

[ CASE REPORT ]

# Coupling of Cortical Hyperintense Signals and Increased Glucose Metabolism in a Case of Anti-GABA<sub>A</sub> Receptor Antibody-associated Encephalitis

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## Abstract:

We herein report a case of anti-gamma aminobutyric acid type A receptor antibody-associated encephalitis (anti-GABA<sub>A</sub>-RE) with progressive aphasia and generalized tonic-clonic seizures. Cerebral magnetic resonance imaging (MRI) showed cortical brain lesions coupled with hypermetabolism on fluorodeoxyglucose-positron emission tomography. After two courses of methylprednisolone pulse therapy, improvements in neurological symptoms without sequelae and the total disappearance of MRI lesions were observed. Upon encountering patients with refractory status epilepticus, multifocal cerebral MRI lesions, and suspected autoimmune encephalitis, especially in cases with thymoma, it would be prudent to suspect anti-GABA<sub>A</sub>-RE and consider the evaluation of anti-GABA<sub>A</sub> receptor antibody and methylprednisolone pulse therapy.

**Key words:** <sup>18</sup>F-fluorodeoxyglucose-positron emission tomography, anti-GABA<sub>A</sub> receptor antibody, autoimmune encephalitis, status epilepticus, paraneoplastic syndrome, thymoma

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## Introduction

Anti-gamma aminobutyric acid type A (GABA<sub>A</sub>) receptor antibody-associated encephalitis (anti-GABA<sub>A</sub>-RE) is a rare autoimmune encephalitis characterized by multifocal brain lesions and convulsive seizures (1). Approximately one-third of anti-GABA<sub>A</sub>-RE patients have a tumor, such as thymoma (1).

We herein report a case of anti-GABA<sub>A</sub>-RE with progressive aphasia and generalized tonic-clonic seizures as well as neuroimaging abnormalities of multifocal hyperintense lesions coupled with increased metabolism on <sup>18</sup>F-fluorodeoxyglucose-positron emission tomography (<sup>18</sup>F-FDG-PET).

## Case Report

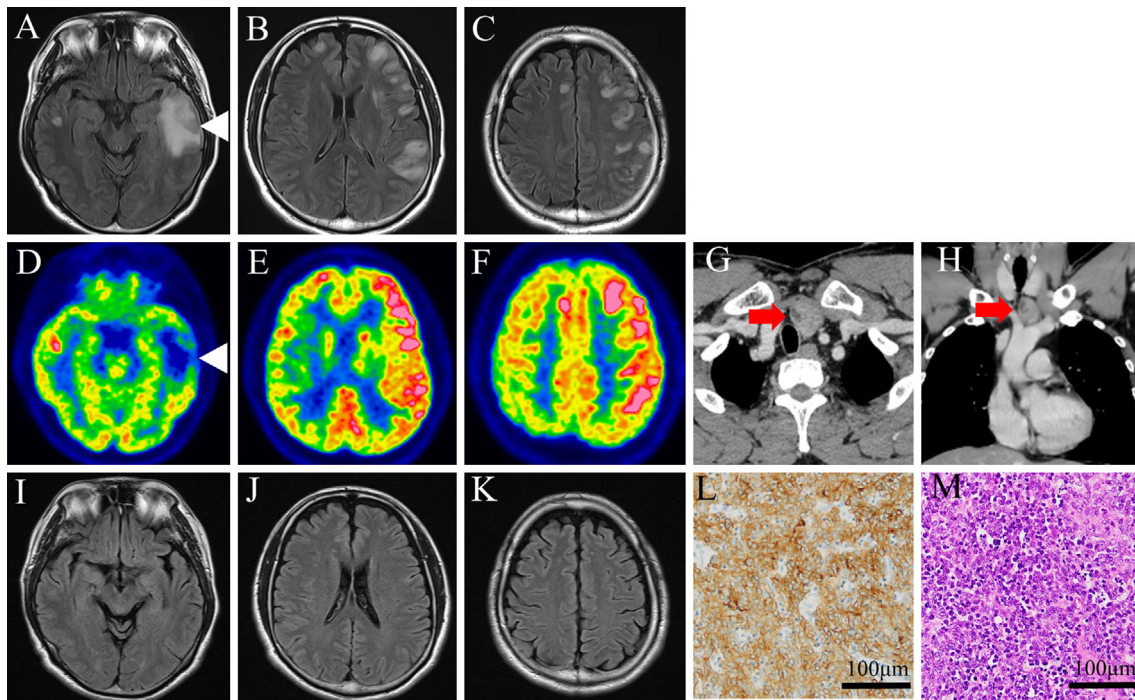
The patient was a 44-year-old man who had been well until 1 month prior to admission, when aphasia occurred and progressed. Five days before admission, cerebral MRI performed at the previous hospital showed bilateral multifocal cortical and subcortical high-intensity lesions on fluid-attenuated inversion recovery (FLAIR) images with a left-sided predominance. The patient was thereafter admitted to our hospital.

