

A Case of Antiglutamic Acid Decarboxylase and Voltage-Gated Potassium Channel Antibody-Associated Limbic Encephalitis With Temporal Lobe Epilepsy

Pınar Gelener¹ , Sevda Diker² , Fırat Keskiner³ 

¹Department of Neurology, University of Kyrenia Faculty of Medicine, Kyrenia, Cyprus

²Department of Neurology, Cyprus International University Faculty of Medicine, Nicosia, Cyprus

³Euromed Imaging Center, Radiology Clinic, İstanbul, Turkey

ORCID iDs of the authors: P.G. 0000-0002-8681-9847; S.D. 0000-0002-8944-0672; F.K. 0000-0002-1277-2257.

Cite this article as: Gelener P, Diker S, Keskiner F. A Case of Antiglutamic Acid Decarboxylase and Voltage-Gated Potassium Channel Antibody-Associated Limbic Encephalitis With Temporal Lobe Epilepsy. *Cyprus J Med Sci* 2021; 6(1): 99-102.

In this report, we present a patient with limbic encephalitis and related temporal lobe epilepsy with antibodies (Abs) against voltage-gated potassium channels complex and glutamic acid decarboxylase. The diagnosis was confirmed after the occurrence of adult-onset partial temporal lobe immune epilepsy accompanying increased T2 signal abnormalities in limbic structures, confirmed by magnetic resonance imaging and positive Abs.

Keywords: Limbic encephalitis, autoimmune epilepsy, anti-GAD antibody, VGKC antibody

INTRODUCTION

Limbic encephalitis (LE) is an autoimmune or paraneoplastic disease. Autoimmune LE is a challenging diagnosis because it is not always included in the typical paraneoplastic/autoimmune panels (1). Autoimmune LE is an immune-mediated inflammation of the limbic system, including the hippocampus, thalamus, hypothalamus, and amygdala (2). Neuropsychiatric symptoms and new-onset seizures are often the presenting symptoms owing to autoimmune damage to limbic structures (3). Specific autoantibodies against neuronal antigens have been defined thus far. The cell surface antigens are the most frequently involved: voltage-gated potassium channel (VGKC) complex is one of them (4).

VGKCs play an important role in the regulation of neuronal excitability controlling cell membrane potential, and the mutations of potassium channel genes are associated with the disturbances of neuronal firing in humans (5).

Anti-glutamic acid decarboxylase (GAD) antibodies (Abs) function against the GAD enzyme, which is essential in the formation of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter found in the brain. The absence or low levels of GABA causes patients to exhibit motor and cognitive symptoms (6):-

The anti-GAD Ab is found in various diseases, including type I diabetes mellitus (DM), and in neurological syndromes, such as stiff person syndrome, paraneoplastic stiff person syndrome, Miller Fisher syndrome, limbic encephalopathy, cerebellar ataxia, eye movement disorders, and epilepsy (6, 7). It affects the medial temporal lobe of the brain, occasionally involving hippocampal atrophy as well (1).

Both VGKC complex and GAD Abs have thus far been implicated in some types of idiopathic and symptomatic epilepsies and refractory seizures (5, 7). Although both the paraneoplastic and nonparaneoplastic LE related to GAD and VGKC complex Abs have been reported, paraneoplastic forms are rare (1, 7). For the most part, the LE associated with VGKC complex and GAD Abs is an immune form of encephalitis responsive to immunotherapy (8):-

