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Autoimmune Encephalitis with VGKC and Anti-LGI1 Antibodies after Asymptomatic COVID-19: A Case Report.

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ABSTRACT

Objectives: To report a patient diagnosed with asymptomatic COVID-19 infection who acutely presented with autoimmune encephalitis involving both anti-LGI-1 and anti-VGKC channels.

Methods: Patient data were obtained from medical records from the Torrecárdenas University Hospital, Almeria, Spain.

The patient was a 34-year-old female who experienced a generalized tonic-clonic seizure and psychomotor restlessness despite being asymptomatic for respiratory symptoms but having confirmed COVID-19 through PCR testing. Serum tests revealed the presence of anti-Voltage-Gated Potassium Channel antibodies (VGKC) and anti-Leucine-Rich Glioma-Inactivated 1 (LGI1) antibodies, while Cerebrospinal Fluid (CSF) analysis detected anti-VGKC antibodies. Magnetic Resonance Imaging (MRI) demonstrated bilateral medial temporal lobe signal changes with lesions in the claustrum and basal ganglia, typically associated with limbic encephalitis in cases with positive anti-VGKC and anti-LGI1 antibodies. Furthermore, the patient exhibited cognitive dysfunction, mental disorders, and hyponatremia, all of which are common features of anti-LGI1 encephalitis. The patient was diagnosed with autoimmune encephalitis involving both anti-LGI-1 and anti-VGKC channels. The patient displayed significant clinical improvement and decreased antibody titers following treatment. Consequently, we propose that double-positive antibodies played a pivotal role in this case.

Discussion: Our case raises awareness of the occurrence of rare autoimmune encephalitis following asymptomatic COVID-19 infection.

Keywords: Autoimmune encephalitis; VGKC; LGI1; COVID-19

BACKGROUND

The COVID-19 disease originated in Wuhan, China, in December 2019, and posed a significant threat to public health worldwide. The major clinical manifestations of COVID-19 infection are pulmonary, however, since the initial outbreak; non-respiratory manifestations have been reported across all age groups [1-3]. There are an increasing number of reports concerning COVID-19-related neurological complications and manifestations. These conditions may result from direct aggression on the Central Nervous System (CNS) or paraviral/post-viral autoimmune processes occurring during the infection [6-8].

Anti-VGKC has been implicated in various neuronal hyper-excitability disorders including Issacs' syndrome, Morvan's syndrome, and limbic encephalitis. Unusual symptoms such as chorea and chronic pain syndrome have also been reported.

Patients with limbic encephalitis and anti-VGKC antibodies typically exhibit medial temporal lobe signal changes, although lesions in the claustrum and basal ganglia have also been reported [9]. It is now understood that anti-VGKC antibodies are not directed against the VGKC itself, but against other cell surface antigens that are part of the VGKC complex; the various known antigenic targets include LG1, contactin-associated protein 2, and contactin 2 [5]. Additional undiscovered targets may be responsible for those who have anti-VGKC antibodies but test negative for LG1, contactin-associated protein 2, and contactin 2.

Anti–LGI1 encephalitis was first described in 2010. It is the second most frequent style of autoimmune encephalitis, featuring limbic encephalitis, cognitive dysfunction, mental disorders, fasciobrachial dystonic seizures, and hyponatremia [10].

We present the case of a 34-year-old female diagnosed with asymptomatic COVID-19 infection who acutely presented with autoimmune encephalitis involving both anti-LGI-1 and anti-VGKC channels, thereby expanding our understanding of the clinical spectrum of encephalitis after COVID-19.

METHODS

Patient data were obtained from medical records from the Torrecárdenas University Hospital, Almeria, Spain. We used the CARE checklist when writing our report [11].

Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from the patient participating in this clinical report.

Data availability

The data supporting the findings of this study are available within the article.

RESULTS

A female patient in her early 30s was admitted to the emergency department due to recurrent episodes of tonic-clonic seizures in the last hours. Four days before the onset of symptoms, SARS-CoV-2 PCR was positive in a nasopharyngeal swab.

