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CASE REPORT

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Autoimmune Encephalitis with Antibodies Against A-Amino-3hydroxy-5-Methyl-4-Isoxazolepropionic Acid Receptor and γ-Aminobutyric Acid-Beta Receptor: Case Report

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ABSTRACT

Introduction: Limbic encephalitis is a rapidly progressing disease that presents with seizures, psychiatric symptoms, and recent memory loss. Detection of more than one autoantibody is a rare condition in this disease where an underlying autoantibody is frequently detected. Although different autoantibodies have been reported in the literature, no case has been reported regarding the association of anti-γ-aminobutyric acid-beta-receptor (anti-$GABA_BR$) and anti-α-amino-3 hydroxy-5-methyl-4-isoxazolepropionic acid (anti-AMPAR).

Case: In this presentation, a 46-year-old female patient with subacute development of short-term memory loss and behavioral symptoms will be described. Anti-$GABA_BR$ and anti-AMPAR were positive in the anti-neuronal antibody panel sent from the cerebrospinal fluid and serum. Small cell lung cancer was detected as a result of malignancy screening tests. The patient's complaints and autoantibody positivity regressed after immunotherapy.

Conclusion: In this case report, a case with coexistence of anti-$GABA_BR$ and anti-AMPAR antibodies, which has not been previously reported in the literature, is described. As more cases with the coexistence of these two antibodies are detected, knowledge on clinical aspect, laboratory and treatment will increase.

Keywords: Anti-α-amino-3 hydroxy-5-methyl-4-isoxazolepropionic acid (anti-AMPAR), anti-γ-aminobutyric acid-beta-receptor (anti-$GABA_BR$), Coexistence of anti-neuronal antibody, limbic encephalitis

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INTRODUCTION

Limbic encephalitis is a disease characterized by subacute seizures, memory loss, psychiatric symptoms, and confusion symptoms. Until now, many autoantibodies that can cause limbic encephalitis have been described. Limbic encephalitis-related autoantibodies can be divided into autoantibodies to neuronal intracellular antigens and autoantibodies that develop on the neuron cell surface. The latter include mainly anti-γ-aminobutyric acid-beta-receptor (anti-$GABA_BR$) and anti-α-amino-3 hydroxy-5-methyl-4-isoxazolepropionic acid receptor (anti-AMPAR) antibodies.

Although anti-$GABA_BR$ antibody is associated with limbic encephalitis, it can cause uncommon clinical phenotypes such as opsoclonus-myoclonus syndrome and cerebellar ataxia. While small cell lung cancer (SCLC) is detected in approximately 50% of patients with anti-$GABA_BR$, more rarely, cases with thymoma, malignant melanoma, breast cancer, rectal cancer, and esophageal cancer are found in the literature. Another type of autoantibody that causes limbic encephalitis is anti-AMPAR, which targets glutamate receptors. Anti-AMPAR antibodies are also associated with many types of cancer, particularly lung and thymoma. Both AMPAR and $GABA_BR$ are involved in synaptic plasticity formation in different processes such as learning, memory, and behavior (1,2).

Highlights

- **Detecting 2 anti-neuronal antibodies is a very rare condition in limbic encephalitis.**
- **We present a case in which we found anti $GABA_BR$ and anti AMPAR antibody association.**
- **This case increases knowledge of limbic encephalitis cases with antibody association.**

While most patients with limbic encephalitis have only one antibody, very few limbic encephalitis cases with more than one autoantibody have been reported in the literature. This paper presents a previously unreported case of limbic encephalitis with anti-$GABA_BR$ and anti-AMPAR antibodies.

CASE

A 46-year-old female patient presented with the complaint of forgetting recent events, repetition of topics and questions, and abnormal behavior

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which started one month prior. Her medical history and family history were unremarkable. She was an active smoker (47 packs-years). On neurological examination, place and time orientation was impaired, she was apathetic, and reaction time was prolonged. Mini-Mental State Examination (MMSE) score was 25 (lost 1 point from place orientation, 2 points from time orientation, and 2 points from attention).

