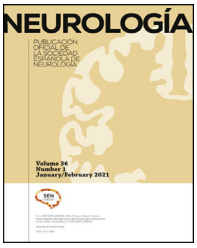
Neurología xxx (xxxx) xxx—xxx

NEUROLOGÍA

www.elsevier.es/neurologia



LETTER TO THE EDITOR

Encephalitis after COVID-19 vaccination☆

Encefalitis después de vacunación para COVID-19

Introduction

Encephalitis is a serious condition that can cause neurological deficits, neuropsychiatric alterations, disability, and even death. The most common causes are infection, autoimmunity, and neoplasms.[1] The incidence of encephalitis is 5—8 cases per 100 000 population. The condition causes changes in level of consciousness, behavioural alterations, fever, seizures, movement disorders, and focal neurological deficits.[1]

Due to the COVID-19 pandemic, several vaccines were developed in 2021 with a view to decreasing the severity and associated mortality of the disease. Trials reported efficacy rates of 94%—95% after administration of the second dose, with few adverse reactions.[2] According to the European Medicines Agency, severe neurological complications are rare (< 0.1%). Cases have been reported of venous sinus thrombosis, facial palsy, Guillain-Barré syndrome, encephalitis, and transverse myelitis after COVID-19 vaccination.[2]

A prospective study conducted in Germany reported venous sinus thrombosis associated with immune thrombotic thrombocytopenia (n = 3), demyelinating diseases (n = 8), inflammatory polyneuropathy (n = 4), and myositis (n = 3), within 6 weeks of vaccination against SARS-CoV-2 and in the absence of any other trigger factor. Most patients were women (female-to-male ratio of 3.2:1) and the median age was 50 years.[3]

We describe the case of a woman who presented rapidly progressive behavioural and cognitive alterations and convulsive status epilepticus following administration of the second dose of the Moderna vaccine (mRNA-1273).

Case report

Our patient was a 36-year-old woman with history of hypothyroidism who had received the second dose of the Moderna vaccine. On day 3 post-vaccination, she presented asthenia, fever, and headache, and on day 7 she displayed confusion, disorientation in time and space, vomiting, and generalised tonic-clonic seizures.

Upon admission, our patient presented confusional symptoms but no focal neurological signs. Several studies were performed and treatment was started with ceftriaxone, vancomycin, and acyclovir. During her stay at the emergency department, she presented convulsive status epilepticus, leading to administration of valproic acid and levetiracetam, orotracheal intubation, and transfer to the intensive care unit.

Laboratory analyses revealed no relevant alterations (Table 1), and a head CT scan revealed a hypodense region in the left temporal pole.

On day 13, she presented aggressiveness, visual hallucinations, delusions of persecution, and another seizure. We suspected acute disseminated encephalomyelitis (ADEM) or postvaccinal encephalitis, and withdrew antimicrobial treatment. Contrast-enhanced MRI did not reveal findings compatible with ADEM; findings were suggestive of autoimmune encephalitis (Fig. 1). We adjusted antiepileptic medications and started treatment with pulses of methylprednisolone dosed at 1000 mg/day for 5 days, with little improvement. We subsequently administered 5 sessions of plasma exchange on alternating days; seizures and neuropsychiatric symptoms improved. Autoimmunity studies and tests for autoimmune encephalitis antibodies (NMDA, GABA, LGI1, CASPR2, AMPA, DPPX) yielded negative results. The patient was diagnosed with encephalitis induced by COVID-19 vaccination. Treatment was continued with oral prednisolone for one month, plus rituximab dosed at 1000 mg on days 0 and 14 and subsequently every 6 months.

A contrast-enhanced MRI study conducted at 6 months revealed resolution of the initial alterations (Fig. 1). During follow-up, the patient was found to have temporal lobe epilepsy, cognitive sequelae (amnesia) and language sequelae, depressive disorder, and non-epileptic seizures.

Discussion

We describe the case of a woman who met criteria for autoimmune encephalitis: *1)* neuropsychiatric symptoms and altered mental status of less than 3 months' progression, and *2)* de novo epileptic seizures and MRI findings suggestive of encephalitis.[4] The progression of the patient's symptoms and their temporal association with COVID-19 vaccination suggest vaccine-induced encephalitis. Treatment with systemic corticosteroids and plasma exchange controlled acute symptoms, although cognitive sequelae and epilepsy persisted in the long term.

Headache, dizziness, and muscle spasms have been reported after COVID-19 vaccination, and are frequently self-limited.[5] However, more severe complications have also been described, including facial palsy, Guillain-Barré syndrome, focal epilepsy,[6] stroke, ADEM, postvaccinal encephalitis,[7,8] and acute encephalopathy.[9]

DOI of refers to article:
https://doi.org/10.1016/j.nrl.2023.03.001.

