

# Autoimmune encephalitis positive for both anti- $\gamma$ -aminobutyric acid B receptor and anticollapsin response-mediator protein 5 antibodies

## A case report

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### Abstract

**Rationale:** Autoimmune encephalitis (AE) is a heterogeneous group of recently identified disorders. Despite severe and even prolonged neurologic deficits, dramatic improvements may occur with proper immunotherapy in some patients with AE. Antineuronal antibodies have been discovered in patients' serum and cerebrospinal fluid (CSF). However, AE with multiple antineuronal antibodies is rare. To date, there are no published reports of AE with both anti- $\gamma$ -aminobutyric acid B receptor (GABA<sub>B</sub>R) and anticollapsin response-mediator protein 5 (CV2) antibodies.

**Patient concerns:** We describe a 46-year-old man who presented with seizures, working memory deficits, and visual hallucinations. We detected anti-CV2 and anti-GABA<sub>B</sub>R antibodies in his serum and CSF. Brain magnetic resonance imaging (MRI) revealed patchy abnormal signals in his left temporal lobe and hippocampus. The patient's symptoms improved after receiving intravenous immunoglobulin injections and glucocorticoids, but his condition relapsed within 4 months, and he was readmitted to our hospital. Repeated MRI scans revealed new lesions in his right temporal lobe and hippocampus.

**Diagnosis:** The AE diagnosis was established from the results of the preliminary physical examination, the laboratory tests, and the imaging findings.

**Interventions:** The patient received intravenous immunoglobulins and glucocorticoids.

**Outcomes:** We followed the patient for 9 months from the date of the patient's second hospital discharge. He experienced no seizures during this period, but his short-term memory deficits and visual hallucinations were not completely alleviated.

**Lessons:** Coexisting anti-CV2 and anti-GABA<sub>B</sub>R antibodies may have synergistic effects and worsen the clinical syndrome. AE with multiple antineuronal antibodies may be relapse-prone. Further studies investigating the relationship between anti-CV2 and anti-GABA<sub>B</sub>R antibodies are warranted.

**Abbreviations:** <sup>18</sup>F-FDG PET = <sup>18</sup>F-deoxyglucose positron emission tomography, AE = autoimmune encephalitis, AEDs = antiepileptic drugs, CA-125 = cancer antigen 125, CSF = cerebrospinal fluid, CT = computerized tomography, CV2 = collapsin response-mediator protein 5, EEG = electroencephalography, GABA<sub>A</sub>R =  $\gamma$ -aminobutyric acid A receptor, GABA<sub>B</sub>R =  $\gamma$ -aminobutyric acid B receptor, MRI = magnetic resonance imaging.

**Keywords:** anti- $\gamma$ -aminobutyric acid B receptor antibody, anticollapsin response-mediator protein 5 antibody, autoimmune encephalitis

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## 1. Introduction

Autoimmune encephalitis (AE), which is also known as autoimmune-mediated limbic encephalitis, is an autoimmune disorder clinically characterized by memory impairment, behavior changes, and seizures. It usually affects the limbic system, brainstem, and cerebellum.<sup>[1]</sup> Antineuronal antibodies can be detected in patients' serum and cerebrospinal fluid (CSF). These antibodies can target antigens located intracellularly or on cell membranes.<sup>[2]</sup> Those targeting intracellular antigens are considered biomarkers for tumors rather than pathogenic mediators of neurological disease,<sup>[3]</sup> and patients expressing them respond relatively poorly to immunomodulatory therapy. However, the likelihood of indicating a tumor varies among antibodies targeting cell membrane antigens,<sup>[4]</sup> and patients expressing these antibodies can clinically benefit from immunomodulatory therapy.<sup>[5]</sup>

AE with multiple antineuronal antibodies is rare. Ren et al<sup>[6]</sup> reported that only 10 out of 531 patients with AE expressed 2 or

more antineuronal antibodies. To date, there are no published reports of AE with both anti- $\gamma$ -aminobutyric acid B receptor (GABA<sub>B</sub>R) and anticollapsin response-mediator protein 5 (CV2) antibodies, which target cell membrane and intracellular antigens, respectively. Herein, we describe a patient with AE who did express both antibodies. We also describe his clinical course over follow-up.