Hematology and serum biochemistry parameters, including complete blood count, thyroid, liver and kidney function tests, glucose, folic acid, and vitamin B12 levels, were within normal limits. Brain magnetic resonance imaging showed hyperintensity in the left parahippocampal, bilateral hippocampal, and amygdala in fluid-attenuated inversion recovery (FLAIR) sequence (Figure 1). Electroencephalography and electromyography were within normal limits. Cerebrospinal fluid (CSF) was clear and colorless. In the CSF cell count, 13 per mm^3 lymphocytes and 6 per mm^3 polymorphonuclear cells were detected. Cerebrospinal fluid cytology was reported as "mildly hypercellular CSF containing lymphocytes and monocytes/macrophages" and no atypical tumor cells were observed. Cerebrospinal fluid biochemistry parameters (including IgG index) and CSF culture result were unremarkable. Antibody screening was done by cell-based assay using an immunofluorescence-based commercial kit (Euroimmun, Luebeck, Germany). The anti-neuronal antibody screening for autoimmune encephalitis gave positive results for anti-$GABA_B$R and anti-AMPAR antibodies at a serum titer of 1/100 and CSF titer of 1/2 for both antibodies (Figure 2). The neuropsychological evaluation resulted in frontal system-related findings such as complex attention impairment, decreased verbal fluency, coping with distractors and impaired response inhibition, impaired learning process in verbal memory, and both frontal (secondary to attention) and primary (temporolimbic) type memory impairment in the patient.

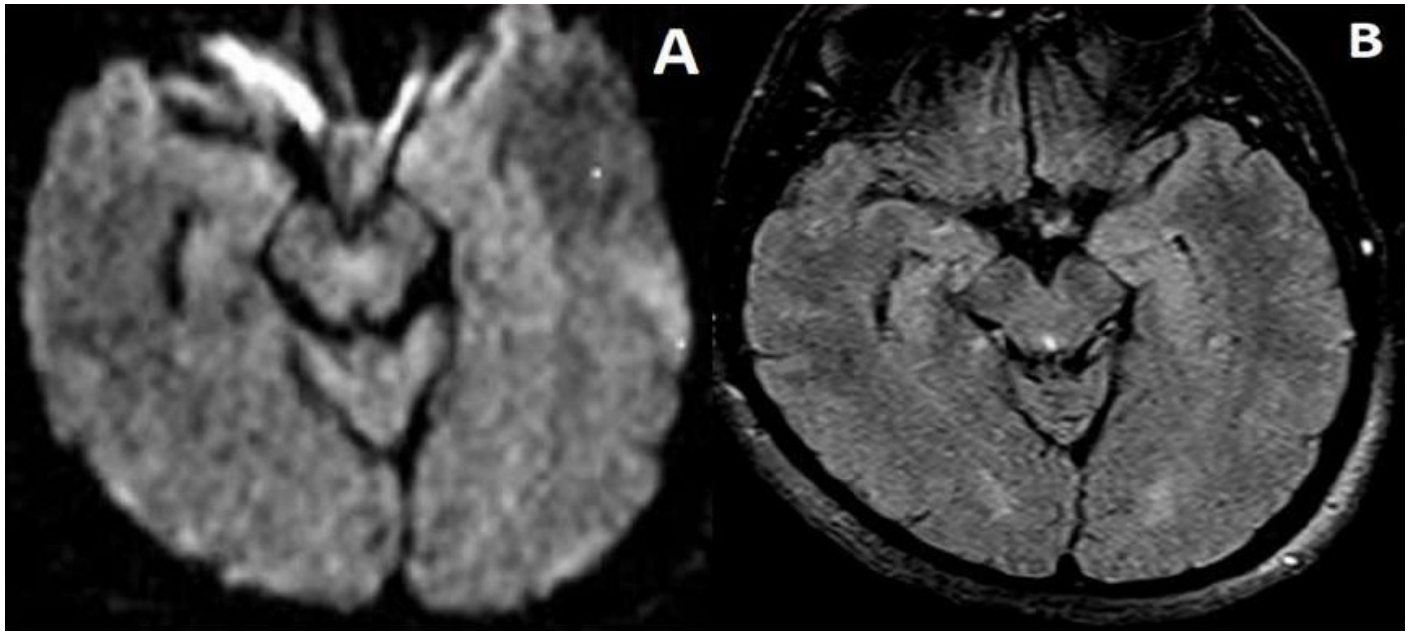

Figure 1. Hyperintensity in the left parahippocampal, bilateral hippocampal and amygdala in fluid-attenuated inversion recovery and diffusion-weighted images in brain magnetic resonance imaging of the patient (**a, b).**