☆ Please cite this article as: López-González R, Otálvaro-Rendón MA, Quintero-Gutiérrez L. Encefalitis después de vacunación para COVID-19. Neurología. 2024. https://doi.org/10.1016/j.nrl.2023.03.001

https://doi.org/10.1016/j.nrleng.2024.02.002

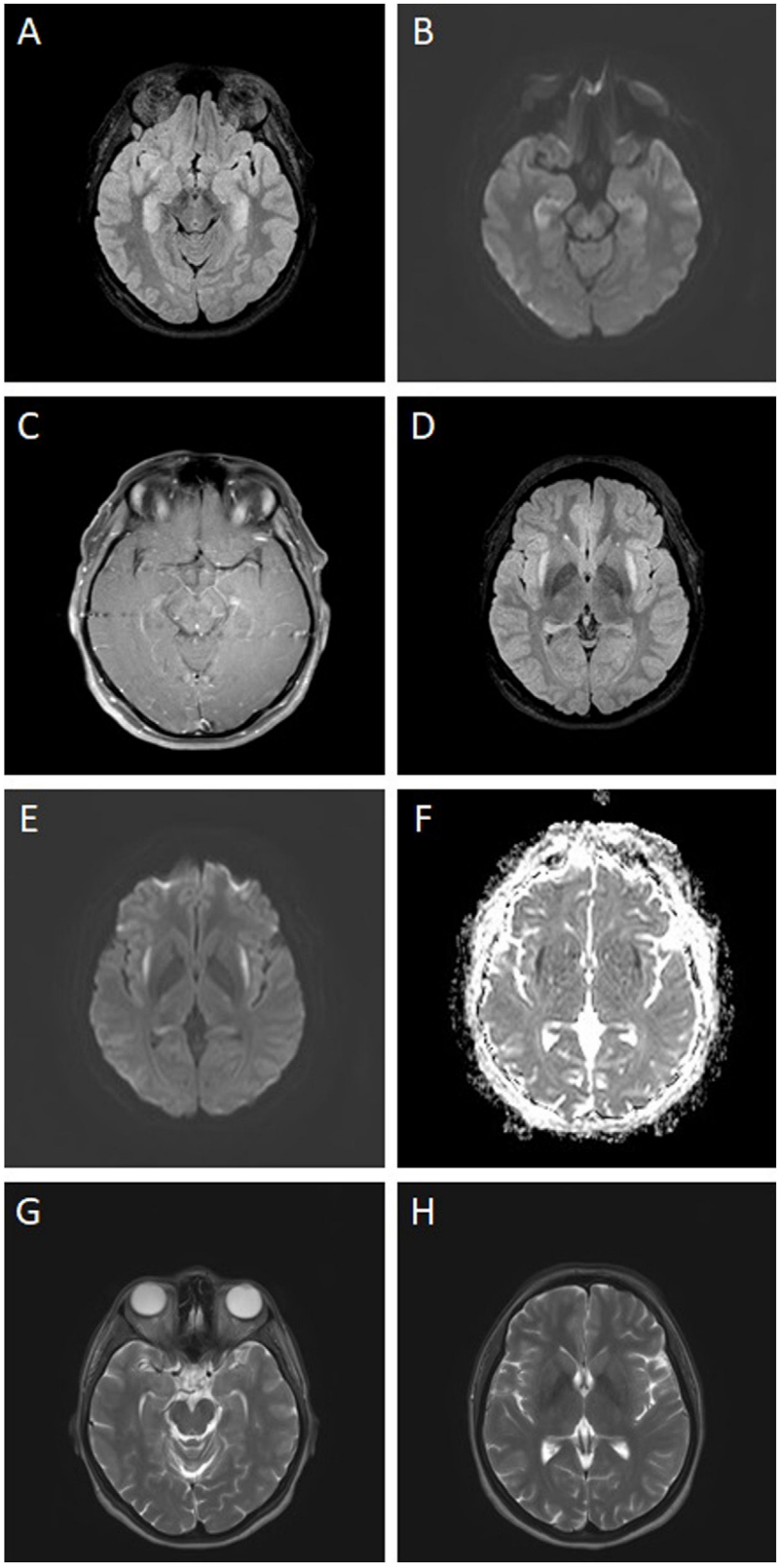


Figure 1 Contrast-enhanced brain MRI study performed at disease onset, showing bilateral hippocampal hyperintensities on T2/FLAIR sequences (A), restricted diffusion (B), and lack of contrast uptake (C). The study also revealed hyperintense lesions in the external capsules on T2/FLAIR sequences (D), with restricted diffusion (hyperintense on diffusion-weighted imaging [E] and hypointense on the apparent diffusion coefficient map [F]). Contrast-enhanced brain MRI study performed at 8 months of follow-up, showing resolution of T2 hyperintensities in the hippocampi (G) and external capsules (H).

Table 1 Results from blood and cerebrospinal fluid laboratory analyses.

