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LETTER TO THE EDITORS

# Anti-LGI1 encephalitis following COVID-19 vaccination: a case series

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Dear Sirs,

Anti-LGI1 encephalitis is a rare homogeneous clinical syndrome, showing early faciobrachial dystonic seizures (FBDS) and other focal seizures, associated with cognitive and behavioral disturbances in the context of limbic encephalitis [1].

COVID-19 is an ongoing pandemic, for which the Italian Ministry of Health adopted a massive vaccination campaign starting January 2021 (https://salute.gov.it). The most frequently employed vaccines are based on mRNA (BNT122b2 and CX-024414) or viral vectors (ChAdOx1-S and Ad26.COV2.S). A few patients presenting with autoimmune encephalitis following COVID-19 vaccinations were reported, including a case diagnosed with anti-LGI1 encephalitis [2–4].

Herein, we report a case series of four Italian patients who developed anti-LGI1 encephalitis temporally associated with prior different COVID-19 vaccinations.

The demographic and clinical characteristics of the four patients are summarized in Table 1. The mean age was 56 years (18–66 years), and two were females. Disease onset occurred after a mean of 13 days (6–23 days) following COVID-19 vaccination (3 mRNA vaccines, 1 viral vector vaccine). Patients presented with FBDS ($n=2$) (Video), other focal seizures ($n=2$), behavioral disturbances ($n=3$), cognitive impairment ($n=2$), and hypersomnia ($n=1$), and hyponatremia was detected in two cases. EEG revealed epileptiform and/or slow abnormalities in the fronto-temporal region in all patients, while MRI revealed T2/FLAIR hyper-intensity of the mesial temporal lobes in two cases (Fig. 1). CSF analysis was unremarkable in three patients and traumatic in case 2. Serum and CSF were analyzed with a standardized cell-based assay (CBA) kit (Euroimmun) for detecting antibodies against neuronal surface antigens (LGI1, CASPR2, NMDAR, AMPAR, $GABA_BR$, and DPPX). The diagnosis of anti-LGI1 encephalitis was based on anti-LGI1 positivity in serum ($n=4$) and CSF ($n=2$) and consistent anatomo-electro-clinical features. Patients were treated with anti-seizure medications ($n=4$), steroid pulse therapy ($n=4$), and intravenous immunoglobulin ($n=1$), resulting in clinical recovery in all subjects. Case 1 died eight months after disease onset due to vanishing bile duct syndrome.

Three patients were living in the metropolitan area of Bologna, northern Italy, with approximately 1.000.000 inhabitants, where only one laboratory performs autoimmune anti-neuronal antibodies testing. In the last year, these were the only patients who tested positive for anti-LGI1 antibodies. During the previous year, only one patient with new-onset anti-LGI1 encephalitis was detected. Informed written consent was obtained for all patients but case 1, who is deceased; ethical committee approval was not required for this study.

We described four patients who developed anti-LGI1 encephalitis with classic clinical features following different

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**Table 1** Patients' demographic and clinical features

| | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Age (years), sex | 73, female | 66, male | 18, female | 66, male |
| City | Rimini | Bologna | Bologna | Bologna |
| Past medical history | Unremarkable | Hypertension | Unremarkable | Polyallergic |
| Previous COVID-19 infection | No | No | No | No |
| Vaccination | Viral vector (ChAdOx1-S), 1st dose | mRNA (BNT62b2) 2nd dose | mRNA (CX-024414) 3rd dose | mRNA (BNT62b2) 2nd dose |
| Days from vaccination to disease onset | 14 days | 6 days | 23 days | 9 days |
| Clinical features | FBDS, behavioral disturbances | Cognitive impairment, behavioral disturbances | Focal seizures, short-term memory impairment | FBDS, focal seizures, behavioral disturbances, hypersomnia |
| Hyponatremia | Yes | No | No | Yes |
| EEG | Bilateral fronto-temporal sharp waves; electrographic temporal seizures | Right fronto-temporal sharp waves; electrographic temporal seizures | Right fronto-temporal sharp waves | Bilateral fronto-temporal epileptiform discharges |
| Brain MRI | Bilateral mesial temporal lobe T2-weighted hyper-intensity with swelling in the left hippocampus | Bilateral mesial temporal lobe T2-weighted hyper-intensity with swelling and contrast enhancement in the right amygdala and hippocampus | Normal | Normal |
| CSF analysis | Normal | Traumatic (protein 83 mg/dl, 11,000/cc erythrocytes, 12/cc leukocytes) | Normal | Normal |
| Anti-LGI1 positivity | Serum and CSF | Serum | Serum | Serum and CSF |
| Immunotherapy | Methylprednisolone 1000 mg for 5 days, subsequent oral steroid tapering | Methylprednisolone 1000 mg for 5 days, subsequent oral steroid tapering | Methylprednisolone 1000 mg for 5 days, subsequent oral steroid tapering | Methylprednisolone 500 mg for 5 days, IVIg 0.4/kg/day for 5 days |
| Other therapies | Valproate | Levetiracetam | Lacosamide levetiracetam | Lacosamide levetiracetam |
| Outcome (time at last follow-up) | Seizure-free, normal mental status<br>Died after 8 months due to vanishing bile duct syndrome | Normal mental status (7 months) | Seizure-free, normal mental status (3 months) | Seizure-free, normal mental status (3 months) |