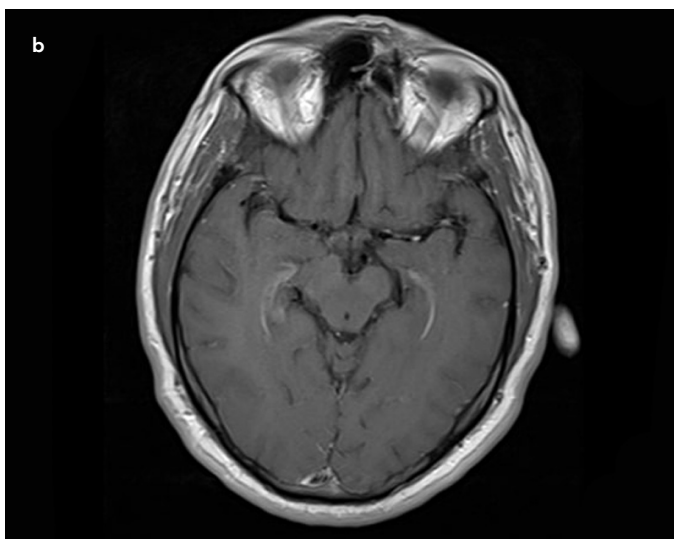
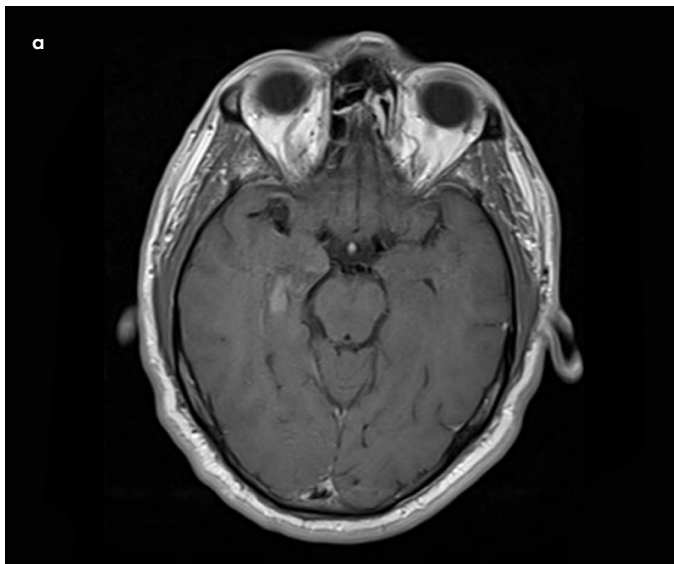


Figure 1. a, b. T1-weighted axial MRI showing hyperintense lesion with contrast enhancement in the right temporal region at disease onset. MRI: magnetic resonance imaging.

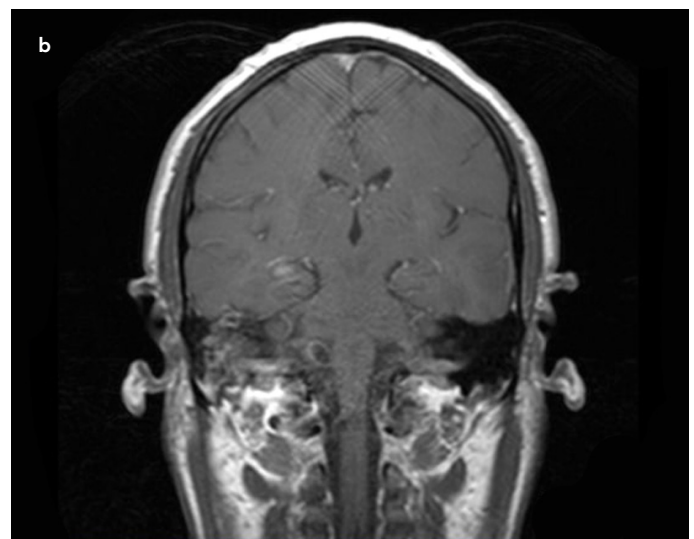
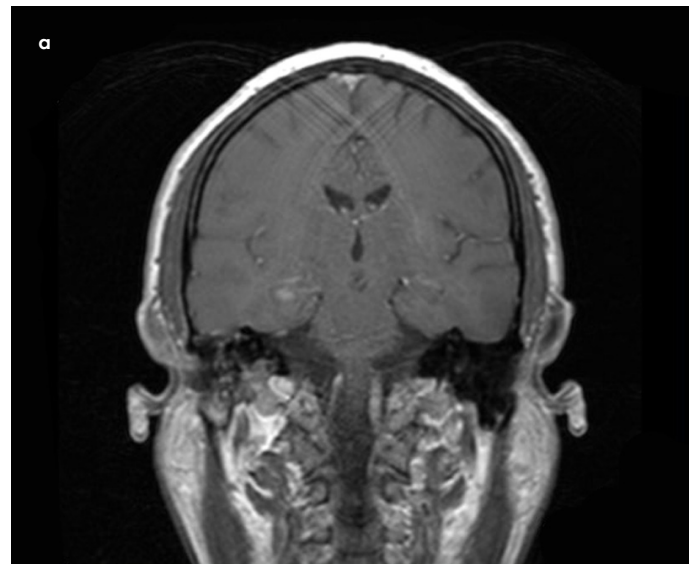


Figure 2. a, b. T1-weighted coronal MRI showing hyperintense lesion and contrast enhancement in the hippocampus. MRI: magnetic resonance imaging.

Neuropsychiatric symptoms, especially anterograde amnesia and new-onset seizures, are often the presenting symptoms owing to autoimmune damage to limbic structures and temporal lobes, as in the case whose details are presented below (3).

