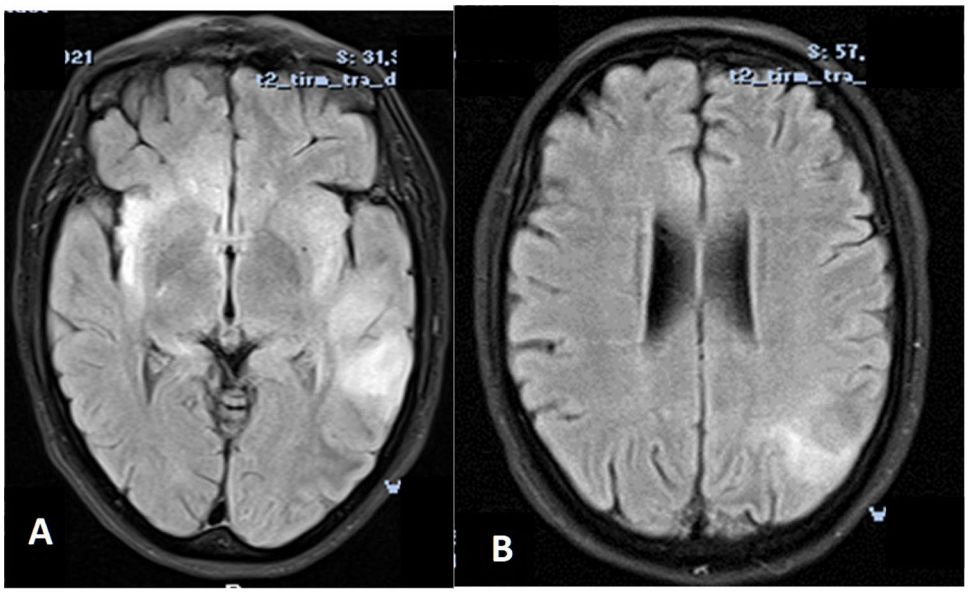

Fig. 2 MRI axial FLAIR sequences revealed extended hyperintensities to occipital (**A**) and frontal lobes (**B**) in case no. 1, 28 days after COVID-19 vaccination

signal (FLAIR and diffusion) in the splenium, with no contrast enhancement after gadolinium injection (Fig. 4). The CSF was colourless, but revealed lymphocytic pleocytosis of 50 leukocytes/µL. Medical treatment, including intravenous lorazepam, levetiracetam, and phenobarbital, was started to control seizures. Anti-infective medication with acyclovir, cefotaxime, and vancomycin was initiated to treat possible infectious meningoencephalitis. Despite the 12-day ongoing treatment, the patient remained drowsy, with a GCS score of 9/14. In view of her young age, persistent seizures, MRI features, and exclusion of other diagnoses (Table 1), autoimmune encephalitis was highly considered. Intravenous immunoglobulins 0.4 g/kg/day were initiated followed by another 5-day cycle of high-dose methylprednisolone 1 g/day leading to an immediate and significant improvement of the symptomatology. The patient regained consciousness on the following day and progressively showed slight improvements in speech and motor function. Her MoCA score improved from 14/30 to 25/30, 2 weeks later, reflecting a marked improvement in her clinical presentation. At discharge, there was still mild cognitive slowing without functional impairment. At the follow-up 2 months later, the patient had sequelae of memory impairment and was maintained on levetiracetam and oral prednisone. Notably, repeated MRI revealed the resolution of the previous abnormalities (Fig. 5).

