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CASE REPORT / OLGU SUNUMU

Epileptic Activity in a Patient with Serum Anti-GAD Antibody-positive Limbic Encephalitis


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Serum Anti-GAD Antikoru Pozitif Limbik Ensefalitli Hastada Epileptik Aktivite

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Summary

Limbic encephalopathy (LE) is an entity, which may present with memory loss, seizure, psychiatric symptoms and is usually accompanied by neuro-radiology imaging findings. In recent years, antibody tests that can be studied in detail have gained importance as markers. Glutamic acid decarboxylase antibody (GAD-Ab) has been reported to be mainly responsible for non-paraneoplastic syndromes. GAD-Ab positivity is predominantly seen in young adult females and temporal lobe epilepsy. Patients with GAD-Ab positive have been reported to respond well or partial to immunotherapy. In this article, we report a 38-year-old woman presenting with seizure and diagnosed with limbic encephalitis who had magnetic resonance imaging and electroencephalograhy findings accompanied by serum GAD-ab positivity was reported. GAD-Ab is considered to play an important role in the prognosis of LE and the other neurological syndromes and should be investigated further.

Keywords: Anti-GAD antibody; epilepsy; limbic encephalitis.

Özet

Limbik ensefalit (LE) bellek kaybı, nöbet, psikiyatrik bulgular ile ortaya çıkabilen çoğunlukla nöro-radyolojik görüntüleme bulgularıyla desteklenebilen bir antitedir. Son yıllarda ayrıntılı çalışılabilen antikor testleri belirteç olarak önem kazanmıştır. Glutamik asit dekarboksilaz antikorunun (GAD-ab) çoğunlukla non-paraneoplastik sendromlardan sorumlu olduğu bildirilmiştir. GAD-ab pozitifliği daha çok genç erişkin kadın hastalarda ve temporal lob epilepsisinde baskın olarak görülmektedir. GAD-Ab olan hastaların immünoterapiye tam veya kısmi yanıt verdiği bildirilmiştir. Bu yazıda, nöbet ile başvuran, manyetik rezonans görüntüleme ve elektoensefalografi bulgularına serum GAD-ab pozitifliğinin eşlik ettiği LE tanısı alan 38 yaşında kadın olguyu sunduk. GAD-ab'nun LE ve diğer nörolojik sendromlarda patogenezde ve prognozda rol oynayabileceği düşünülmektedir.

Anahtar sözcükler: Anti-GAD antikor; epilepsy; limbik ensefalit.

Introduction

Limbic encephalitis (LE) is an entity, which may present with memory loss, seizure, psychiatric symptoms and is usually accompanied by neuro-radiology imaging findings.[1] The electroencephalography (EEG) findings, cerebrospinal fluid (CSF) changes, serological examinations and neoplasia screening are significant indicators that support the diagnosis in patients with autoimmune neurologic syndromes. Accompanying EEG pathologies and antibody tests have gained importance in recent years. In this article, a patient with LE, who presented with seizure, positive EEG findings and serum glutamic acid decarboxylase antibody (GAD-Ab) positivity, has been reported.

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Case Report

A 38-year-old female patient was admitted to the emergency department with generalized tonic-clonic seizure, which she had experienced twice during the recent 24 hours before her admission. It was learned that she did not have a history of seizure in her medical history. On her first examination during the post-ictal period, the level of consciousness was a state of confusion, and cooperation was limited. No lateralizing finding was present. She was treated with intravenous levetiracetam for seizure control. No pathologic finding was detected on routine laboratory tests and the cranial computerized tomography. Her general condition did not improve on the follow-up. On control neurological examination, she awakened with the verbal stimulus, eye contact and verbal response were not present, and the tendency to sleep continued when the stimulus was terminated, she moved her left upper extremity to a lower extent. EEG revealed bilateral temporal intermittent rhythmic delta activity (TIRDA) (Fig. 1). Cranial magnetic resonance imaging (MRI) revealed a hyperdense field and edema in bilateral limbic and para-limbic regions on fluid-attenuated inversion recovery (FLAIR) and T2 sequences consistent with limbic encephalitis (Fig. 2). Lumbar punc-

