$GABA_B$ receptor antibodies in limbic encephalitis and anti-GAD–associated neurologic disorders

A. Boronat, BSc
L. Sabater, PhD
A. Saiz, MD
J. Dalmau, MD, PhD
F. Graus, MD

Address correspondence and reprint requests to Dr. Francesc Graus, Servei de Neurologia, Hospital Clínic, Villarroel 170, Barcelona 08036, Spain
fgraus@clinic.ub.es

ABSTRACT

Background: γ-Aminobutyric acid-B receptor antibodies ($GABA_B$R-ab) were recently described in 15 patients with limbic encephalitis (LE), associated with small-cell lung cancer (SCLC) or with concurrent glutamic acid decarboxylase (GAD) antibodies. We analyzed the frequency of $GABA_B$R-ab in 147 patients with LE or neurologic syndromes associated with GAD-ab.

Methods: We examined the presence of $GABA_B$R-ab in 70 patients with LE (33 paraneoplastic with onconeural antibodies, 18 paraneoplastic without onconeural antibodies [5 with Gad-ab], and 19 idiopathic with either GAD-ab [5 patients] or seronegative) and 77 patients with GAD-ab-associated neurologic syndromes other than LE (29 stiff-person syndrome, 28 cerebellar ataxia, 14 epilepsy, and 6 with diverse paraneoplastic neurologic syndromes). $GABA_B$R-ab were analyzed in serum or CSF by indirect immunofluorescence on HEK293 cells transfected with $GABA_{B1}$ and $GABA_{B2}$ receptor subunits.

Results: $GABA_B$R-ab were detected in 10 of the 70 patients with LE (14%). Eight had SCLC and 2 were idiopathic. One of the 8 patients with LE with SCLC had an additional onconeural antibody (Hu) and 2 GAD-ab. $GABA_B$R-ab were identified in 7 (70%) of the 10 patients with LE and SCLC without onconeural antibodies. $GABA_B$R-ab antibodies were not found in patients with GAD-ab and stiff-person syndrome, idiopathic cerebellar ataxia, or epilepsy. However, one patient with GAD-ab, paraneoplastic cerebellar ataxia, and anaplastic carcinoid of the thymus also presented $GABA_B$R-ab.

Conclusions: $GABA_B$R-ab are the most common antibodies found in LE associated with SCLC previously considered "seronegative." In patients with GAD-ab, the frequency of $GABA_B$R-ab is low and only observed in the context of cancer. ***Neurology*® 2011;76:795–800**

GLOSSARY

AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **BRSK** = brain serine/threonine kinase; **$GABA_B$R-ab** = γ-aminobutyric acid-B receptor antibodies; **GAD** = glutamic acid decarboxylase; **LE** = limbic encephalitis; **LGI1** = leucine-rich, glioma-inactivated 1; **NMDAR** = *N*-methyl-D-aspartate receptor; **PCD** = paraneoplastic cerebellar degeneration; **SCLC** = small-cell lung cancer; **SPS** = stiff-person syndrome; **VGKC** = voltage-gated potassium channel.

Recent studies show that some cases of encephalitis in adults and children may be caused by an autoimmune dysfunction that generates antibodies against surface proteins of the CNS synapses.[1] At present, the target antigens include the excitatory glutamate *N*-methyl-D-aspartate (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPAR) receptors, the inhibitory γ-aminobutyric acid-B ($GABA_B$) receptor, and the leucine-rich, glioma-inactivated 1 (LGI1) protein.[2-5]

Patients with any of these autoimmunities may present with a typical syndrome of limbic encephalitis (LE), characterized by short-term memory loss, behavioral disturbances, confusion, and seizures, or in the case of NMDAR antibodies, a widespread encephalitis expressed with subacute atypical psychosis, catatonia, dyskinesias, autonomic instability, and central hypoventilation. Overall, these disorders may be paraneoplastic or idiopathic, the associated

From the Service of Neurology (A.B., L.S., A.S., F.G.), Hospital Clinic and Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain; and Department of Neurology (J.D.), University of Pennsylvania, Philadelphia.