Case no. 3

A 63-year-old cognitively normal female developed, 2 weeks after receiving the third dose of BNT162b2 Comirnaty®, BioNTech and Pfizer, progressive mental alteration with anterograde amnesia, loss of attention and concentration, murmuring, and unsteadiness. Two days later, she presented to the emergency department, as she experienced periods of unresponsiveness and sudden loss of consciousness. Upon presentation, the patient was afebrile and had status epilepticus, with normal systolic and diastolic blood pressure values of 120 mmHg/70 mmHg, respectively. She did not complain about headaches or visual disturbances. Her past medical history included well-controlled hypertension, gout, and coronary heart disease. MRI was notable for subcortical and cortical oedema, with a predominance of hyperintensity on T2-weighted/FLAIR in parietal and occipital lobes (Fig. 6). Laboratory investigations were unremarkable except for an inflammatory syndrome (CRP 61 mg/L) with a normal white blood cell count and absence of renal impairment. CSF analysis revealed significant pleocytosis and elevated protein levels. Her status epilepticus resolved when treated with intravenous levetiracetam and valproic acid. She had received a 7-day course of ceftriaxone, vancomycin, and acyclovir for presumed meningoencephalitis, but her disorientation and aggressiveness worsened. As the extensive diagnostic workup remained negative, antimicrobial therapy was discontinued, and AIE was considered. Intravenous methylprednisolone (1 g/day) was then administered, and the patient started to respond with considerable improvement. She became able to understand and answer questions, and her neurological deficits gradually resolved thereafter (with an improvement of her MoCA score from 15/30 to 25/30, 2 weeks later). After 2 months of hospitalisation, amnesia persisted as the only residual neurological deficit observed.

Table 1 Summary of investigations, management, and outcome in the three cases

Investigations		Case no. 1	Case no. 2	Case no. 3
CSF analysis	Cell counts Normal range: less than 5 white blood cells/mm^3)	Normal cell count	Lymphocytic pleocytosis (50 cells/)	Lymphocytic pleocytosis (34 cells/mm^3)
	Total protein Normal range 20–40 mg/dl	Normal	70	32
	CSF/plasma glucose ratio: Normal range ≥ 0.5	0.56	0.6	0.69
Biological tests: Blood count, serum electrolytes, renal function, hepatic enzymes, liver enzymes thyroid hormone levels, C-reactive protein		Without abnormalities	Lymphocytopenia: (1000 lymphocytes/μL)	Inflammatory syndrome (CRP 61 mg/L)
Cranial MRI		Hyperintense inflammatory T2-weighted/FLAIR signals in limbic system and temporal lobes	Diffuse brain oedema with hyperintense signal on the splenium with no contrast enhancement after gadolinium injection	Subcortical and cortical oedema with a predominance of hyperintensity on T2-weighted/FLAIR in parietal and occipital lobes
EEG findings		Unremarkable	Unremarkable	Unremarkable
Pathogen screening panel for: - Virology PCR (HSV, VZV, CMV, EPV, COVID-19 virus, HIV, Wile Nile, and Enterovirus virus) - Blood and CSF culture of non-viral agents (mycobacterium tuberculosis, *L. monocytogenes*, *N. meningitidis*, *S. agalactiae*, *S. pneumonia*, *E. coli* K1, *H. influenza*, *Lyme*) - Fungi: toxoplasmosis		Negative	Negative	Negative
Panel for systemic causes: Antibodies for anti-ANCA, anti-DNA, anti-SS-A, anti-SS-B, anti-cardiolipin, anti-CCP, rheumatoid factor, C3/C4 concentrations, Coombs' test, anti-thyroglobulin		Negative	Negative	Negative
Autoimmune cell-based encephalitis panel: Antibodies for anti-NMDA, anti-VGKC, anti-LGI1, anti-GABAb, anti-GAD, *anti-MOG ab/aquaporine-4*) `		Negative	Negative	Negative
Paraneoplastic screening: - Computed tomography of the chest, abdomen and pelvis - Paraneoplastic antibodies: (anti-Yo, anti-Hu, CEA19.9, CA125, CA15.3, and anti-amphiphysin)		Negative	Negative	Negative
Proposed treatment:		5 days methylprednisolone (1 g/day) and IVIG. 4 g/kg/ day	5 days methylprednisolone (1 g/day) and IVIG. 4 g/kg/ day	5 days methylprednisolone (1 g/day)
Outcome:		Marked improvement and discharge on oral steroid	Marked improvement and discharge on oral steroid	Marked improvement and discharge on oral steroid

NMDAR N-methyl D-aspartate receptor, *VGKC* voltage-gated potassium channel, *GAD* glutamate decarboxylase