## 2. Ethics

This report was approved by the ethics committee of the First Hospital of Jilin University, Changchun, China. The patient provided written informed consent for this report, and his information has been anonymized.

## 3. Case report

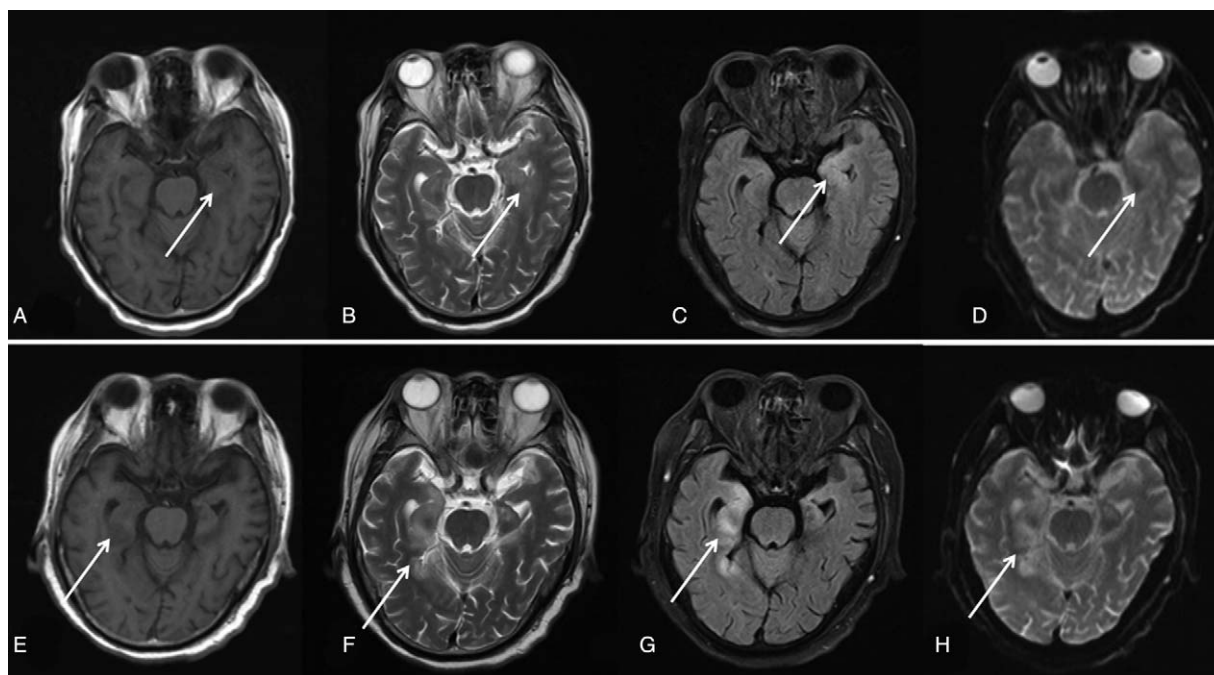
A 46-year-old man was admitted to our hospital due to recurrent seizures. Five days before his admission, he had a seizure that presented as a paroxysmal right arm jitter and lasted approximately 3 minutes. During the following 5 days, his seizures became increasingly frequent, and he developed short-term memory impairment and visual hallucinations. After admission, the partial seizures progressed into generalized seizures, so the patient was transferred to the neurological intensive care unit and received antiepileptic drugs (AEDs) including diazepam, sodium valproate, phenobarbital, and levetiracetam. His medical history was unremarkable except for type II diabetes and hypertension.

He exhibited impaired consciousness at admission, but his neurologic examination revealed no positive findings apart from bilateral Babinski signs. Over the following days, eye examinations revealed no photophobia, tears, ciliary body congestion, aqueous humor turbidity, or iris swelling. Brain magnetic resonance imaging (MRI) performed on admission revealed