A neurological examination revealed non-fluent aphasia, acalculia, agraphia, right-left disorientation, and finger agnosia. He also showed hypoesthesia on the right side of his face, hyperreflexia of the right lower extremity, and myoclonic jerks in the right limbs and abdominal muscles. A blood examination revealed normal liver and renal functions, creatine kinase and C-reactive protein levels, and blood cell

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**Figure.** Neuroimaging and pathological findings of a patient with anti-GABA<sub>A</sub> receptor antibody-associated encephalitis. Cerebral MRI before methylprednisolone pulse therapy showed multifocal cortical and subcortical FLAIR high-intensity lesions in the bilateral frontal, temporal, and parietal lobes with left-sided predominance (A-C). Cerebral <sup>18</sup>F-FDG-PET performed close to MRI showed an increased metabolism in most lesions coupled with FLAIR hyperintensity (D-F). In contrast, a hyperintense lesion on the left lower temporal lobe showed a decreased metabolism (white arrowheads) (A and D). Contrast-enhanced chest CT revealed a heterogeneously enhanced anterosuperior mediastinal tumor (G and H, red arrows). Cerebral MRI after two courses of methylprednisolone pulse therapy confirmed the total disappearance of the lesions (I-K). Microscopic findings of the tumor revealed the features of thymoma: type AB according to the WHO classification (L and M). Immunostaining labeled by cytokeratin (L) and Hematoxylin and Eosin staining (M) showed spindle-shaped epithelial tumor cells with the infiltration of lymphocytes. Scale bar=100 μm.

counts. A cerebrospinal fluid (CSF) examination showed an elevated opening pressure of 310 mmH<sub>2</sub>O but with normal cell counts and protein and glucose levels. Herpes simplex virus DNA and varicella-zoster virus DNA evaluated by polymerase chain reaction using CSF were negative. The levels of lactate and the lactate-to-pyruvate ratio in the serum and CSF were normal. The serum beta-D-glucan level was normal. An interferon-gamma release assay was negative. Antibodies against thyroid peroxidase, thyroglobulin, cardiolipin, and aquaporin-4 (AQP4) in the serum were negative, and antibodies against myelin-oligodendrocyte glycoprotein (MOG) in the serum and CSF were also negative. Oligoclonal bands in the CSF were negative. Antibodies against amphiphysin, CV2, PNMA2, Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65, and Tr in the serum were negative. The levels of protein C and protein S were normal.

Electroencephalography (EEG) revealed periodic lateralized epileptiform discharges in the left hemisphere. On the day of admission, the patient developed generalized tonic-clonic seizures, so the intravenous administration of levetiracetam was initiated.

The majority of multifocal cortical and subcortical FLAIR

high-intensity lesions were coupled with increased glucose metabolism on <sup>18</sup>F-FDG-PET (Figure A-F). However, a hyperintense lesion on the left lower temporal lobe showed a decreased metabolism (Figure A, D, white arrowheads). An anterosuperior mediastinal tumor was detected on contrast-enhanced chest CT (Figure G, H, red arrows). There was no uptake on <sup>18</sup>F-FDG-PET in systemic organs other than the brain. A random skin biopsy was negative for malignant cells. Based on the medical history of the patient, neuroimaging findings, and the complication of a mediastinal tumor, anti-GABA<sub>A</sub>-RE was considered.