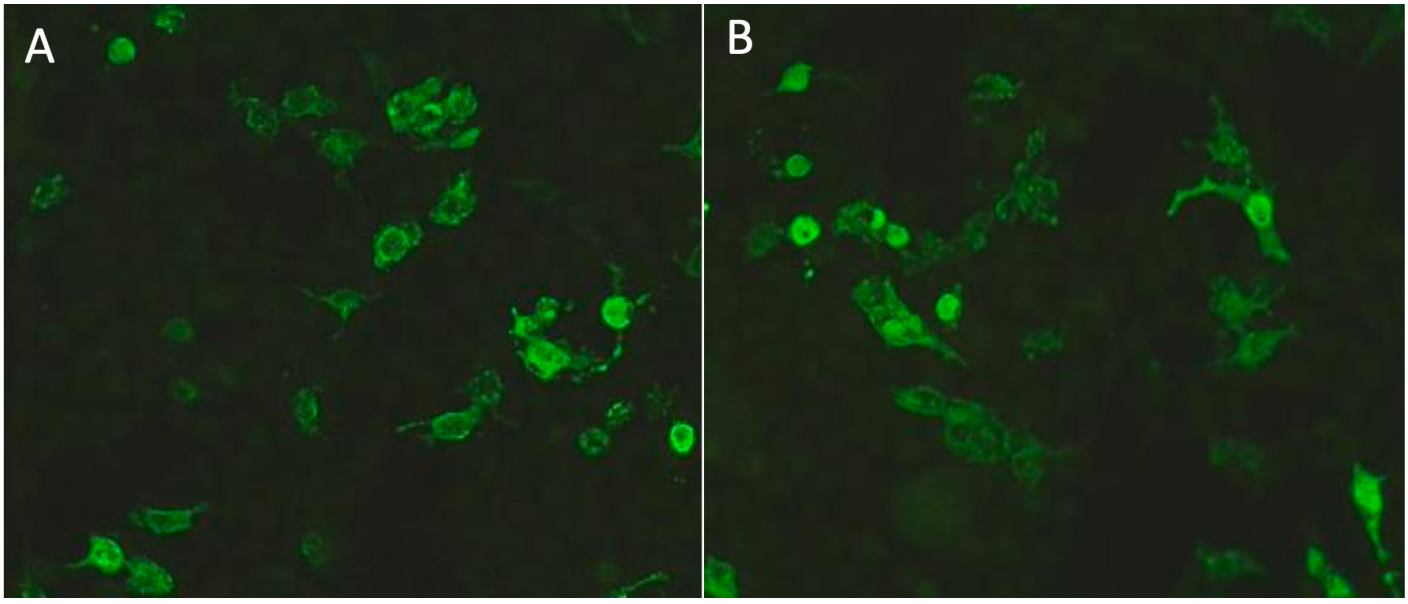

Figure 2. Serum antibodies of the patient react with human embryonic kidney 293 (HEK293) cells expressing γ-aminobutyric acid (GABA) type B receptor ($GABA_B$R) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) (green fluorescence, panel **a and b**). Original magnification 20×. EUROIMMUN, Autoimmune Encephalitis Mosaic 1, FA 112 d-1005-1.

In the whole-body positron emission tomography examination performed for malignancy screening, a mass of 4.5×3.7 cm was observed in the superior lobe of the left lung with a nearby satellite lesion. Pathological examination of the specimen obtained by bronchoscopy was consistent with SCLC.

The patient was diagnosed with paraneoplastic limbic encephalitis with clinical features, imaging findings, tumor screening results, and anti-AMPAR and anti-$GABA_B$R antibody positivity in serum/CSF. The patient received 1 g/day pulse intravenous methylprednisolone (IVMP) for five days and 30 g/day (75 kg patient) intravenous immunoglobulin (IVIG) treatment with a dose calculation of 0.4 g / kg/day. Following the treatment, the patient suffered from nausea and vomiting, and syndrome of inappropriate antidiuretic hormone secretion was diagnosed with a serum sodium level of 120 mmol/L (range, 135–145). Sodium level returned to normal following hypertonic solution infusion and fluid restriction treatment.