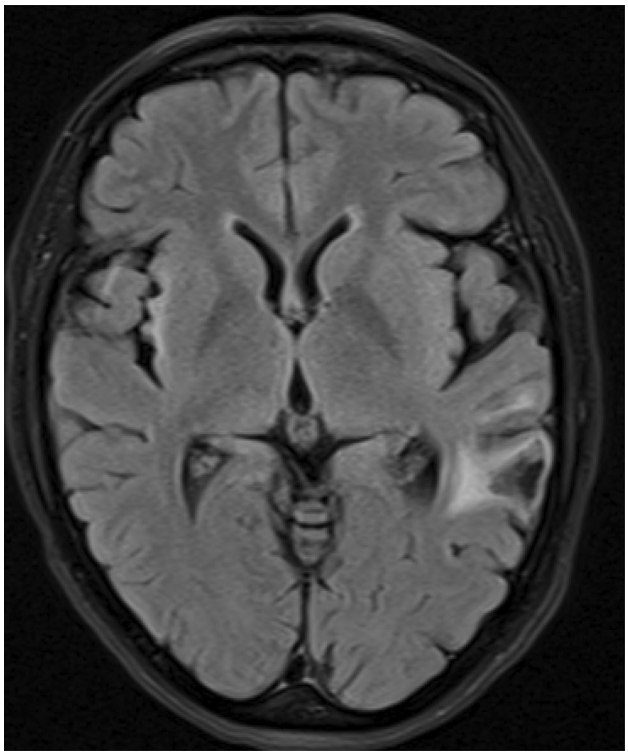

Fig. 3 MRI axial FLAIR sequence showed clear improvement of FLAIR hyperintensities but with appearance of atrophy next to lesions in case no. 1, 4 months after COVID-19 vaccination

Discussion

We report a case series of three clinical pictures consistent with the diagnosis of AIE triggered by COVID-19 vaccines. In all three cases, criteria for possible AIE defined by Graus et al. were fulfilled [6] including (i) subacute onset of brainstem and cerebellar signs, (ii) new focal CNS findings or CSF pleocytosis or neuroimaging findings or seizures not explained by a previously known seizure disorder, and (iii) exclusion of alternative causes. Consequently, the diagnosis of AIE was established in our cases, and immunosuppressive therapy was initiated with remarkable improvement. In view of the suggestive temporal relationship between vaccination and symptom onset and the exclusion of differential diagnoses including infective and non-infective causes, COVID-19-induced AIE was "probable" with a score of 6, according to the Naranjo probability scale [7]. Owing to the lack of any identifiable direct causative biomarkers or antibodies, we cannot be decisively conclusive.

Various neurologic complications may occur following vaccination, with SARS-CoV-2 being no exception. Mild, ambulatory, manageable, and transient neurological ADRs involving, dizziness, headache, myalgia, muscle spasms, and paraesthesia are the most widely mentioned [3]. Nevertheless, severe neurological complications, including vaccine-induced thrombotic thrombocytopenia with cerebral venous thrombosis, GBS, optic neuritis, polymyositis, myasthenia, and transverse myelitis, have been reported [8], many of which are of autoimmune nature [9]. A wide variety of autoimmune neurological syndromes have been reported following different types of viral vaccination: GBS and giant cell arteritis following influenza vaccine, CNS demyelination following HPV, hepatitis A or B, rabies, and measles vaccination [10]. AIE is a non-infectious immune-mediated disease of the central nervous system that implicates a widely variable spectrum of clinical presentations, ranging from the relatively mild or insidious onset of cognitive impairment to more complex forms of encephalopathy with refractory seizures. Might be triggered by vaccination, AIE has been described previously with H1N1 influenza or poliomyelitis vaccines [11]. COVID-19 vaccines, as well, have recently

