Mateus Mistieri Simabukuro, MD*
Mar Petit-Pedrol, BS*
Luiz H. Castro, MD
Ricardo Nitrini, MD, PhD
Leandro Lucato, MD
Antônio Alberto Zambon, MD
Lis Gomes Silva, MD
Gabriela Carneiro Rosa Fortes, MD
Herval Ribeiro Soares Neto, MD
Josep O. Dalmau, MD, PhD

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$GABA_A$ RECEPTOR AND LGI1 ANTIBODY ENCEPHALITIS IN A PATIENT WITH THYMOMA

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Autoimmune encephalitis related to antibodies against neuronal cell surface and synaptic proteins is a new category of disorders in which the targets are well-known proteins and receptors involved in synaptic transmission and neuronal excitability. $GABA_A$ receptor is one of the latest identified antigens within this category.[1] High-titer serum and CSF $GABA_A$ receptor antibodies were recently reported in 6 patients with autoimmune encephalitis associated with seizures or status epilepticus, 4 of them requiring pharmacologic-induced coma. Patients' brain MRIs showed characteristic multiple cortical and subcortical abnormalities with fluid-attenuated inversion recovery (FLAIR)/T2 hyperintensity. Antibodies to LGI1 are associated with limbic encephalitis previously attributed to voltage-gated potassium channels (VGKC).[2] Coexistence of these antibodies is rare and intriguing.

We report here the presence of antibodies to the $GABA_A$ receptor and LGI1 in a patient with autoimmune encephalitis and thymoma.

Case. A 45-year-old woman presented with subacute onset of memory loss, confabulation, and behavioral changes. Eight years earlier she was diagnosed with myasthenia gravis (MG) associated with type B2 thymoma, which was treated with surgery and radiation therapy. Four years later, she developed retroperitoneal and mediastinal metastases that were surgically removed. In addition, she had well-controlled epilepsy since childhood and had been asymptomatic on phenobarbital, pyridostigmine, prednisone, and azathioprine.

On examination, she was disoriented to time and space, showed impaired memory with confabulations, demonstrated mild executive dysfunction, and had a Mini-Mental State Examination (MMSE) score of 20. The remainder of the neurologic and physical examination was unremarkable. Brain MRI showed multiple cortical and subcortical T2/FLAIR hyperintense non-contrast-enhancing lesions with extensive mesial temporal lobe involvement that was worse on the right side (figure 1). CSF was normal. EEG showed periodic lateralized epileptiform discharges (PLEDs) in the right temporal region and left temporal onset electroencephalographic seizures without clinical manifestations. Brain fluorodeoxyglucose (FDG) PET showed uptake in the right insular and temporal regions. Whole-body FDG-PET disclosed a hypermetabolic pleural lesion. Additional laboratory tests showed moderately increased C-reactive protein (33.3 mg/dL) and erythrocyte sedimentation rate (28 mm), and positive acetylcholine receptor, antinuclear antibody, and double-stranded DNA antibodies. Thyroid and GAD65 antibodies were negative.