Upon admission, the patient was afebrile, and the neurological examination was normal. The routine blood test parameters, including hemogram and clotting, renal and liver function tests were also normal. Baseline brain Computed Tomography (CT) was performed, which showed no evidence of acute lesions (Figure 1A). The patient was treated acutely with levetiracetam, and after 24 hours of observation, the patient was discharged from the hospital in the absence of new epileptic seizures.

One month later, the patient returned to the emergency department due to worsening neurologic symptoms which consisted of insomnia, nervousness, and behavioral disorders. Levetiracetam was discontinued and she was treated with lacosamide.

The next day (24 hours after admission) the patient presented a decline in the state of consciousness. The cranial nerve examination was normal, with no signs of limb weakness, ataxia, pyramidal or extrapyramidal signs, or gait abnormalities. Blood analysis revealed only hyponatremia with a serum sodium level of 113 mmol/L (normal range, 135–155 mmol/L). The patient was diagnosed with a syndrome of inappropriate antidiuretic hormone secretion.

A new brain CT scan revealed many hypodense areas affecting several regions' white matter-gray matter interface (Figure 1B). These lesions were not present in the previous CT. They were associated with a mass effect on the frontal horn of the right lateral ventricle, which was obliterated. Following intravenous contrast administration, no pathological enhancement was observed.

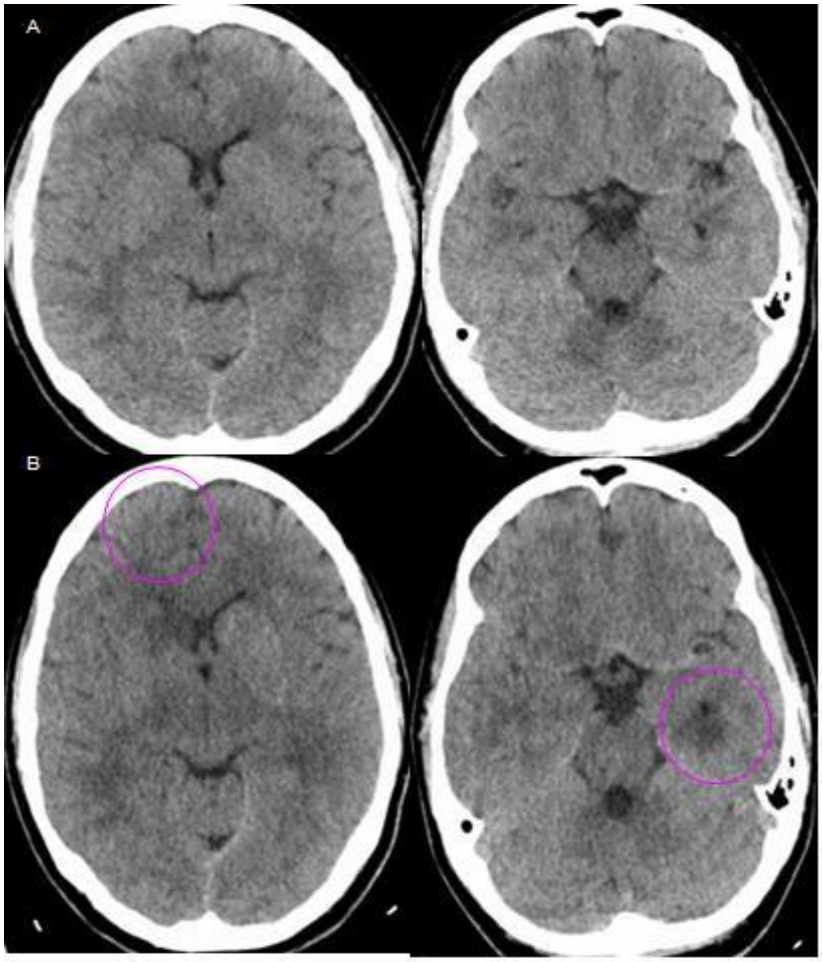

Figure 1: (A) First unenhanced CT imaging of the brain showed no evidence of acute lesions. (B). Second unenhanced CT shows many hypodense areas that affect the white matter-gray matter of several regions (pink circles), not present in the previous CT scan.

CT: Computed Tomography.

A thoracic-abdominopelvic CT scan was conducted to rule out neoplastic disease, but it did not reveal any abnormalities.