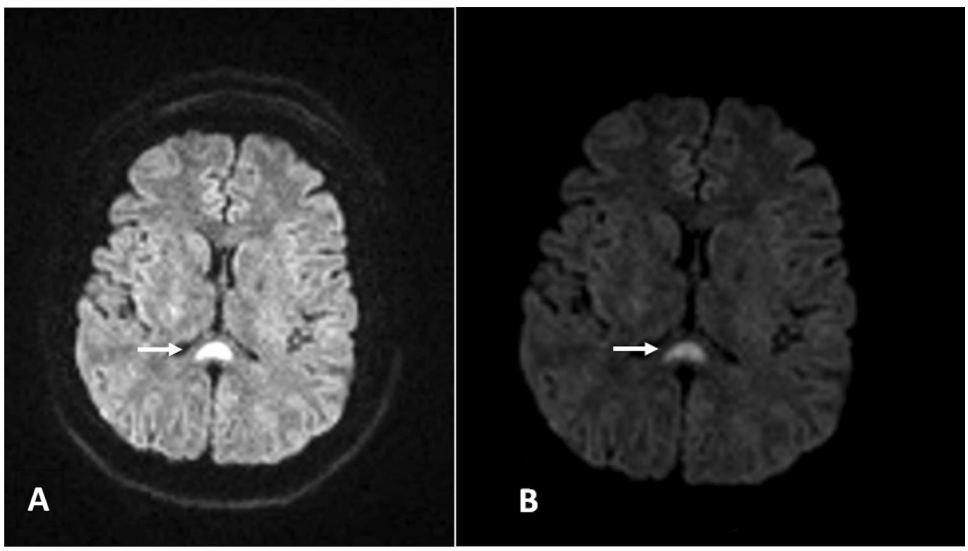

Fig. 4 MRI FLAIR (**A**) and diffusion (**B**) brain showed diffuse brain oedema with a hyperintense) signal in the splenium in case no. 2, 20 days after COVID-19 vaccination

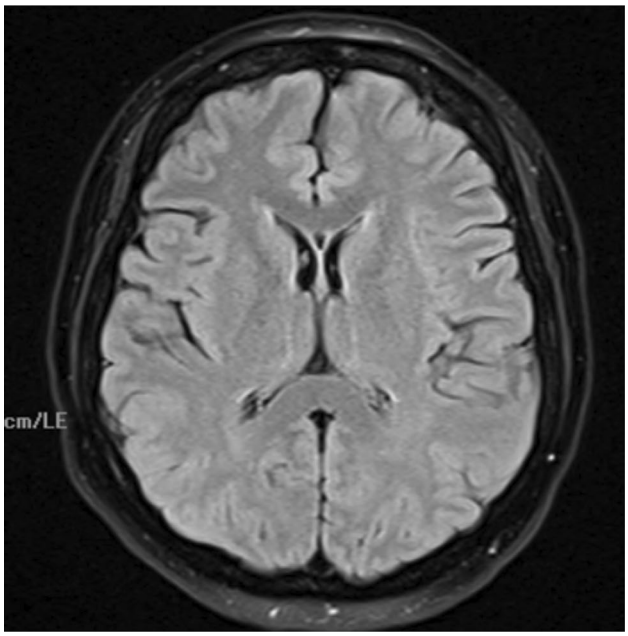

Fig. 5 MRI brain FLAIR axial sequence showed marqued improvement of lesions splenium in case no. 2, 40 days after COVID-19 vaccination

been linked to AIE as increasing cases are emerging, despite the unproven direct causality. To our knowledge, 32 cases of AIE induced by COVID-19 vaccines have been reported in the literature (Table 2 summarises all previous case reports/series of AIE related to COVID-19 vaccines).