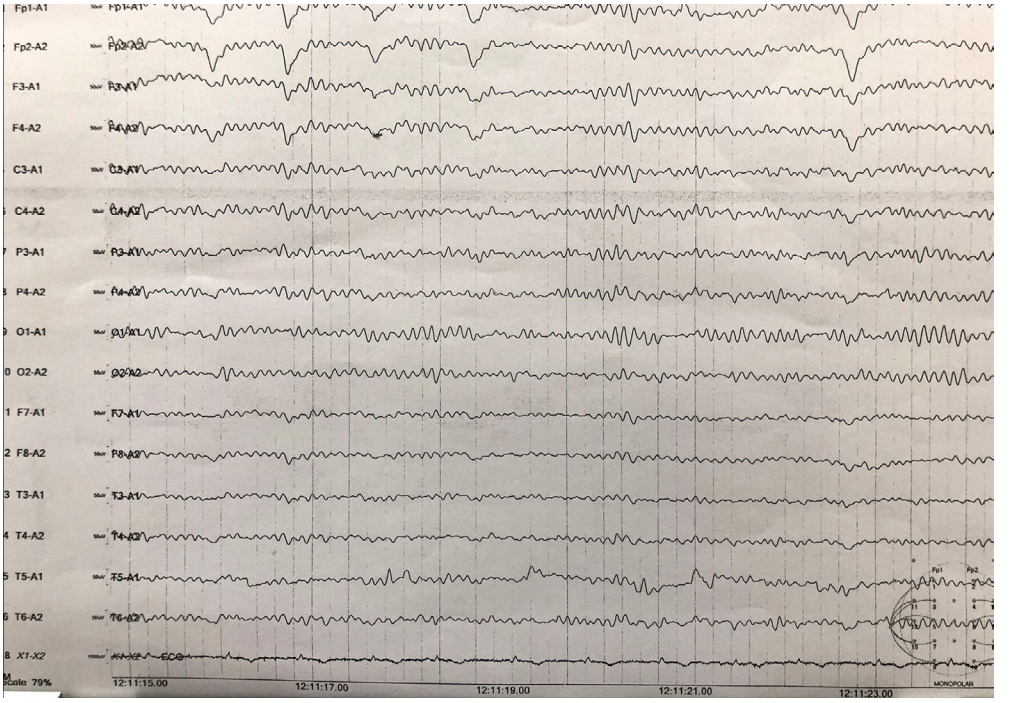

Fig. 1. EEG revealed bilateral temporal intermittent rhythmic delta activity (TIRDA).

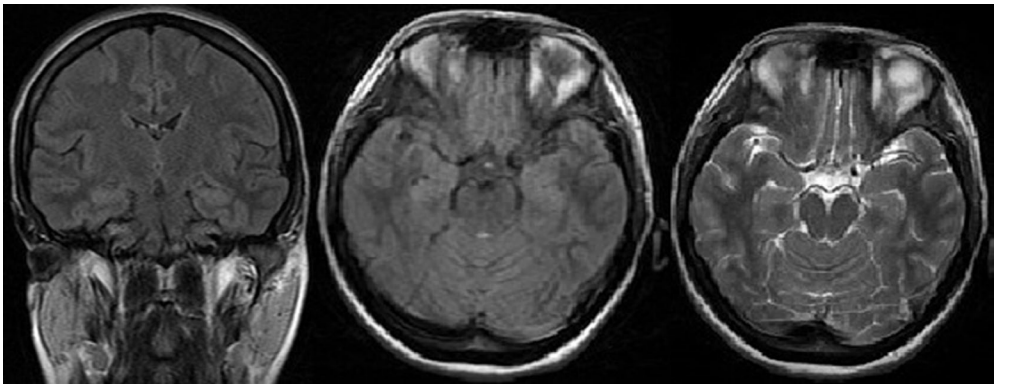

Fig. 2. Cranial MRI revealed a hyperdensity and edema in bilateral limbic and paralimbic regions on FLAIR and T2 sequences consistent with limbic encephalitis.

ture was performed and the CSF protein was determined as 77.3 (15–45 mg/dl). HSV type 1 and type 2 were found to be negative twice, and CSF culture result was normal. IVIG treatment was started in the dose of 0.4 mg/kg/day for five days with a diagnosis of LE. The seizure was controlled with 500 mg bid levetiracetam (UCB pharma, Braine-L Alleud, Belgium), no abnormality was detected except amnesia lasting for the recent one week. Paraneoplastic screening tests (tumor marker tests, thoracic and abdominal computed tomography (CT), mammography and pap smear tests) were negative. On the paraneoplastic panel analysis, while the serum GAD-Ab was positive [183,5 IU/ml (<10)], the CSF GAD-Ab was negative. The other paraneoplastic antibodies (Anti-N-methil-D-aspartate receptor (NMDA), anti glutamate receptor (AMPA-R1/R2), contactin associated protein 2 (CASPR2), leucine-rich glioma inactivated (LGI1), gamma-aminobutyric acid (GABA-R)) were negative. The patient was discharged with a diagnosis LE and followed-up for two years regularly for malignancy screening. There was no seizure after discharge, and control MRI was normal. Written consent was obtained from the patient's relatives.