Brain MRI revealed non-enhancing, bilateral hyperintensities on T2 and fluid-attenuated inversion recovery (FLAIR) sequences in the mesial temporal lobes, hippocampi, right cingulate, insula, caudate, and anterior putamen, along with scattered subcortical white matter hyperintensities (Figure 2A) no microhemorrhages were observed on T2* imaging. The diffusion-weighted image (DWI) showed no restriction. The findings were consistent with limbic encephalitis.

Whole-body 18F-Fludeoxyglucose PET/CT revealed several intracerebral hypermetabolic foci, without evidence of local foci of hypermetabolism in other areas of the body suggestive of macroscopic tumor activity.

Neuroimmunology tests detected positive anti-VGKC and anti-LGI1 antibodies in the serum, while anti-VGKC antibodies were also positive in CSF.

CSF PCR yielded negative results for streptococci, meningococcus, haemophilus, listeria, Escherichia coli, covid-19, human herpesvirus 1, 2, and 6, enteroviruses, parechovirus, cytomegalovirus, varicella-zoster virus, and cryptococcus. Additionally, human immunodeficiency virus and treponemal serology tests were negative.

After being diagnosed with autoimmune encephalitis caused by post-COVID autoantibodies, the patient was treated with corticosteroids, and symptoms were gradually resolved. The patient was discharged from the hospital with no symptoms.

A 2-month follow-up brain MRI revealed complete resolution of the previous lesions (Figure 2-B).

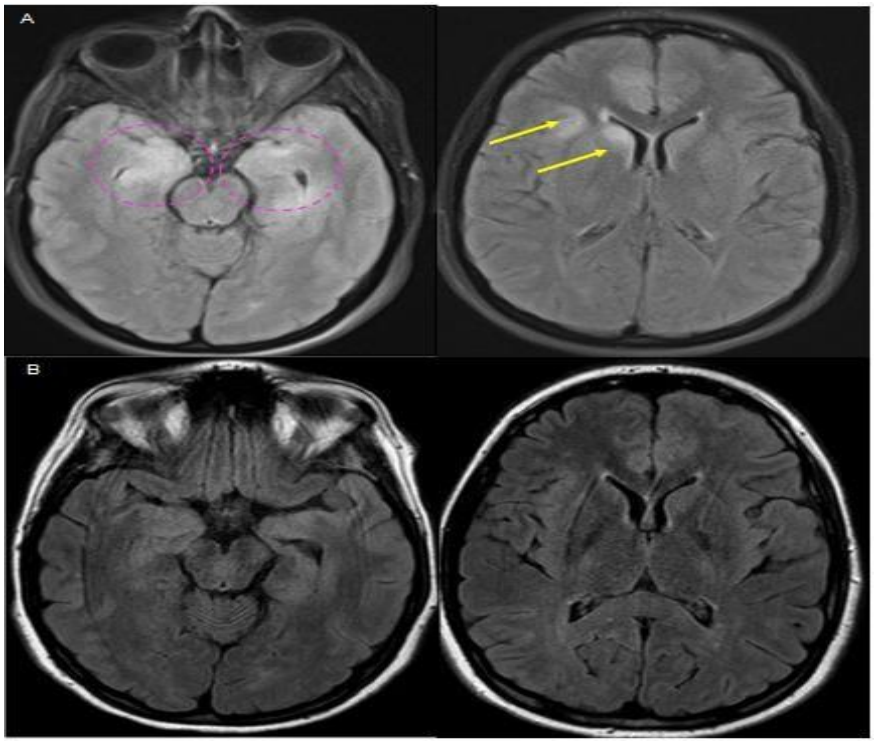

Figure 2: (A) MRI of the brain shows a bilateral mesial temporal lobe increased T2-FLAIR sequence signal extending along the hippocampal head (pink circles), added to hyperintensities in the right cingulate, insula, and caudate (yellow arrows). (B) MRI performed 2 months after being discharged from the hospital showing complete resolution of previous lesions.

MRI: Magnetic Resonance Imaging; FLAIR: Fluid-Attenuated Inversion Recovery.