Before the identification of the anti-GABA<sub>A</sub> receptor antibody, methylprednisolone pulse therapy (1,000 mg/day for 3 days) was initiated, followed by oral prednisolone at 30 mg/day. Marked improvements were obtained in neurological findings and cerebral MRI lesions, and a second course of methylprednisolone pulse therapy was performed. Cerebral MRI performed after two courses of methylprednisolone pulse therapy confirmed the total disappearance of lesions (Figure I-K).

On the 54th day of admission, the patient underwent resection of the mediastinal tumor. Microscopic findings of

the tumor revealed the features of thymoma: type AB according to the WHO classification (Figure L, M). There was no recurrence of neurological abnormalities with oral levetiracetam and prednisolone at 15 mg/day. The patient was discharged on the 63rd day without any impairments. The anti-GABA<sub>A</sub> receptor antibody was found to be positive in both serum and CSF specimens before the initiation of steroid therapy, and the patient was diagnosed with anti-GABA<sub>A</sub>-RE. Antibodies against N-methyl-D-aspartate (NMDA) receptor, aminomethylphosphonic acid (AMPA) receptor, GABA<sub>B</sub> receptor, mGluR1 receptor, mGluR5 receptor, leucine-rich glioma-inactivated protein 1 (LGI1), contactin-associated protein 2 (Caspr2), dipeptidyl-peptidase-like protein-6 (DPPX), Neurexin-3, and Iglon5 in the serum and CSF were negative.

## Discussion

In cases of autoimmune encephalitis, the limbic system is generally the most frequently affected area, with cerebral FLAIR MRI showing hyperintensity and hypometabolism being detected on <sup>18</sup>F-FDG-PET (2, 3). In the present case, <sup>18</sup>F-FDG-PET showed hypermetabolism in the majority of lesions coupled with FLAIR hyperintensity. GABA<sub>A</sub> and GABA<sub>B</sub> receptors exert inhibitory effects on the central nervous system, and anti-GABA<sub>A</sub> receptor and anti-GABA<sub>B</sub> receptor antibodies may suppress GABA receptor functions (2, 4). The neuronal activation of lesions may occur in anti-GABA<sub>A</sub>-RE or anti-GABA<sub>B</sub> receptor antibody-associated encephalitis (anti-GABA<sub>B</sub>-RE), resulting in increased glucose metabolism on <sup>18</sup>F-FDG-PET. Among previously reported cases of anti-GABA<sub>A</sub>-RE, only a single case report presented neuroimaging findings of <sup>18</sup>F-FDG-PET, showing hypermetabolism in cortical lesions with FLAIR MRI hyperintensity (5). Similarly, in another report of anti-GABA<sub>B</sub>-RE, <sup>18</sup>F-FDG-PET showed hypermetabolism in lesions (6).

The density of GABA<sub>A</sub> receptors in the brain is higher in the cerebral cortices than in other areas (7). Consistent with this finding, cerebral MRI of cases of anti-GABA<sub>A</sub>-RE often show multifocal cortical and subcortical lesions (1), while those of anti-GABA<sub>B</sub>-RE predominantly show limbic lesions (6). Therefore, the preferentially affected sites of MRI lesions in anti-GABA<sub>A</sub>-RE or anti-GABA<sub>B</sub>-RE are important for clinically distinguishing between these two disorders.

However, in contrast to a previously reported case of anti-GABA<sub>A</sub>-RE (5), <sup>18</sup>F-FDG-PET in the present case also showed partial hypometabolism in the left lower temporal lobe. According to previous findings, <sup>18</sup>F-FDG-PET of epilepsy patients exhibited hypometabolism during the interictal phase after complex partial seizures (8). Although clearly recognizable recurrent seizures were not detected in the present case, EEG revealed epileptic discharges localized at the left cerebral hemisphere, suggesting nonconvulsive status epilepticus associated with anti-GABA<sub>A</sub>-RE. The complication of another autoimmune encephalitis may cause hypometabolism on <sup>18</sup>F-FDG-PET; however, the present case did not

show the clinical findings of common types of autoimmune encephalitis, which frequently affect the limbic system (6). Since improvements in neurological symptoms without sequelae were observed with methylprednisolone pulse therapy, the involvement of another paraneoplastic neurological syndrome is unlikely. Therefore, the mixed findings of <sup>18</sup>F-FDG-PET in the present case may be explained by hypermetabolism due to the involvement of an anti-GABA<sub>A</sub> receptor antibody and hypometabolism due to concomitantly occurring seizures.