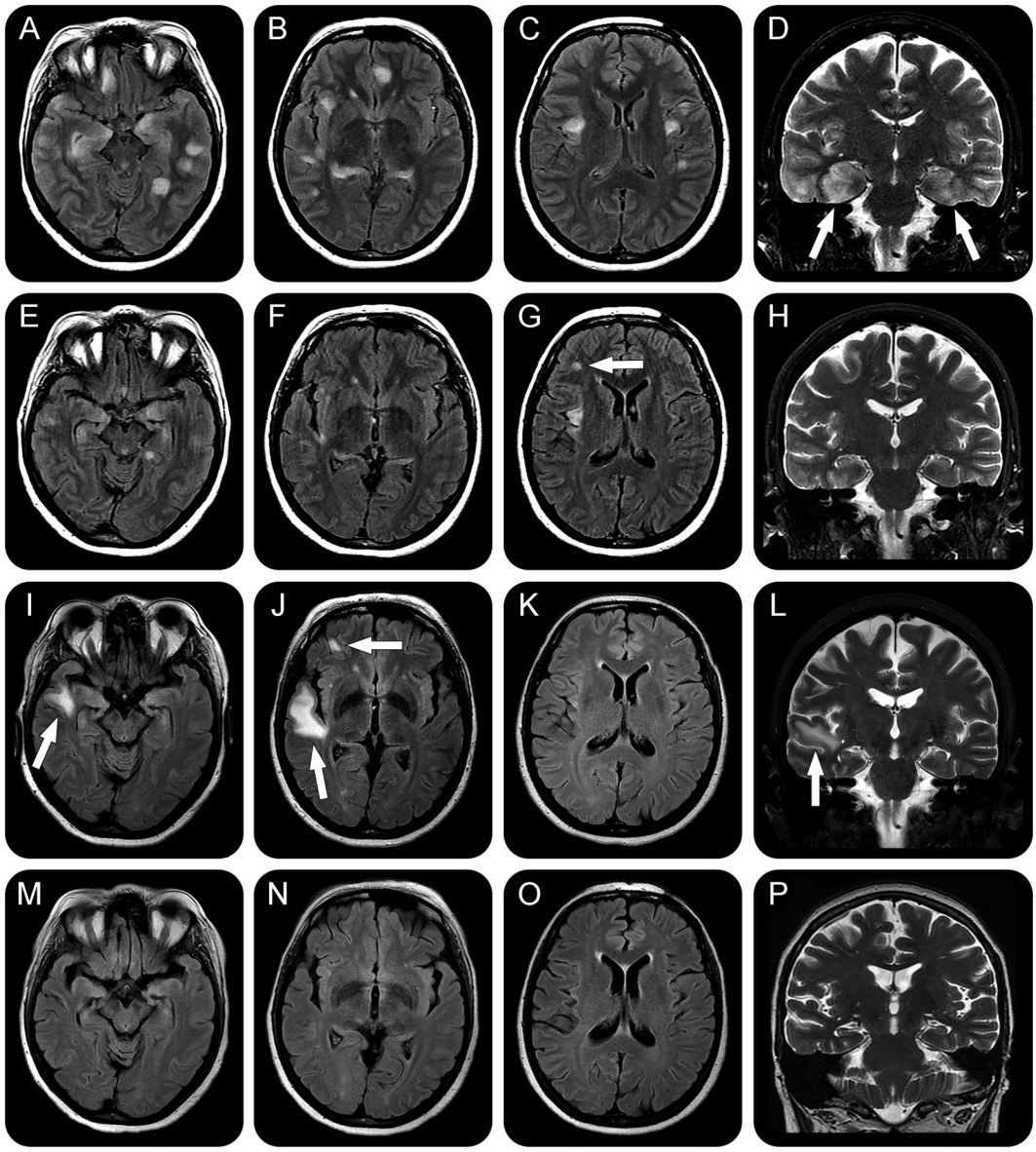
Methylprednisolone 1 g per day for 5 days was started, followed by 6 plasma exchange sessions. After treatment, she scored 25 points on the MMSE, and her memory and anxiety improved. Follow-up brain MRI showed substantial reduction in the number and size of all abnormalities, mainly in the temporal lobes (figure 1), and the PLEDs resolved. Antibodies against cell surface or synaptic proteins were assessed in serum and CSF obtained before immunotherapy using rat brain immunohistochemistry and cell-based-assays, as reported[1,2] These studies showed high levels of serum (1:320) and CSF (1:80) antibodies against the $GABA_A$ receptor and low levels of antibodies against LGI1 (serum 1:80, CSF 1:20). Antibodies against $GABA_B$ receptor, AMPA receptor, NMDA receptor, Caspr2, GlyR, mGLUR5, and mGLUR1 were negative.