DISCUSSION

Our patient presented with generalized tonic-clonic seizure and psychomotor restlessness during respiratory asymptomatic COVID-19 disease which was confirmed by PCR testing. Anti-VGKC antibodies and anti-LGI1 antibodies were positive in serum, and anti-VGKC was also detected in CSF. Furthermore, she presented with cognitive dysfunction, mental disorders, and hyponatremia which are common in cases of anti-LGI1 encephalitis.

Our patient exhibited medial temporal lobe MRI signal changes along with lesions in the claustrum and basal ganglia, which are typically observed in cases of limbic encephalitis associated with anti-VGKC and anti-LGI1 antibodies. The patient was finally diagnosed with anti-LGI-1 and anti-VGKC autoimmune encephalitis.

Following treatment, the patient demonstrated clinical improvement with a decline in antibody titers. Therefore, we consider double-positive antibodies to be the "culprit" antibodies.

Neurological manifestations of COVID-19 appear to be more common in patients with severe respiratory disease [12]. However, our patient had minimal respiratory involvement. This case illustrates that neurological manifestations associated with COVID-19 infection are not necessarily linked to critical illness.

Among patients who presented autoimmune encephalitis after COVID-19, only a few are positive cases for IgG and IgM in CSF for SARS-CoV-2 [13,14]. In The present case, next-generation sequencing for pathogen detection in CSF yielded a negative result. It was speculated that the presence of the virus in CSF may be transient.

Many cases of autoimmune encephalitis with different antibodies (single or combination of two antibodies/co-expression) following COVID-19 have been reported, we identified a total of 25 reported cases (summary Table 1). However, autoimmune encephalitis with both anti-VGKC and anti-LGI1 receptor antibodies following COVID-19 has not been reported before. Different antineuronal antibodies are associated with distinct subtypes of autoimmune encephalitis. When encountered with overlapping of multiple antibodies, it is important to identify coexisting antibodies or culprit antibodies.

Additionally, we must consider that several major neurological complications, despite their unproven causality, have been reported since the introduction of the COVID-19 vaccine 4. We have identified a total of 7 reported cases (see summary in Table 2).

The underlying mechanisms of autoimmune encephalitis after COVID-19 infection have not yet been elucidated. The most plausible mechanism involves molecular mimicry in response to the COVID-19 infection. Another possible mechanism is the overproduction of inflammatory cytokines, known as cytokine storm after SARS-CoV-2 infection. The third possible scenario is the direct invasion of the virus into the CNS. However, further studies are required to identify the precise mechanism of how such virus effects lead to CNS autoimmunity.

In conclusion, this case serves to raise awareness of the rare occurrence of autoimmune encephalitis following COVID-19, emphasizing the importance of timely diagnosis, and treatment to achieve a favorable prognosis.

Table 1: Overview of published case reports of autoimmune encephalitis with positive pathological antibody secondary to COVID-19 infection.

Reported cases of anti-NMDAR encephalitis associated with COVID-19 infection							
Author	Year	Country	Total number of cases	Age	Gender	Antibody	Imaging findings
Panariello et al.	2020	Italy	1	23	Male	NMDAR	-Brain CT scan: normal
Alvarez Bravo et al.	2020	Spain	1	30	Female	NMDAR	-Brain CT scan: normal -Brain MRI: hyperintensities

							in the hippocampus on FLAIR sequence.
Allahyari et al.	2021	Iran	1	18	Female	NMDAR	-Brain CT scan: generalized brain edema.
McHattie et al.	2021	UK	1	53	Female	NMDAR	-Brain MRI area of hyperintensity on the FLAIR sequences in the amygdala and in the putamen.
Monti et al.	2020	Italy	1	50	Male	NMDAR	-Brain MRI: normal
Moideen et al.	2020	India, UK	1	17	Male	NMDAR	-Brain MRI: normal
Burr et al.	2021	USA	1	2	Female	NMDAR	-Brain MRI: normal
Sanchez-Morals et al.	2021	Mexico	1	14	Male	NMDAR	-Brain MRI: normal
Sarigecili et al.	2021	Turkey	1	7	Male	NMDAR	-Brain MRI: normal
Autoimmune encephalitis (anti-NMDAR and anti-glutamic acid decarboxylase 65 co-expression)							
Valadez-Calderon et al.	2022	Mexico	1	28	Male	NMDAR and GAD65	-Brain MRI: FLAIR and DWI showed hyperintensities in the bilateral anterior cingulate cortex and bilateral temporal lobes.
Anti NMDA receptor antibody associated ADEM in patient with COVID-19							
Naidu et al.	2023	South Africa	1	50	Female	NMDA	Cytotoxic MRI changes in the brain and spinal cord. The bilateral symmetric involvement of the corticospinal tract on MRI was considered unusual.
Reported cases of encephalitis with anti-MOG antibodies associated with Covid-19.							
De Ruijter et al.	2020	Netherlands	1	15	Male	MOG	-Brain and orbits MRI: bilateral optic neuritis.
Zhou et al.	2020	USA	1	26	Male	MOG	-Brain MRI: bilateral optic neuritis. Rest of brain and spine were normal.