In our cases, the diagnosis of a seronegative AIE was established, based on the exclusion of pathogen-induced encephalitis, the dramatic improvement after receiving methylprednisolone, supporting an immune-mediated mechanism. In view of the lack of antibody detection, the diagnosis of a seronegative AIE was retained. Our results are in line with the majority of AIE cases reported in the literature, in which antibody panels were negative (Table 1). Only two cases reported by Zlotnick et al. and Flanney et al. described AIE with respectively positive pathological antibody anti-LGI1 and anti-NMDAR induced by BNT162b2 vaccine [12, 13]. Autoimmune encephalitis is reported to occur within the first week following COVID-19 vaccination (26 /32 cases), which are the case of patients 1 and 3, with an onset time of 3 and 2 days, respectively. However, a long frame time of 20 days between vaccination and AIE was observed in patient 2. This similar long-onset (21 days) of AIE has been outlined in two cases reported by Takata et al. and Grosi et al. indicating that AIE may exhibit a variable incubation period [14, 15]. All of our cases were related to mRNA-based vaccines (Comirnaty®: 2, Spikevax®: 1), which is in accordance with the majority of AIE reported in the literature (19/32: Spikevax® (13/32), Comirnaty® (6/32)), followed by viral vector vaccines (11/32). Only two cases were related to an inactivated COVID-19 vaccine [16, 17]. Like other reported cases of immune-mediated encephalitis, all three patients responded well to immunosuppressive therapy. In fact, appropriate, early, and intense treatment is important to achieve a good outcome in AIE [16]. Corticosteroids are frequently the first choice to manage AIE, followed by intravenous immunoglobulin and plasmapheresis [5]. Nevertheless, some sporadic cases reported the use of rituximab as a second-line immunotherapy in order to treat AIE induced by COVID-19 vaccine [13, 18, 19]. Fortunately, our patients responded well to methylprednisolone alone or combined to intravenous immunoglobulin. It was considered that AIE after COVID-19 vaccination have good prognosis when diagnosed and treated timely and properly as most described cases had a favourable outcome (Table 1).

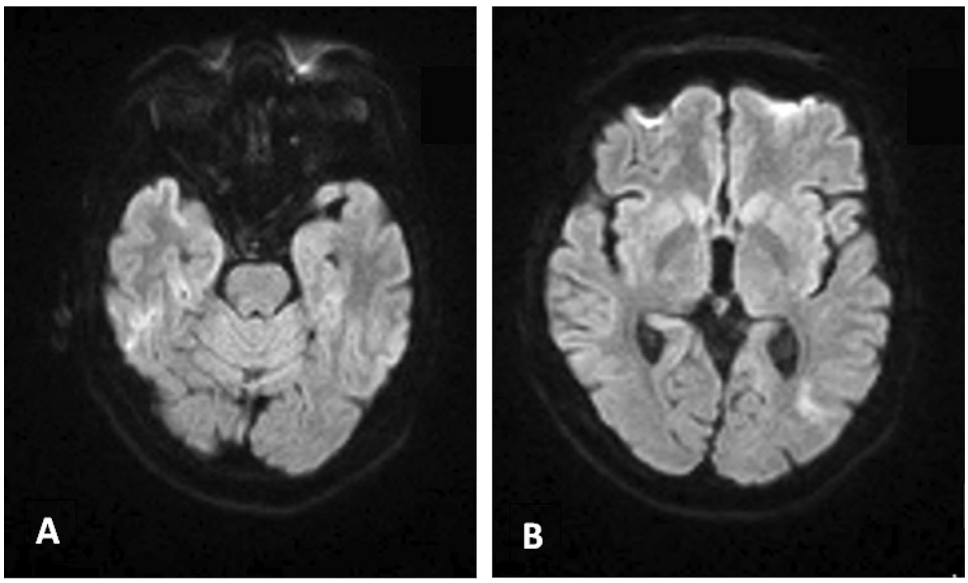

Fig. 6 MRI showed subcortical and cortical oedema, with a predominance of hyperintensity on FLAIR in parietal (**A**) and occipital lobes (**B**) in case no. 3, 2 days after COVID-19 vaccination

Table 2 Overview of published case reports of autoimmune encephalitis after vaccination against COVID-19