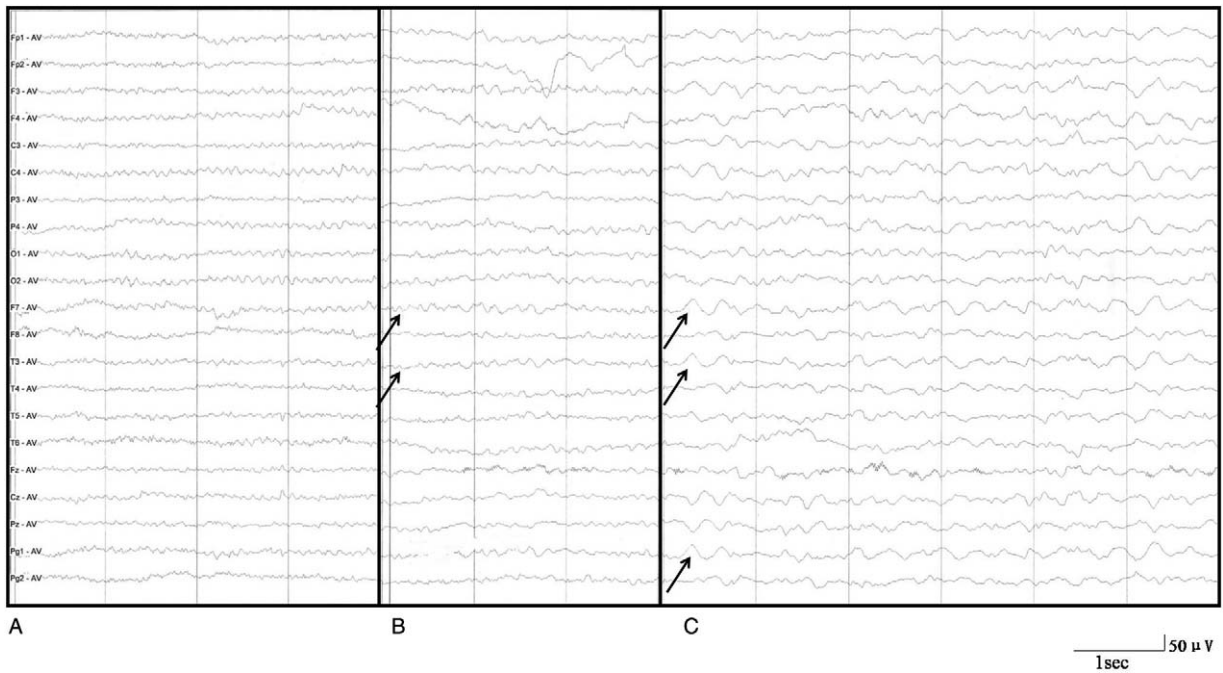
patchy lesions in his left temporal lobe and hippocampus (Fig. 1 A–D). Video electroencephalography (EEG) (Fig. 2) recorded periodic epileptiform discharges and rhythmic jitter in his right arm. Cell-based antineuronal antibody assays (Euroimmun, Lübeck, Germany) detected anti-GABA<sub>B</sub>R and anti-CV2 antibodies in both the serum and the CSF. Routine CSF analysis revealed slightly elevated protein levels (0.63 g/L, normal range: 0.15–0.45 g/L) and increased numbers of white blood cells ( $14 \times 10^9/L$ , normal range:  $0–8 \times 10^9/L$ ), of which 90% were lymphocytes and 9% were monocytes. Tumor marker screening revealed elevated serum levels of cancer antigen 125 (CA-125) (202.48 U/mL, normal range: 0–35 U/mL). However, pulmonary computerized tomography (CT) and whole-body <sup>18</sup>F-deoxyglucose positron emission tomography (<sup>18</sup>F-FDG PET) scans revealed no malignancies. Troponin I monitoring showed that his troponin I levels fluctuated between 0.177 and 0.035 ng/mL (normal range: 0–0.034 ng/mL), and electrocardiography revealed frequent atrial extrasystoles.

We diagnosed AE according to the new diagnostic criteria proposed by Graus et al.<sup>[7]</sup> Thirteen days after the disease onset, we initiated immunotherapy with intravenous immunoglobulin injections (0.4 g/[kg × day] for 5 consecutive days) and methylprednisolone. Considering methylprednisolone's cardiovascular side effects, we initially set the dose at 500 mg/day and halved it every 3 days. Forty days after symptom onset, the patient was discharged with an oral prednisone prescription. The prednisone dose started at 60 mg/day and decreased by 4 mg/day every 5 days. The treatment successfully alleviated the patient's symptoms and substantially reduced his seizure frequency, but his short-term memory impairment and occasional visual hallucinations remained.

Four months after discharge, the patient was readmitted to our hospital because of recurrent seizures occurring over 9 days.