The patient's treatment was administered as 1 g/week IVMP and 30 g/month IVIG for 3 months. Cisplatin and etoposide treatment was started following the diagnosis of SCLC (stage 2B). In the second week of immunotherapy, the patient's complaints regressed. No cells were detected in the repeat CSF examination. Serum autoimmune encephalitis panel tests became negative one month after the initiation of treatment. While AMPAR antibody diminished in CSF following treatment, $GABA_B$R antibody persisted. Both AMPAR and $GABA_B$R antibodies vanished in control CSF specimen obtained 3 months after the treatment. Cerebrospinal fluid cytology was reported as acellular material. Mini-mental state examination score increased to 28 (lost 1 point from place orientation and 1 point from attention).

DISCUSSION

Although the relationship between the immune response that develops through autoantibodies and cancer has been known for a long time, data on the mechanism of autoantibody formation is limited. One possible mechanism is that cancer can express antigens found in neurons due to mutations that develop in tumoral tissue and activate the immune system. Since more than one antigen can be expressed in this process, more than one autoantibody can be produced simultaneously (3).

Arino et al. found that the probability of detecting cancer in etiology was higher in patients who had multiple neuronal surface autoantibody (4). It is also known that multiple autoantibodies detected simultaneously can help predict the underlying cancer type. Horta et al. found that the probability of SCLC, which is 83% when the anti-Hu antibody is detected alone, is 100% when the anti-Hu antibody coexists with anti-collapsin response mediator protein-5 (CRMP-5) antibody or P / Q voltage-gated calcium channel antibody (5). It is known that both anti-$GABA_B$R and anti-AMPAR neuronal autoantibodies are most frequently associated with SCLC. In the present case with both coexisting autoantibodies, SCLC was detected in accordance with this information.

Coexisting autoantibodies may show clinical and neuroradiological features that are not specific to the type of neuronal autoantibody detected. For example, in anti-$GABA_B$R-associated limbic encephalitis, progressive sensorimotor neuropathy may be observed if the anti-Hu antibody is present, while psychiatric findings are evident in combination with anti-NMDA receptor antibody. In anti-AMPAR limbic encephalitis, optic neuropathy with anti-CRMP-5 and sensory neuropathy with anti-amphiphysin have been reported. In our case, no finding exceeding the limbic encephalitis clinic was found. Nevertheless, psychosis and seizures that are commonly associated with AMPAR and $GABA_B$R encephalitis were not observed, suggesting that coexistence of two different antibodies might somehow be attenuating the impact of these antibodies on behavioral and epilepsy network. Also, withdrawal of antibodies from the serum before CSF and cessation of anti-AMPAR before $GABA_B$R emphasizes the diversity of antibody production dynamics of different anti-neuronal antibodies.

Multiple neuronal antibodies are rare. Ren Haito et al. found multiple anti-neuronal antibodies in only 10 cases out of the 531 autoimmune encephalitis case series they published (6). In the literature review, no case was found in which the association of anti-AMPAR and anti-$GABA_B$R antibodies was detected.

In this case report, we present the first case of autoimmune encephalitis in which anti-AMPAR and anti-$GABA_B$R coexistence was detected. The clinical features of the presented case demonstrated the characteristics of anti-$GABA_B$R and anti-AMPAR antibodies, which are commonly known to cause limbic encephalitis. As the number of cases showing the coexistence of anti-$GABA_B$R and anti-AMPAR autoantibodies increases, more data about the clinical picture, treatment, and prognosis will be obtained.

Informed Consent: Signed Informed Consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- FUD, BS, BB; Design- FUD; Supervision- BS, BB, ET; Resource- BB, İHG, HAH, VY, ET; Materials- VY, ET; Data Collection and/or Processing- FUD, BS; Analysis and/or Interpretation- BB, ET; Literature Search- FUD; Writing- FUD, BB; Critical Reviews- HAH, ET, İHG, BB.

Conflict of Interest: The authors declared that there is no conflict of interest.

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