							-MRI of the spine: patchy T2 hyperintensities associated with mild central thickening and gadolinium enhancement.
Sawalha et al.	2020	USA	1	44	Male	MOG	-Brain MRI: bilateral optic neuritis. Rest of brain and spine were normal.
Zoric et al.	2021	Serbia	1	63	Male	MOG	-Brain MRI: Normal appearing orbits and optic nerves.
Khan et al.	2021	India	1	11	Male	MOG	-Brain MRI: bilateral optic neuritis. Rest of brain and spine were normal.
Kogure et al.	2021	Japan	1	47	Male	MOG	-Brain MRI: bilateral optic neuritis. Rest of brain and spine were normal.
Durovic et al.	2021	Greece	1	22	Male	MOG	-Brain MRI: multiple T2 and FLAIR hyperintensities, predominantly cortically, without any contrast enhancement
Peters J et al.	2021	USA	1	23	Male	MOG	-First brain MRI: normal -Second brain MRI: diffuse cortical hyperintensity in FLAIR sequence, with leptomeningeal enhancement.
Tsouris Z et al.	2022	Greece	1	59	Female	MOG	-Brain MRI: bilateral optic neuritis and high-intensity lesions in the pons.
Autoimmune encephalitis LGI1 and CASPR2 associated with COVID 19: Morvan syndrome							
Kilic et al.	2021	Turkey	1	3	Female	LGI1 and	-Brain MRI:

						CASPR2	normal -Spine MRI: revealed diffuse thickening and enhancement of cauda equina nerve roots.
Anti-IgLON5 disease and anti-LGI1 encephalitis following COVID-19							
Li Y et al.	2023	China	1	40	Male	IgLON5 and LGI1	-Brain MRI: T2 and FLAIR hyperintensities in the basal ganglia. -PET-CT: hypermetabolism level of bilateral caudate nucleus, putamen, and temporal lobes.
Bickerstaff encephalitis with anti-GQ1b IgG antibodies after COVID-19							
Ayuso et al.	2020	Spain	1	20	Female	GQ1b IgG	Brain MRI: T2 and FLAIR hyperintensities in the flocculus and the nodulus with weak restriction of the nodulus on DWI, and lineal gadolinium enhancement of dorsal medulla.
Kimura et al.	2021	Japan	1	68	Female	GQ1b IgG	MRI-brain: normal
Brain stem encephalitis with Anti-GAD65 as a complication of COVID-19							
Shamier et al.	2023	Netherlands	1	51	Female	GAD65	MRI-brain: normal
Overview of published case reports of autoimmune encephalitis with positive pathological antibody after vaccination against COVID-19:							
Zlotnick et al.	2022	Israel	1	48	Male	LGI1	-Brain MRI: hyperintense signal on both medial temporal lobes including the parahippocampal gyrus on FLAIR and DWI.
Lewis et al.	2023	USA	1	56	Male	LGI1	-Brain MRI: FLAIR abnormal signal involving bilateral mesial temporal lobes, left temporal

							pole, and left insula.
Asioli et al.	2022	Italy	4	18,66,66,73	2 female 2 male	LGI1	-Brian MRI: FLAIR hyper-intensity of the mesial temporal lobes in two cases
Flanney et al.	2021	USA	1	20	Female	NMDA	-Brain CT scan: normal -Brain MRI: normal

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