Discussion

The cause-effect relationship between the antibodies and the disease is controversial. The glutamic acid decarboxylase (GAD) enzyme catalyzes the conversion of glutamate to gamma-aminobutyric acid (GABA) through decarboxylation. GAD-Ab attacks the GAD 65 enzyme and hinders the conversion of glutamate to GABA. Encephalomyelitis-related neurological findings are suggested to develop through alteration in the functioning of GABAergic neurons in deficiency of GABA, which is an inhibitor (i.e., Stiffman syndrome). On the other hand, GAD's being an intracellular enzyme and the antibody's not passing through the membrane suggests that antibodies arise from cellular destruction after the seizure.[2]

Detection of GAD-Ab has been reported in patients with diabetes mellitus and Stiffman syndrome.[3] However, it has also been suggested to play a role in the etiopathogenesis of LE and cerebellar degeneration.[4,5] GAD-Ab has been detected in 17.5% of autoimmune encephalitis patients.[2] Accompanying neoplasia has been reported in LE patients with GAD-Ab positivity in a limited number of patients in the literature.[2,6] Also, a study reported that GAD-Ab related LE should be investigated for GABA-R Ab, which could be associated with small-cell lung cancer.[7] Neoplasia was not detected in the first examination of our patient. The rate of GAD-Ab with the neurologic syndrome was reported to be higher among females.[6] Similarly, our patient was also female.

A recent study reported six patients GAD-Ab positive LE.[8] Five patients had very high (>2,000 IU/ml) and one patient had high (52–251 IU/ml) serum titers. CSF GAD-Ab was positive in two patients with very high titers. One patient with high titer had negative in CSF and one patient's CSF GAD-Ab was not performed.[8] Our patient's serum GAD-Ab was positive [183,5 IU/ml (<10)], the CSF GAD-Ab was negative. We thought that the CSF level had dropped below the measurement level of the kit because serum GAD level was low. If the serum level increased to a high level (>1,000 IU/ml), it also released in CSF. Since our patient did not have type 1 diabetes mellitus, 183 IU/ml could be considered as a reasonable positivity.

GAD-Ab positivity has been reported to be present in patients with seizures.[9] Similarly, high GAD-Ab has been determined in 2.1% of patients with seizures and these patients have been reported to be resistant to drugs, and frontal and temporal focal activity have been detected on EEG.[10] However, Malter et al.[11] reported that a high level of GAD-Ab was reported in acute and subacute epilepsy and also in LE, which is not paraneoplastic, and mesiotemporal encephalitis findings were seen on MRI. The coexistence of a non-convulsive status and GAD-Ab has also been reported in the literature.[12] In our case, hyperintensity and edema in bilateral limbic areas on MRI, presence of serum GAD-Ab and FIRDA on EEG were detected. Early-stage neoplasia screening was found to be negative, and the patient was followed-up for two years, six months period regularly. Additionally, in the literature, a rare GAD-Ab LE was reported, which was presented with brainstem symptoms.[13]

The treatment of autoimmune LE includes IVIg, plasma exchange, immunosuppressive agents.[11,14,15] Response to treat with these combinations is variable and depends on antineuronal antibodies, for example, VGKC positive LE is more treatable than with GAD-Ab LE.[16,17] In the literature, GAD-Ab positive patients have been reported to well-treated with immunotherapy. Also, clinical and EEG findings were recovered with this treatment.[2,10,18] Similarly, our patient has dramatically responded to IVIG therapy.

GAD-Ab is mainly responsible for nonparaneoplastic syndromes. GAD-Ab positivity is predominantly seen in young

adult females and temporal lobe epilepsy.[2] GAD-Ab is considered to play an important role in the prognosis of LE and the other neurological syndromes and should be investigated further.

Informed Consent

Written consent was obtained from the patient's relatives.

Peer-review

Externally peer-reviewed.

Conflict of interest

The authors declare that they have no conflict of interest.

Authorship Contributions

Concept: Z.Ö.A., D.K.; Design: Z.Ö.A., D.K.; Supervision: Z.Ö.A., D.K.; Materials: Z.Ö.A., D.K.; Data collection &/or processing: Z.Ö.A., D.K.; Analysis and/or interpretation: Z.Ö.A., D.K.; Literature search: Z.Ö.A., D.K.; Writing: Z.Ö.A., D.K.; Critical review: Z.Ö.A., D.K.

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