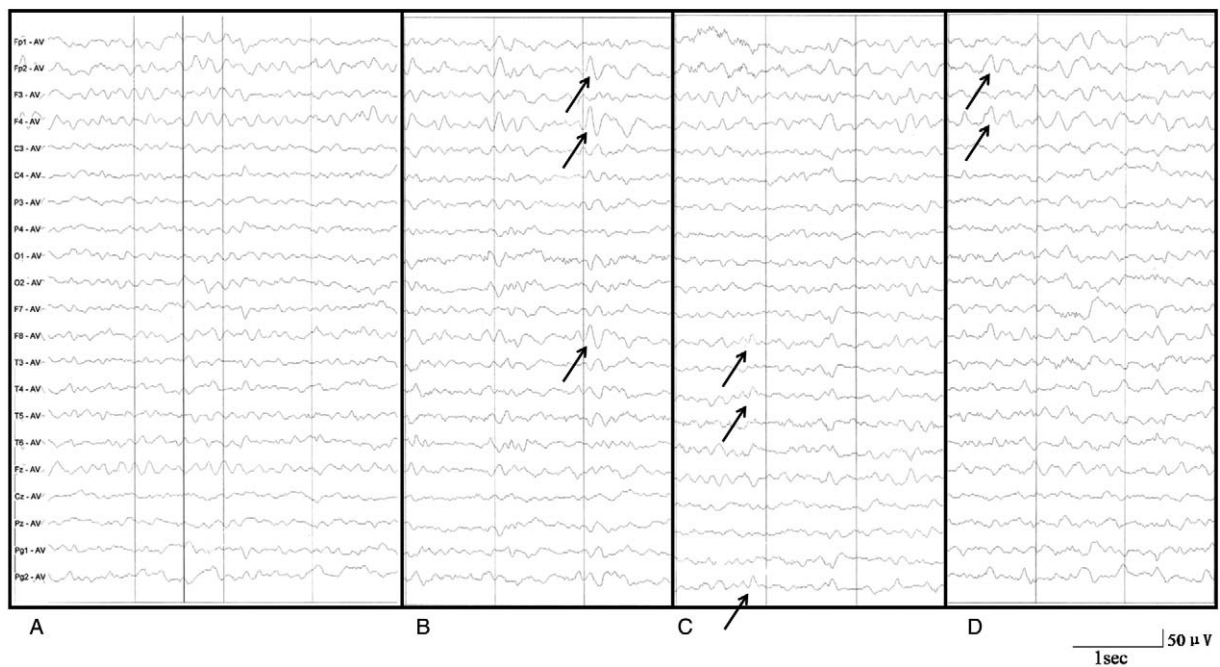
**Figure 1.** (A–H) A brain MRI scan performed 5 days after the disease onset revealed patchy lesions in the left temporal lobe and hippocampus (A–D). The lesions exhibited low signal intensities on a T1-weighted imaging sequence (A) and high signal intensities on T2-weighted imaging (B), FLAIR (C), and DWI (D) sequences. Twenty-four days after the relapse, repeated brain MRI scans revealed new right temporal lobe and hippocampal lesions (E–H). The lesions exhibited low signal intensities on T1-weighted imaging (E) and high signal intensities on T2-weighted imaging (F), FLAIR (G), and DWI (H) sequences. DWI = diffusion-weighted imaging, FLAIR = fluid-attenuated inversion recovery, MRI = magnetic resonance imaging.



**Figure 2.** A 20- to 40- $\mu$ V, 8-Hz background  $\alpha$  rhythm was recorded in the left parietal and occipital lobes, where its amplitude was lower than that in the offside (A). During a seizure, low amplitude fast activity appeared in the left temporal region (B, marked with solid arrow) and gradually developed into medium-amplitude  $\theta$  and  $\delta$  activity (C, marked with solid arrow). Eventually, the voltage decreased and the background rhythm returned.