Three months after discharge, the patient was having a good recovery, but the brain MRI showed a new subcortical lesion in the right frontal lobe. She underwent repeat methylprednisolone and plasma exchange and surgical removal of the pleural lesion, whose pathology was consistent with thymoma. Tumor antigen expression was examined in tissue obtained from the first thymoma resection (8 years earlier), which showed lack of $GABA_A$ receptor and LGI1 reactivity (not shown), and in tissue from the pleural lesion, which showed expression of both antigens (figure 2). After the indicated treatment, the patient's neurologic function returned close to baseline, and a repeat brain MRI showed resolution of all lesions.

Discussion. Although thymoma is frequently associated with autoimmune disorders, the most common being MG,[3] encephalitis associated with thymoma is rare. A review of the literature demonstrates 30 previously reported cases (table e-1 at Neurology.org/nn).

Supplemental data at Neurology.org/nn

Figure 1 Follow-up of brain MRI

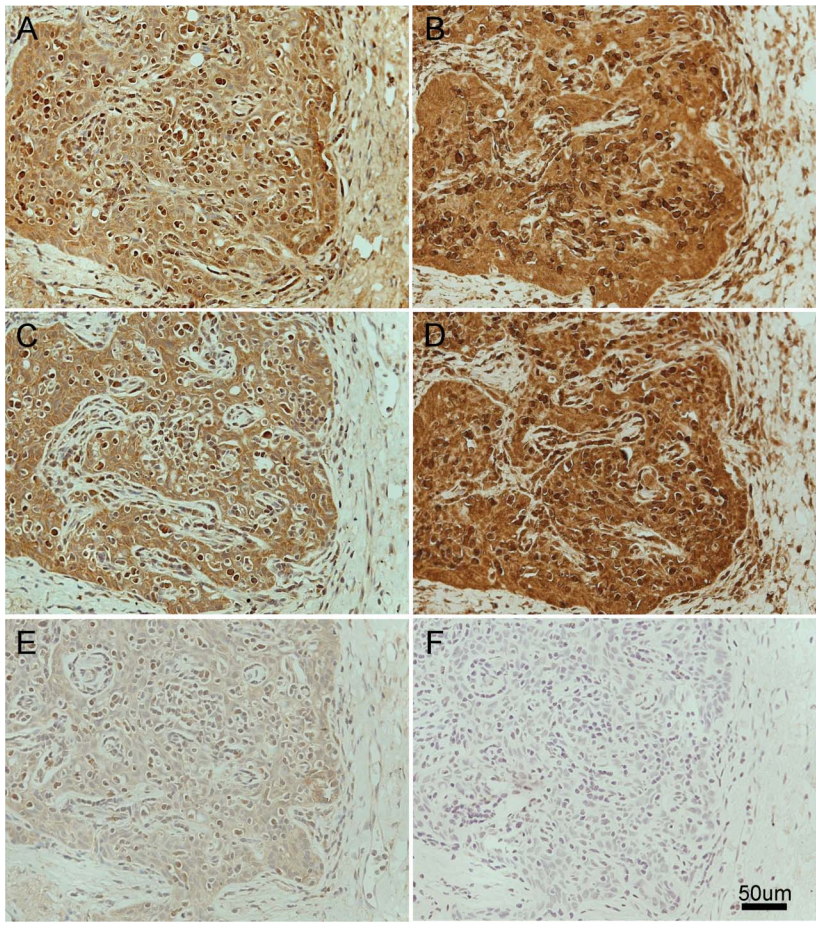


Axial fluid-attenuated inversion recovery (A–C, E–G, I–K, and M–O) and coronal T2-weighted (D, H, L, P) images. Initial exam (A–D) shows multiple hyperintensities involving both hemispheres, without restriction on diffusion sequences. Note the prominent bilateral mesial temporal lobe involvement, mainly on the right side (arrows in D). A repeat MRI 40 days later (E–H) shows a substantial reduction in the number and size of the lesions; however, a new hyperintensity in the subcortical region of the right frontal lobe is evident (arrow in G). There is also an interval enlargement of the lateral ventricles and sulci. A third brain MRI, 108 days after the first one (I–L), demonstrates new predominantly subcortical lesions (arrows in I, J, and L), while the previous ones have disappeared. The last MRI (M–P), 143 days after the first one, shows that after immunotherapy and removal of the metastatic thymoma all abnormalities have disappeared.