CASE PRESENTATION

A 57-year-old man was referred to the neurology department with new-onset complex partial and secondary generalized refractory seizures occurring during the day. A detailed anamnesis revealed a history of confusion, disorientation, agitation, and sleep that had been worsening over a period of 3 weeks. The

Main Points:

- Antiglutamic acid decarboxylase and voltage-gated potassium channel antibody-associated limbic encephalitis with temporal seizures is an immune cause of epilepsy in adults.
- Paraneoplastic forms are rare.
- The patient had a good recovery after immune treatment.

temporal lobe seizures were typically right-sided faciobrachial dystonic type, involving the ipsilateral face, arm, and leg.

According to his medical history, he had been recently diagnosed with type 2 DM. On admission, the neuropsychological examination revealed that he was alert and cooperative but disoriented in terms of time and place. The examination did not reveal any lateralizing or focal neurological signs. The Mini-Mental State Examination (MMSE) score was 18 of 30. Laboratory tests, including electrolytes, blood count, infectious markers, and thyroid tests, were all within normal limits. The biochemistry of cerebrospinal fluid (CSF) was normal, and herpes simplex virus types 1 and 2 polymerase chain reactions were also negative. The glucose level was 52 mg/dL, total protein level was 42.69 mg/dL, sodium level was 136 mmol/L, chloride level was 123 mmol/L, and please erase this part as the result is not clear. in the CSF samples. There were no cells in direct cytology, and the CSF culture was negative. The oligoclonal band and immunoglobulin G index were not studied because there was no suspicion of any demyelinating disease. Electroencephalography showed focal sharp waves over the right anteromedial temporal regions.

The brain magnetic resonance imaging (MRI) (1.5T MRI Scanner; Siemens Healthineers, Erlangen, Germany) showed a T2 high-signal change in the hippocampus (bilateral medial temporal lobes), especially from the right temporal region to the hippocampus, with contrast enhancement (Figures 1a and b and 2a and b). Diffusion-weighted imaging and apparent diffusion coefficient values were normal.

VGKC complex Abs were positive with titers of 142 pmol/L in the serum by radioimmunoassay (reference: 100 pmol/L). In addition, GAD Abs showed a level of 82.56 IU/mL (reference: 5-10 IU/mL). Serology for onconeural Abs and NMDA-R, AMPA-R1, AMPA-R2, CASPR2, LGI-I, and GABA-R Abs were negative.

Extensive investigations, including neck ultrasonography, thoracoabdominal computed tomography, serum and urine protein electrophoresis, and immunofixation electrophoresis, did not reveal the presence of any malignancy.

The patient was started on carbamazepine treatment, and he also received a standard 5-day course of intravenous immunoglobulin (IVIG) (0.4 mg/kg/day). Clinical improvement, including seizure control and MMSE scores of 30 of 30, were sustained after a month.

To the best of our knowledge, this is the first case of LE associated with both anti-GAD and VGKC Abs together in the English literature and the first reported case of LE in North Cyprus. Informed consent was obtained from the patient.

DISCUSSION

Patients presenting with amnesic symptoms and newly onset seizures are frequent in neurological practice. Identifying those with possible reversible symptoms is important. Our patient presented with amnesic syndrome and refractory partial secondary generalized seizures. New-onset temporal lobe seizures (according to the old epilepsy classification), particularly when intractable with memory loss and behavioral and psychiatric features, raise the suspicion of autoimmune LE (7). Ab screening should be considered in adult-onset seizures, especially when combined with MRI findings consistent with LE as in this case. Owing to advances in neuroimmunology, several Abs related to immune-mediated encephalitis have been identified so far; therefore, it can be difficult to initially determine which Ab is responsible for the presented case. Hence, IVIG treatment was started with an initial diagnosis of LE rather than waiting for the results of Ab testing, which could take several weeks. Further screenings did not suggest the presence of malignancy, and after anti-GAD and anti-VGKC Abs were found to be positive, the patient was diagnosed with immune-mediated LE. The diagnosis was based on the detection of Abs along with the clinical history, MRI findings, and exclusion of malignancy.

GAD Abs are usually nonparaneoplastic and are typically related to stiff person syndrome and cerebellar ataxia. However, it has been suggested that patients with GAD Abs should be screened for an underlying neoplasm if they develop classical paraneoplastic syndromes such as LE (9).

In addition, GAD Abs are present in 15% to 35% of patients with newly diagnosed type 2 DM at an age younger than 45

years and only in 7% to 9% of older patients and approximately 80% of newly diagnosed patients with type 1 DM, although at lower titers and against different epitopes from those seen in neurological disease. The presented case had type 2 DM, but we were not able to study different epitopes of GAD (6,10).

Anti-VGKC Ab-associated encephalopathy is a relatively common form of autoimmune and potentially treatable LE and immune epilepsy.