Multifocal brain lesions can be caused by tumors, demyelinating diseases, infections, and mitochondrial encephalomyopathy, as well as autoimmune encephalitis. Infection is the most common cause of encephalitis, and herpes simplex virus and varicella-zoster virus are common infectious agents (9). In cases with viral infection, the clinical presentation and data from MRI and CSF specimens may resemble those in cases with autoimmune encephalitis (2). Therefore, herpes simplex virus and varicella-zoster virus infections should be ruled out by polymerase chain reaction using CSF.

The most common autoimmune encephalitis in patients with thymoma was previously reported to be anti-GABA<sub>A</sub>-RE (10). Among paraneoplastic autoimmune encephalitis cases, refractory status epilepticus and FLAIR images showing multifocal cortical and subcortical lesions are specific features of anti-GABA<sub>A</sub>-RE (2). Imaging features of lesions of anti-GABA<sub>A</sub>-RE were previously reported to show neither mass effect, enhancement, nor restricted diffusion (2, 11). These features would be useful for differentiating from other etiologies, such as metastasis of thymoma.

The present case report highlights the efficacy of steroid therapy and thymectomy and the characteristic findings of <sup>18</sup>F-FDG-PET in anti-GABA<sub>A</sub>-RE. Upon encountering patients with refractory status epilepticus, multifocal cortical and subcortical MRI lesions, and suspected autoimmune encephalitis, especially in cases with thymoma, it would be prudent to suspect anti-GABA<sub>A</sub>-RE and consider evaluating the anti-GABA<sub>A</sub> receptor antibody and administering methylprednisolone pulse therapy.

### Author's disclosure of potential Conflicts of Interest (COI).

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### References

- Guo CY, Gelfand JM, Geschwind MD. Anti-gamma-aminobutyric acid receptor type A encephalitis: a review. *Curr Opin Neurol* **33**: 372-380, 2020.

2. Dalmau J, Graus F. Antibody-Mediated Encephalitis. *N Engl J Med* **378**: 840-851, 2018.
3. Probasco JC, Solnes L, Nalluri A, et al. Abnormal brain metabolism on FDG-PET/CT is a common early finding in autoimmune encephalitis. *Neurol Neuroimmunol Neuroinflamm* **4**: e352, 2017.
4. Ohkawa T, Satake S, Yokoi N, et al. Identification and characterization of GABA(A) receptor autoantibodies in autoimmune encephalitis. *J Neurosci* **34**: 8151-8163, 2014.
5. Vacchiano V, Giannoccaro MP, Napolitano RP, et al. Combined brain positron emission tomography/magnetic resonance imaging in GABA(A) receptor encephalitis. *Eur J Neurol* **26**: e88-e89, 2019.
6. Bordonne M, Chawki MB, Doyen M, et al. Brain (18)F-FDG PET for the diagnosis of autoimmune encephalitis: a systematic review and a meta-analysis. *Eur J Nucl Med Mol Imaging* **48**: 3847-3858, 2021.
7. Nørgaard M, Beliveau V, Ganz M, et al. A high-resolution in vivo atlas of the human brain's benzodiazepine binding site of GABA (A) receptors. *Neuroimage* **232**: 117878, 2021.
8. Leiderman DB, Albert P, Balish M, Bromfield E, Theodore WH. The dynamics of metabolic change following seizures as measured by positron emission tomography with fludeoxyglucose F 18. *Arch Neurol* **51**: 932-936, 1994.
9. Granerod J, Ambrose HE, Davies NW, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis* **10**: 835-44, 2010.
10. Guasp M, Landa J, Martinez-Hernandez E, et al. Thymoma and Autoimmune Encephalitis: Clinical Manifestations and Antibodies. *Neurol Neuroimmunol Neuroinflamm* **8**: 2021.
11. Deng B, Cai M, Qiu Y, et al. MRI Characteristics of Autoimmune Encephalitis With Autoantibodies to GABAA Receptor: A Case Series. *Neurol Neuroimmunol Neuroinflamm* **9**: 2022.

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