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antibodies are probably pathogenic, and, unlike onconeural antibodies, the presence of these antibodies does not necessarily indicate that the patient has an underlying tumor.[1]

Antibodies to $GABA_B$ receptor ($GABA_BR$-ab) were recently identified in 15 patients with idiopathic or paraneoplastic LE.[4] Seizures were the presenting clinical symptom in 13 patients. Seven of the 15 patients had lung tumors and 5 of these were small-cell lung cancer (SCLC). Three patients also had glutamic acid decarboxylase antibodies (GAD-ab). Ten patients received treatment for the LE and 9 showed neurologic improvement.[4]

We previously described that the concurrent detection of onconeural antibodies, particularly against amphiphysin, and antibodies against neuronal surface proteins was not unusual in patients with paraneoplastic LE and lung cancer.[6] The aim of the present study was to analyze the presence of $GABA_BR$-ab in patients with paraneoplastic (with and without onconeural antibodies) and idiopathic LE, and neurologic syndromes associated with GAD-ab.

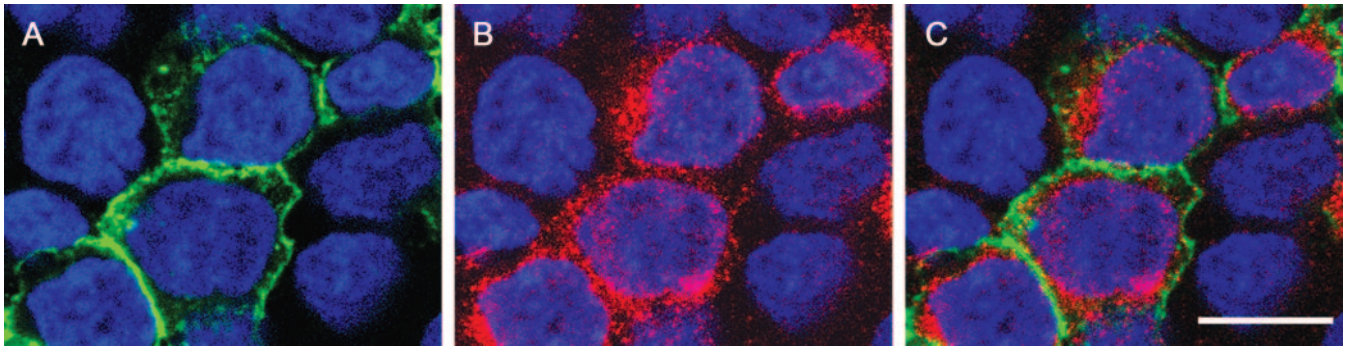
METHODS **Patients.** We reviewed 147 patients with final diagnosis of LE, or with other neurologic syndromes associated with GAD-ab whose serum or CSF was sent to our laboratory (Barcelona, Spain) for analysis of antineuronal antibodies. LE was defined by the subacute onset of short-term memory loss, behavior change, seizures, and involvement of the temporal lobes by EEG, imaging studies, or postmortem examination. LE was considered definite paraneoplastic if a tumor was diagnosed or the serum presented well-characterized onconeural antibodies (Hu, Yo, Ri, CV2, Ma2, amphiphysin).[7] The diagnosis of definite idiopathic LE required the absence of cancer and well-characterized onconeural antibodies, and a follow-up of at least 3 years. Patients with LE with a shorter follow-up were classified as possible idiopathic LE. Patients with GAD-ab were classified, as previously reported, in one of the following groups: stiff-person syndrome (SPS), cerebellar ataxia, isolated epilepsy, and paraneoplastic neurologic syndromes.[8] The information was obtained from forms filled out by the referring neurologists, telephone interviews, and review of the clinical records.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Ethics Committee of the Hospital Clinic. Samples are deposited in the collection of biological samples named "neuroinmunologia" registered in the biobank of Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Barcelona, Spain.

Immunologic studies. Onconeural antibodies, SOX1-ab, and GAD-ab were screened by immunohistochemistry performed on frozen sections of paraformaldehyde-perfused rat cerebellum using an avidin-biotin immunoperoxidase technique and confirmed by immunoblot when indicated.[7] GAD-ab were confirmed by radioimmunoassay.[8] Neuropil antibodies were screened by immunohistochemistry on frozen sections of rat brain postfixed with 4% paraformaldehyde.[2] The presence of AMPA glutamate receptor antibodies was confirmed by immunofluorescence on HEK-293 cells transfected with plasmids containing the appropriate antigens,[3] and voltage-gated potassium channel (VGKC) antibodies were confirmed by radioimmunoassay.