Reference/ year	Gender/age	Comorbid conditions	Dose's number	Type of vaccine/	Onset time (days)	Neuroimaging findings	EEG recordings	CFS finding	Extensive workup	Therapy	Outcome
Zuhorn et al./2021 [25]	F/21	Obesity	1	ChAdOx1 nCov-19	5	Unremarkable	Diffuse abnormally slow theta rhythms without epileptiform activity	Lymphocytic pleocytosis	Negative	MP	Partial recovery
	F-6	NM	NM	ChAdOx1 nCov-19	6	Unremarkable	Diffuse abnormally slow theta rhythms without epileptiform activity	Lymphocytic pleocytosis	Negative	MP	Partial recovery
	M/63	NM	NM	ChAdOx1 nCov-19	8	Unremarkable	Normal	Lymphocytic pleocytosis	Negative	Refused by patient	Partial recovery
Zlotnick et al./2022 [12]	M/48	No	2	BNT162b2, BioNTech and Pfizer	20	Hyperintense signal on both medial temporal lobes	Normal	Normal	Positive antibodies for anti-LGI1	MP	Partial recovery
Kobayashi et al./2022 [26]	F46	No	2	BNT162b2, BioNTech and Pfizer	5	Lesion on the dorsal pons across the midline and no gadolinium	NM	Normal	Negative	MP	Partial recovery
Sluyts et al./2022 [27]	M/48	Transgenderism	2	mRNA-1273, Spikevax® COVID-19	6	Unremarkable	Normal	Lymphocytic pleocytosis	Negative	MP	Partial recovery
Kwon and Kim/2021 [19]	F/57	Hypertension	2	ChAdOx1 nCov-19	5	Restricted diffusion along the left insular and mesial temporal cortices with corresponding hyperintensity on fluid-attenuated inversion recovery	Intermittent generalised rhythmic delta activity	Lymphocytic pleocytosis	Negative	MP + rituximab	Partial recovery
Vences et al./2021 [28]	M/72	Hypertension/type 2 diabetes	1	BNT162b2, BioNTech and Pfizer	1	Encephalitis at the anterior frontal and bilateral temporal lobes	NM	Elevated protein	Negative	MP	Partial recovery
Abu-Riash et al./2021 [16]	M/20	No	2	BBIBP-CorV Sinopharm®	Few days later	Suggestive of autoimmune encephalitis involving the limbic system	Rain epileptiform activity	Lymphocytic pleocytosis	Negative	MP	Total recovery

Table 2 (continued)

Reference/ year	Gender/age	Comorbid conditions	Dose's number	Type of vaccine/	Onset time (days)	Neuroimaging findings	EEG recordings	CFS finding	Extensive workup	Therapy	Outcome
Flannery et al./2021 [13]	F/20	No	1	BNT162b2, BioNTech and Pfizer	7	Unremarkable	Normal	Lymphocytic pleocytosis	Positive antibodies for anti-NMDA	MP + rituximab	Partial recovery
Tarazona et al./2021 [29]	F/28	No	NM	ChAdOx1 nCov-19	10	Unremarkable	Diffuse cerebral suffering, more accused on the left hemisphere	Lymphocytic pleocytosis	Negative	MP + intravenous immunoglobulin	Total recovery
Takata et al./2022 [14]	F/22	No	2	ChAdOx1 nCov-19	21	Unremarkable	Normal	Lymphocytic pleocytosis	Negative	No immunosuppressive therapy	Partial recovery
Rosso et al./2022 [30]	F/69	Hypertension, end-stage renal disease on haemodialysis, diabetes, atrial fibrillation, and COVID-19 infection	1	mRNA-1273, Spikevax® COVID-19	1	Unremarkable	NM	NP	Negative	No immunosuppressive therapy	Total recovery
McCullogh et al./2022 [31]	F/76	Hypertension, alcohol use and shingles	2	mRNA-1273, Spikevax® COVID-19	1	T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities in the parieto-occipital lobes and pulvinar of the thalami	Seizure foci in bilateral posterior quadrants	Elevated protein	Negative	No immunosuppressive therapy	Partial recovery
Fan et al./2022 [32]	F/22	No	2	mRNA-1273, Spikevax® COVID-19	6	mild hypoperfusion in the right temporal region,	Normal	Elevated protein	Negative	MP	
Grosi/2022 [33]	M/55	Chronic lymphocytic leukaemia	2	BNT162b2, BioNTech and Pfizer	21	Unremarkable	Normal	Lymphocytic pleocytosis	Negative	No immunosuppressive therapy	Total recovery
Khedr/2022 [20]	M/30	No	2	ChAdOx1 nCov-19	Following days	Unremarkable	Normal	Lymphocytic pleocytosis	Negative	MP	Total recovery