FBDS, faciobrachial dystonic seizures; IVIg, intravenous immunoglobulin

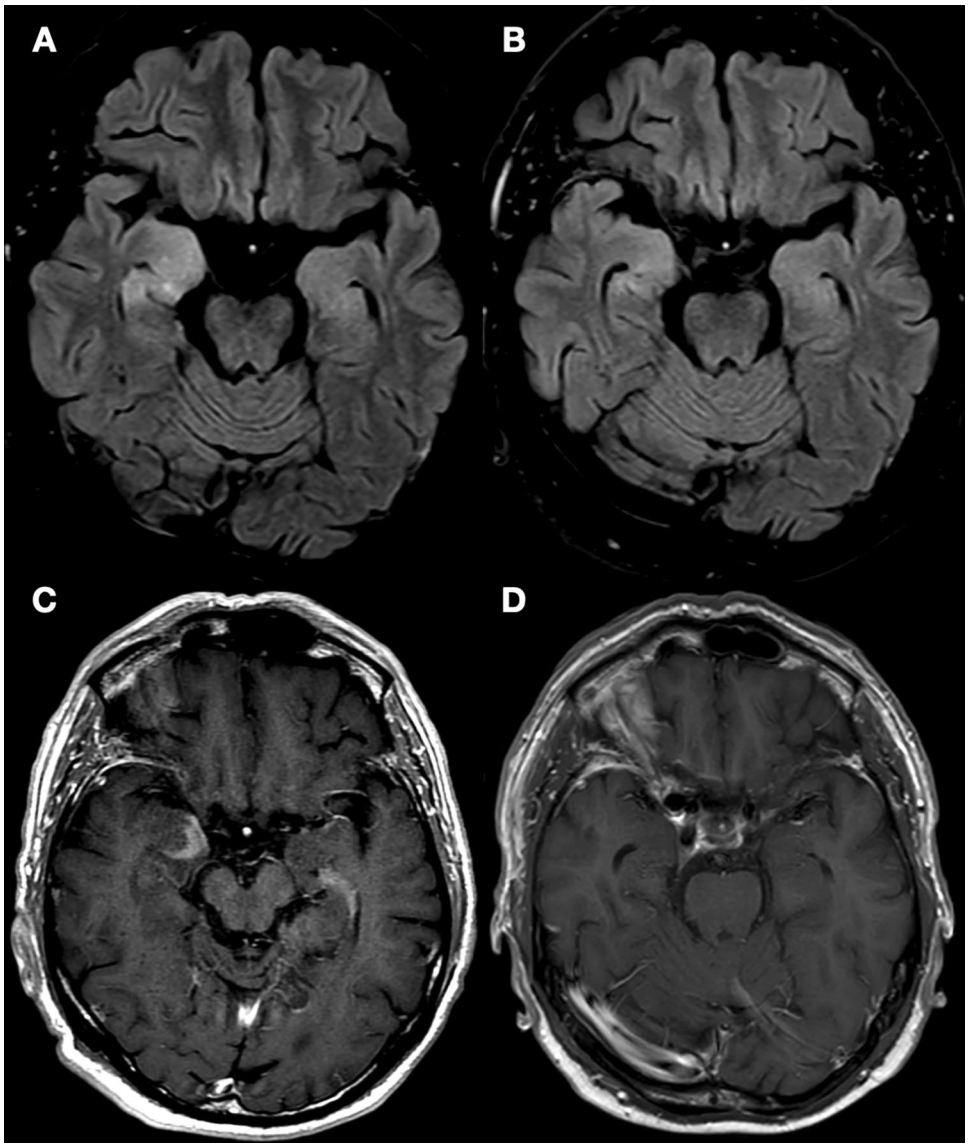


**Fig. 1** Brain MRI in Case 2. **A** Axial fluid-attenuated inversion recovery (FLAIR) images showed a right-predominant hyper-intensity of the mesial temporal lobes and swelling of the right amygdala. **B** Post-contrast T1-weighted sequences showed enhancement in the right amygdala. After 5 months from the introduction of steroid therapy, a control brain MRI shows a significant reduction of mesial temporal lobes hyper-intensity in FLAIR sequences (**C**) and a complete resolution of pathological contrast enhancement (**D**)

COVID-19 vaccinations. The mean time from vaccination to disease onset was approximately 2 weeks, as in the only previously reported case [4]. Anti-LGI1 encephalitis represents an extremely rare disease, with a reported annual incidence ranging from 0.4/million (95% CI 0.3–0.5) in a French study [5] to 0.83/million (95% CI 0.45–1.40) in a nationwide Dutch study [1]. To our knowledge, it has not been previously associated with any other vaccination. Considering the population of Bologna, the crude incidence of anti-LGI1 encephalitis during the last year was 3/million (95% CI 0.6–8.8), with positive anti-LGI1 testing detected only in the three herein reported cases from Bologna. On the other hand, in the same area, there was just one patient with new-onset anti-LGI1 encephalitis during the previous year. We did not observe any further cases of autoimmune encephalitis following COVID-19 vaccinations. Even though this epidemiological data should be considered cautiously, the presence of a strict temporal relationship between disease onset and vaccination lets us hypothesize that anti-LGI1 encephalitis may represent a rare complication of COVID-19 vaccination. Four patients developed anti-LGI1 encephalitis after the vaccination with two different mRNA vaccines (three cases from this report, one previously reported [4]), while case 1 was administered a viral vector vaccine; therefore, should this association be confirmed, the trigger would not be a specific COVID-19 vaccine, but rather the immune response generated by the encoded SARS-CoV-2 spike protein or by shared adjuvants [6]. This might speculatively happen due to molecular mimicry and immune cross reaction, a process by which several other vaccines have been suspected to trigger autoimmunity, likely in genetically predisposed subjects [7]. However, as for other reported neurological and systemic autoimmune manifestations, whether the association of anti-LGI1 encephalitis with COVID-19

vaccines is coincidental or causal remains to be definitely determined [2–4, 6]. Additionally, the extraordinary benefits of mass COVID-19 vaccination in preventing disease morbidity and mortality surely outweigh the risk of developing autoimmune disorders in general and anti-LGI1 encephalitis specifically, especially considering the good clinical response of this condition to immunotherapies [1].

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## Declarations

**Conflicts of interest** The authors declare that they have no competing interests.

**Consent for publication** Informed written consent was obtained for all patients but case 1, who is deceased.

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