These patients often developed clinical features of limbic dysfunction and coexistence of other autoimmunities, similar to the case reported here, but the target antigens were largely unknown. After the initial description of anti-$GABA_A$ receptor encephalitis, Ohkawa et al.[4] reported 2 cases with anti-$GABA_A$ receptor encephalitis and thymoma. These 2 patients had been previously reported as having limbic encephalitis associated with VGKC antibodies[5,6] and shared similarities with our patient, including subacute onset of cognitive and memory deficits associated with thymoma recurrence or residual thymoma, coexistence of LGI1 or Caspr2 antibodies with $GABA_A$ receptor antibody, and remarkable brain MRI abnormalities, which are strikingly similar to those reported in other patients with $GABA_A$ receptor encephalitis.

Our patient provides 2 novelties: First, high levels of $GABA_A$ receptor antibodies were found both in serum and CSF; In the above-mentioned 2 cases with thymoma, the antibody testing was performed only in serum. Second, to our knowledge, this is the

Figure 2 Expression of $GABA_A$ receptor and LGI1 by patient's thymoma



Tissue sections of the patient's thymoma incubated with biotinylated immunoglobulin G (IgG) from a patient with only $GABA_A$ receptor antibodies (A), another patient with only LGI1 antibodies (C), and a control subject without antibodies (E) compared with the reactivity of a commercial antibody against $GABA_A$ receptor (B) (rabbit polyclonal anti-α1 $GABA_A$ receptor, abcam, ab33299, diluted 1:50), a commercial antibody against LGI1 (D) (rabbit polyclonal anti-LGI1, abcam, ab30868, diluted 1:50), and the secondary antibody alone (F). Note the similar pattern of reactivity of human antibodies and commercial antibodies, indicating that the tumor expresses epitopes of $GABA_A$ receptor and LGI1 proteins. The dilution of human IgG was 1:50. All sections were mildly counterstained with hematoxylin.

first case in which expression of the $GABA_A$ receptor is demonstrated in the tumor. It is interesting that this receptor and LGI1 were not detected in the initial sample of tumor obtained 8 years earlier but were present in the most recent sample. These findings raise the question of whether thymoma could express different antigens during its progression, leading to manifestations of different paraneoplastic diseases, as occurred in our and other cases of thymoma-associated encephalitis.[5–7]

This report emphasizes the importance of aggressive immunotherapy along with surgical removal of the tumor in the category of disorders associated with antibodies against relevant cell surface antigens ($GABA_A$ receptor, LGI1), which in our case resulted in clinical and radiologic improvement. This is in contrast with the previously reported patient, who was treated with immunotherapy but did not have tumor removal and had persistent severe cognitive deficits.[5,6]

*These authors contributed equally to the manuscript.

From the Neurology Division (M.M.S., L.H.C., R.N., A.A.Z., L.G.S., G.C.R.F., H.R.S.N.) and Radiology Institute (L.L.), Hospital das Clínicas, São Paulo University, São Paulo, Brazil; August Pi i Sunyer Biomedical Research Institute (IDIBAPS) (M.P.-P., J.O.D.), Barcelona, Spain; Department of Neurology (J.O.D.), University of Pennsylvania, Philadelphia, PA; and Catalan Institution for Research and Advanced Studies (ICREA) (J.O.D.), Barcelona, Spain.

Author contributions: Dr. Simabukuro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He contributed to study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. M. Petit-Pedrol contributed to analysis and interpretation of data and critical revision of the manuscript for important intellectual content. Dr. Castro contributed to study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Dr. Nitrini contributed to study concept and design and critical revision of the manuscript for important intellectual content. Dr. Lucato contributed to analysis and interpretation of data and critical revision of the manuscript for important intellectual content. Dr. Zambon contributed to analysis and interpretation of data and critical revision of the manuscript for important intellectual content. Dr. Silva

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Correspondence to Dr. Simabukuro: mateus.simabukuro@hc.fm.usp.br

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