Table 2 (continued)

Reference/ year	Gender/age	Comorbid conditions	Dose's number	Type of vaccine/	Onset time (days)	Neuroimaging findings	EEG recordings	CFS finding	Extensive workup	Therapy	Outcome
	M/39	No	NM	ChAdOx1 nCov-19	15	Unremarkable	background slowing with no specific epileptiform discharge	Lymphocytic pleocytosis	Negative	MP + rituximab	Fatal
	M/38	No	1	ChAdOx1 nCov-19	5	Hyperintense inflammatory signals in cerebellum and brainstem	NM	Normal	Negative	MP + rituximab + tocilizumab	Fatal
Shin et al./2022 [18]	F/53	NM	1	ChAdOx1 nCov-19	5	Mild swelling of the right hippocampus	diffuse beta wave activity, with intermittent generalised delta waves	Normal	Negative	Rituximab	Partial recovery
Asaduzzaman et al./2022. [34]	F/15	No	2	BNT162b2, BioNTech and Pfizer	1	Unremarkable	NM	Normal	Negative	MP	Partial recovery
Liu et al./2021 [35]	F/86	Diastolic dysfunction, chronic kidney disease stage 3, glaucoma, cataracts, and Type 2 diabetes mellitus	1	mRNA-1273, Spikevax® COVID-19	7	Unremarkable	Non-convulsive focal status epilepticus		Negative	No immunosuppressive therapy	Total recovery**
	M/73	Crohn's, hereditary hemochromatosis, hypertension and hyperlipidaemia	1	mRNA-1273, Spikevax® COVID-19	7	Unremarkable	non-convulsive status epilepticus	Normal	Negative	No immunosuppressive therapy	Partial recovery
Al-Mashdali et al./2021 [36]	M/32	No	1	mRNA-1273, Spikevax® COVID-19	1	Unremarkable	normal	Elevated protein	Negative	MP	Total recovery

Table 2 (continued)

Reference/ year	Gender/age	Comorbid conditions	Dose's number	Type of vaccine/	Onset time (days)	Neuroimaging findings	EEG recordings	CFS finding	Extensive workup	Therapy	Outcome
Torrealba-Acosta et al./2021 [37]	M/77	Coronary artery disease, hyperlipidaemia and hypothyroidism	1	mRNA-1273, Spikevax® COVID-19	3	Unremarkable	normal	Lymphocytic pleocytosis	Negative	MP	Total recovery
Shyu et al./2022 [38]	F/58	No	7	mRNA-1273, Spikevax® COVID-19	3	Unremarkable	Normal	Lymphocytic pleocytosis	Negative	MP	Total recovery
	M/21	No	NM	mRNA-1273, Spikevax® COVID-19	7	Unremarkable	a continuous diffuse slowing in the theta and delta ranges, indicating moderate	Lymphocytic pleocytosis	Negative	MP	Total recovery
Li et al./2022 [39]	M/5	No	1	ChAdOx1 nCov-19	5	Pachymeningeal enhancement without definite abnormal signal intensity over brain parenchyma	NM	Lymphocytic pleocytosis	Negative	Dexamethasone	Total recovery*
Cepero et al./2021 [40]	F/67	Rheumatoid arthritis, Sjogren's syndrome, chronic obstructive pulmonary disease	1	mRNA-1273, Spikevax® COVID-19	1	Unremarkable	Normal	Nm	Negative	MP	Total recovery*
Abu-Abaa et al./2022 [41]	M/75	coronary artery disease, hypertension, and diabetes	2	mRNA-1273, Spikevax® COVID-19	1	Periventricular hyperintensities	Posterior dominant rhythm of mixed theta and delta waves	lymphocytic pleocytosis	Negative	No immunosuppressive therapy	Total recovery

Table 2 (continued)