Antineuronal antibody tests showed lower serum and CSF antibody titers than those detected 4 months earlier. Furthermore, MRI scans revealed new right temporal lobe and hippocampal lesions (Fig. 1E–H). The video EEG examination revealed that his partial seizures originated from the right temporal lobe (Fig. 3). We conducted pulmonary CT and scrotal

Doppler ultrasound cancer screenings, and all results were negative. We again treated the patient with intravenous immunoglobulin injections (0.4 g/[kg  $\times$  day] for 5 consecutive days) and methylprednisolone. The methylprednisolone dose started at 1000 mg/day and was halved every 3 days before eventually being substituted with oral prednisone, the dose of



**Figure 3.** The  $\alpha$  rhythm was not obvious, and the  $\theta$  wave was increased in the background (A). In the interictal discharge, sharp slow wave and slow wave activity appeared in the right frontal and right anterior temporal regions (B, marked with solid arrow). During seizure onset, medium-amplitude  $\theta$  wave activity appeared in the right temporal region (C, marked with solid arrow). Its amplitude increased, and the right frontal region was affected (D, marked with solid arrow). The voltage eventually decreased, and background rhythms returned.

which started at 60 mg/day and was decreased by 4 mg/day every 7 days until it reached 28 mg/day. The seizures did not recur after the application of the AEDs diazepam, sodium valproate, and levetiracetam. Thirty-seven days after the recurrent seizure onset, the patient was again discharged. His psychiatric problems and visual hallucinations then worsened, so he was prescribed risperidone. Over a follow-up period lasting 9 months from the date of the patient's second hospital discharge, no further seizures occurred, and his Modified Rankin Scale score improved from 5 to 3. However, his short-term memory impairment and occasional visual hallucinations were not completely alleviated.

#### 4. Discussion

In this report, we described a man with AE with anti-GABA<sub>B</sub>R and anti-CV2 antibodies. His main symptoms were seizures, memory deficits, and visual hallucinations. Despite proper immunotherapy, his clinical presentation was severe and exhibited a "relapsing-remitting" course.

GABA receptor dysfunction is associated with neurological and psychiatric disorders such as depression, insomnia, anxiety, and epilepsy. Epilepsy is the main early manifestation of AE with anti-GABA<sub>B</sub>R antibodies, though memory and behavior disorders can also be observed.<sup>[8]</sup> Patients with this AE subtype also have a low relapse rate.<sup>[2]</sup> AE with CV2-antibody is relatively rare. In addition to epilepsy and other common AE symptoms, cerebellar ataxia, peripheral neuropathy, chorea, uveitis, and personality disorders have been reported for this subtype. Of these symptoms, only epilepsy was observed in this case. Our patient initially presented with recurrent seizures and exhibited short-term memory problems and occasional visual hallucinations during follow-up. Visual hallucinations have not been reported in AE with anti-GABA<sub>B</sub>R or anti-CV2 antibodies, though it is common in AE with anti-N-methyl-D-aspartate receptor antibodies. Therefore, the presence of multiple antineuronal antibodies may affect the clinical manifestations of AE and cause severe clinical syndromes. This is consistent with Ren et al's report<sup>[6]</sup> that the presence of multiple antineuronal antibodies may cause superposition or variation of clinical syndromes.

In most paraneoplastic neurologic syndrome cases, neurologic symptoms precede tumor diagnoses.<sup>[9]</sup> We detected elevated serum levels of CA-125 in this case, which is believed to be associated with various tumors such as cancers of the ovary, cervix, pancreas, colon, and lung. However, the <sup>18</sup>F-FDG PET cancer scans returned negative results, and no oncological symptoms were observed during follow-up.

Despite medical interventions, our patient experienced a relapse within 4 months, which is consistent with Gagnon et al's report<sup>[10]</sup> of a patient with AE with anti-GABA<sub>A</sub>R and antiglutamate decarboxylase 65 antibodies who endured severe relapses. It is therefore plausible that AE with multiple antineuronal antibodies is relapse-prone.

During the second hospitalization, we increased the patient's methylprednisolone dosage and prolonged the immunomodulatory treatment, and his syndrome did not relapse during the follow-up period. The relationship between anti-GABA<sub>B</sub>R and anti-CV2 antibodies is unknown, and it is worth investigating whether they coexist or whether one induces production of the other.

#### 5. Conclusion

Coexisting anti-CV2 and anti-GABA<sub>B</sub>R antibodies may have synergistic effects that influenced our patient's clinical symptoms. AE with multiple antineuronal antibodies may be relapse-prone. Further studies into the relationship between anti-CV2 and anti-GABA<sub>B</sub>R antibodies are warranted.

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