LE, faciobrachial dystonic seizures, and neuromyotonia are the most common neurological phenotypes of the VGKC complex (2). Typical faciobrachial dystonic seizures were detected in the presented case.

Because anti-GAD and anti-VGKC Abs-related LE does not automatically exclude the possibility of malignancy, further investigations are recommended as in our case (11).

There are various Abs defined under the VGKC complex such as LGI-I and CASPR2. However, there this presented case. Although VGKC complex Abs were positive with titers of 142 pmol/L in the serum by radioimmunoassay (reference: 100 pmol/L), CASPR2, LGI-I, and GABA-R Abs were negative. Therefore, this group of patients may represent a different phenotype (12).

This is a case of immune-mediated LE associated with both anti-GAD and VGKC Abs together. The encephalitis was fully reversible in terms of seizure and memory after treatment.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - P.G.; Design - P.G.; Supervision - F.K.; Resource - S.D.; Materials - P.G.; Data Collection and/or Processing - P.G.; Analysis and/or Interpretation - P.G.; Literature Search - S.D.; Writing - P.G., S.D., F.K.; Critical Reviews - F.K., S.D.

Conflict of Interest: Authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Kobaidze K, Harrison A, Burklin Y, Patidar V, Riccardi M. Autoimmune limbic encephalitis (case reports). *Georgian Med News* 2017; 266: 69-74.
2. Spiegel DR, Samaras A, Oldham CL, Kaloji M, Warren A, Maj S, et al. Likely Case of Limbic Encephalitis in a Patient With Voltage-Gated Potassium Channel Complex Antibody, Without a Known Antigenic Target: A Review of the Disease State and Value of Antibody Titers. *Psychosomatics* 2017; 58(6): 669-75. [\[Crossref\]](#)
3. Ganguli A, Fitzgerald R, Walker L, Beadsworth M, Mwandumba HC. Voltage-gated potassium-channel antibody-associated limbic encephalitis presenting as acute psychosis. *J Neuropsychiatry Clin Neurosci* 2011; 23(2): E32-E34. [\[Crossref\]](#)
4. Celicanin M, Blaabjerg M, Maersk-Moller C, Beniczky S, Marner L, Thomsen C, et al. Autoimmune encephalitis associated with voltage-gated potassium channels-complex and leucine-rich glioma-inactivated 1 antibodies-a national cohort study. *Eur J Neurol* 2017; 24(8): 999-1005. [\[Crossref\]](#)

5. Maurer-Morelli CV, Marchesini RB, Secolin R, Santos NF, Kobayashi E, Cendes F, et al. Linkage study of voltage-gated potassium channels in familial mesial temporal lobe epilepsy. *Arq Neuropsiquiatr* 2007; 65(1): 20-3. [\[Crossref\]](#)
6. Tohid H. Anti-glutamic acid decarboxylase antibody positive neurological syndromes. *Neurosciences* 2016; 21(3): 215-22. [\[Crossref\]](#)
7. Finelli PF. Autoimmune limbic encephalitis with GAD antibodies. *Neurohospitalist* 2011; 1(4): 178-181. [\[Crossref\]](#)
8. Yoo JY, Hirsch LJ. Limbic encephalitis associated with anti-voltage-gated potassium channel complex antibodies mimicking creutzfeldt-jakob disease. *JAMA Neurol* 2014; 71(1): 79-82. [\[Crossref\]](#)
9. Ariño H, Höftberger R, Gresa-Arribas N, Martínez-Hernández E, Armutoglu T, Krüger MC, et al. Paraneoplastic neurological syndromes and glutamic acid decarboxylase antibodies. *JAMA Neurol* 2015; 72(8): 874-81. [\[Crossref\]](#)
10. Nakajima H, Nakamura Y, Inaba Y, Tsutsumi C, Unoda K, Hosokawa T, et al. Neurologic disorders associated with anti-glutamic acid decarboxylase antibodies: A comparison of anti-GAD antibody titers and time-dependent changes between neurologic disease and type 1 diabetes mellitus. *J Neuroimmunol* 2018; 317: 84-9. [\[Crossref\]](#)
11. Harrower T, Foltynie T, Kartsounis L, De Silva RN, Hodges JR. A case of voltage-gated potassium channel antibody-related limbic encephalitis. *Nat Clin Pract Neurol* 2006; 2(6): 339-43. [\[Crossref\]](#)
12. Bastiaansen AE, van Sonderen A, Titulaer MJ. Autoimmune encephalitis with anti-leucine-rich glioma-inactivated 1 or anti-contactin-associated protein-like 2 antibodies (formerly called voltage-gated potassium channel-complex antibodies). *Curr Opin Neurol* 2017; 30(3): 302-9. [\[Crossref\]](#)