Parameter	Results	Reference values
CSF opening pressure	24 cm H_2O	6—25 cm H_2O
Leukocytes	10 600/μL	4500—11 000/μL
Neutrophils	5430/μL (51.2%)	1500—8000/μL
Lymphocytes	3580/μL (33.8%)	1500—4000/μL
Haemoglobin	13 g/dL	12—16 g/dL
Platelets	10 600/μL	150 000—450 000/μL
Potassium	3.8 mmol/L	3.5—5.1 mmol/L
Sodium	138 mmol/L	136—145 mmol/L
C-reactive protein	0.62 mg/dL	0.4—1 mg/dL
CSF cytochemical findings		
- Proteins	21.5 mg/dL	8—32 mg/dL
- Glucose	65 mg/dL	40—70 mg/dL
- pH	7.37	
- Leukocytes	0/mL	0—8/mL
- Erythrocytes	0/mL	0—10/mL
- Gram stain	No microorganisms	
- Culture	Negative	
- India ink stain	Negative	
- KOH test	Negative	
- Cryptococcal antigen	Negative	
- FilmArray	Negative	
HIV	Negative	
VDRL test	Non-reactive	
TSH	2.166 μU/mL	0.55—4.78 μU/mL
anti-ANA	Negative	
anti-ENA (anti-Sm, anti-RNP, anti-Ro, anti-La)	Negative	
Folic acid	9.9 ng/mL	> 5.38 ng/mL
Vitamin B_{12}	463	211—911 pg/mL
Autoimmune encephalitis panel (NMDA, GABA, LGI1, CASPR2, AMPA, DPPX)	Negative	

The hypothesis of postvaccinal encephalitis in patients receiving mRNA vaccines is based on the fact that antigens are recognised as potential pathogens, leading to the synthesis and release of interleukins (IL-1, IL-6), tumour necrosis factor-α (TNF-α), and prostaglandin E2, mimicking the response to natural infection. Stimulation of the immune system triggers a series of events, including phagocytosis, release of inflammatory mediators, complement activation, and cell recruitment, which may cause neuroinflammation secondary to microglial activation, depending on the individual's immunogenetic background and innate immune memory.[8,10]

Our patient's history and response to treatment are consistent with previous reports of encephalitis following COVID-19 vaccination, in which no infection or autoimmunity was observed. Although outcomes are generally favourable, our patient presented sequelae.

Conclusion

Despite the temporal connection between our patient's symptoms and COVID-19 vaccination, we cannot be certain of a causal association. This type of adverse reaction to COVID-19 vaccines is rare, and the benefits of mass vaccination campaigns outweigh the risks. Longer follow-up is needed to determine whether COVID-19 vaccines may cause neurological disorders.

Ethical considerations

Our patient gave written informed consent to the publication of images and clinical data.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Ellul M, Solomon T. Acute encephalitis - diagnosis and management. Clin Med. 2018;18:155—9, http://dx.doi.org/10.7861/clinmedicine.18-2-155.
2. Anand P, Stahel VP. Review the safety of Covid-19 mRNA vaccines: a review. Patient Saf Surg. 2021;15:20, http://dx.doi.org/10.1186/s13037-021-00291-9.
3. Lu L, Xiong W, Mu J, Zhang Q, Zhang H, Zou L, et al. The potential neurological effect of the COVID-19 vaccines: a review. Acta Neurol Scand. 2021;144:3—12, http://dx.doi.org/10.1111/ane.13417.

4. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15:391—404, http://dx.doi.org/10.1016/S1474-4422(15)00401-9.
5. Zlotnik Y, Gadoth A, Abu-Salameh I, Horev A, Novoa R, Ifergane G. Case report: anti-LGI1 encephalitis following COVID-19 vaccination. Front Immunol. 2022;12:813487, http://dx.doi.org/10.3389/fimmu.2021.813487.
6. Ghosh R, Dubey S, Roy D, Mandal A, Naga D, Benito-León J. Focal onset non-motor seizure following COVID-19 vaccination: a mere coincidence? Diabet Metab Syndr. 2021:1023—4, http://dx.doi.org/10.1016/j.dsx.2021.05.003.
7. Al-Mashdali AF, Ata YM, Sadik N. Post-COVID-19 vaccine acute hyperactive encephalopathy with dramatic response to methylprednisolone: a case report. Ann Med Surg. 2021;69:102803, http://dx.doi.org/10.1016/j.amsu.2021.102803.
8. Zuhorn F, Graf T, Klingebiel R, Schäbitz W-R, Rogalewski A. Postvaccinal encephalitis after ChAdOx1 nCov-19. Ann Neurol. 2021;90:506—11, http://dx.doi.org/10.1002/ana.26182.
9. Liu BD, Ugolini C, Jha P. Two cases of post-moderna COVID-19 vaccine encephalopathy associated with nonconvulsive status epilepticus. Cureus. 2021, http://dx.doi.org/10.7759/cureus.16172, e16172.
10. Giannotta G, Giannotta N. Vaccines and neuroinflammation. Int J Pub Heal Safe. 2018;3:2.

Reydmar Lopez-Gonzalez[a,b,*],
Maria Alejandra Otalvaro-Rendon[a,c],
Laura Quintero-Gutierrez[a,d]

[a] *Hospital San Vicente Fundacion Rionegro, Medellin, Colombia*
[b] *Universidad de Antioquia, Medellín, Colombia*
[c] *Fundación Universitaria San Martín, Medellín, Colombia*
[d] *Universidad Pontificia Bolivariana, Medellín, Colombia*

[*] Corresponding author.
E-mail address: reydmar.lopez@sanvicentefundacion.com (R. Lopez-Gonzalez).