Reference/ year	Gender/age	Comorbid conditions	Dose's number	Type of vaccine/	Onset time (days)	Neuroimaging findings	EEG recordings	CFS finding	Extensive workup	Therapy	Outcome
Vences et al./2022 [28]	F/33	No	2	BBIBP-CorV Sinopharm®	3	Lesions in the bilateral caudate nucleus and non-specific demyelinating lesions at the supratentorial and infratentorial compartments	Normal	Normal	Negative	MP + intravenous immunoglobulin	Total recovery
Albsheer et al./2022 [42]	F/35	No	2	mRNA-1273, Spikevax® COVID-19	2	Limbic encephalitis	NP	Lymphocytic pleocytosis	Negative	MP + intravenous immunoglobulin + rituximab	Partial recovery
Mansour et al./2022	F/40	Rheumatoid arthritis, pneumonia and chronic sinusitis	1	BNT162b2, BioNTech and Pfizer	3	Bilateral hyperintense T2/FLAIR signals in the temporal lobes and limbic systems	NP	Normal	Negative	MP + intravenous immunoglobulin	Partial recovery
	F/35	Hypothyroidism, palpitations and eczema	1	mRNA-1273, Spikevax® COVID-19	21	Diffuse brain oedema with a hyperintense signal in the splenium,	NP	Lymphocytic pleocytosis	Negative	MP + intravenous immunoglobulin	Partial recovery
	F/63	Hypertension, gout, and coronary heart disease	15	BNT162b2, BioNTech and Pfizer	3	Subcortical and cortical oedema, with a predominance of hyperintensity on T2-weighted/ FLAIR in parietal and occipital lobes	NP	Lymphocytic pleocytosis	Negative	MP	Partial recovery

F female, *M* male, *MP* methylprednisolone, *NM* not mentioned, *NP* not performed, *NMDAR N*-methyl D-aspartate receptor, *LGI1* leucine-rich glioma-inactivated 1

*Reintroduced with no relapse

**Reintroduced with relapse

Nevertheless, fatality can complicate the course of AIE: two cases were described in the literature by Kheder et al. following ChAdOx1 nCov-19 vaccination, in which, despite an aggressive immunosuppressive therapy including rituximab/tocilizumab and methylprednisolone, clinical features of patients deteriorated leading to death [20]. In view of the potential severity and as long as the pathological mechanism of COVID-19 vaccine–induced autoimmune disease disturbance remained unclear, COVID-19 vaccines had to be definitively contraindicated in our cases.

Indeed, several pathogenic mechanisms have been postulated to ascertain how COVID-19 vaccines can lead to AIE. Molecular mimicry is believed to be one of the main immunopathogenic factors. In fact, antibodies against spike proteins produced by vaccines can trigger an undesired immune response. Neuro-inflammation process caused by COVID-19 vaccines is claimed to be also the consequence of exaggerated immune response to mRNA vaccines with a strong expression of pro-inflammatory cytokines and a T cell response reaching the brain known as cytokine storm–associated encephalopathy [21–23]. Another plausible explanation is that vaccine adjuvants are implied in post-vaccination autoimmune reaction, mainly BNT162 adjuvant polyethylene glycol (PEG), as it has been considered to be a trigger of autoimmune syndrome induced by adjuvants (ASIA-syndrome) [24].

Here, we report three cases of encephalitis fulfilling the criteria of possible autoimmune AIE and believed to be related to COVID-19 vaccines. Despite its rare occurrence, AIE following COVID-19 vaccination should be considered with timely treatment, and a favourable prognosis can be obtained. Post-licencing vaccine safety surveillance for potential adverse events is essential for vaccine safety and public confidence. Thus, further large pooled observational epidemiologic data are required before attributing definite causality.

Author contribution Khadija Mansour and Zohra Chadli wrote the manuscript. Samia Younes and Ichrak Ghachem made the diagnosis, patient supervision, and patient follow-up. Haifa Ben Romdhane, Najah Ben Fadhel, and Nadia Ben Fredj performed the drug probability scale. Aouam Karim, Amel Chaabane, and Naceurs Boughatas performed a literature search. All authors read and approved the final manuscript.

Data availability The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Written informed consent was obtained from described patients to publish their clinical details.

Competing interests The authors declare no competing interests.

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