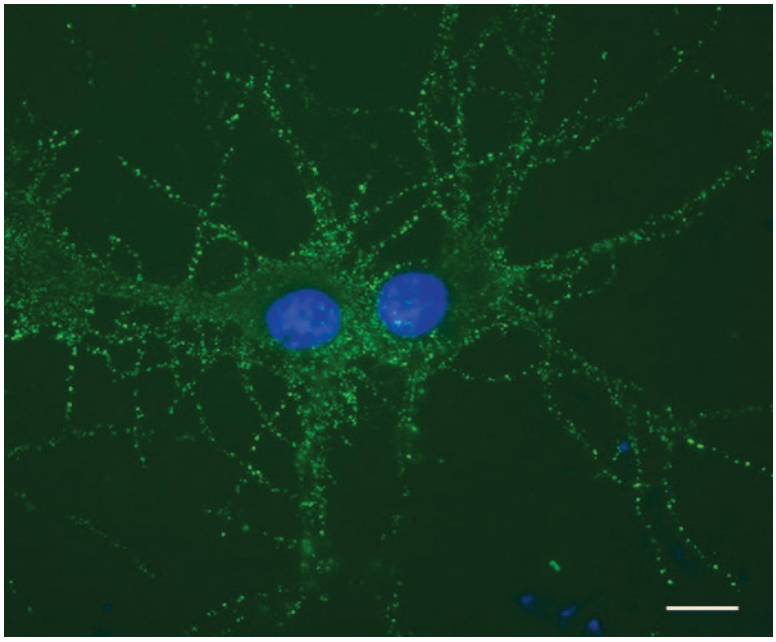
$GABA_BR$-ab were screened on HEK293 cells transfected with plasmids containing rodent $GABA_{B1}$ and $GABA_{B2}$ in equimolar ratios.[4] Positive samples were also analyzed by immunocytochemistry of rat hippocampal neuronal cultures. Both techniques have previously been described.[4] Briefly, HEK293 transfected cells were incubated with the patients' serum (dilution 1:20) or CSF (1:2) for 1 hour at 37°C, washed, fixed with 4% paraformaldehyde, permeabilized with triton X, incubated with a rabbit polyclonal $GABA_{B1}$ antibody (1:1,000) (Santa Cruz Biotechnology, sc-14006; Santa Cruz, CA) followed by the appropriate Alexa Fluor secondary antibodies (Molecular Probes, Eugene, OR). For immunocytochemistry of rat hippocampal neuronal cultures, live neurons grown on coverslips were incubated with the patients' serum (1:100) or CSF (1:2) for 1 hour at 37°C, washed, fixed with 4% paraformaldehyde, and immunoreacted with antihuman immunoglobulin G Alexa Fluor second-

Figure 1 **Detection of γ-aminobutyric acid-B receptor antibodies ($GABA_BR$-ab) using a HEK293 cell-based assay**



HEK293 cells were transfected to express $GABA_{B1/B2}$ receptor and incubated live, not permeabilized, with a patient's CSF. Afterwards, cells were fixed, permeabilized, and incubated with a polyclonal antibody against an intracellular epitope of the B1 subunit of the $GABA_B$ receptor. Note that patient's CSF stains the cell surface of cells that specifically express $GABA_B$ receptors (A), as demonstrated by the intracellular reporter antibody (B). Both reactivities are shown merged in C. Nuclei counterstained with DAPI. Scale bar = 20 μm.

Figure 2 Primary culture of rat hippocampal neurons incubated in vivo with CSF of a patient with γ-aminobutyric acid-B receptor antibodies



There is an intense punctate reactivity in the neuronal membrane consistent with immunoreactivity against a surface antigen. Scale bar = 20 μm.

ary antibody. Results were photographed under a fluorescence microscope using Zeiss Axiovision software (Zeiss, Thornwood, NY). To confirm the specificity of the neuronal reactivity, all positive samples were preabsorbed with the non-neuronal cell line HEK293 to remove antibodies that could react with non neuronal specific surface antigens.

RESULTS Eleven of the 147 patients tested positive for $GABA_BR$-ab on the screening of HEK293 cells transfected with the B1 and B2 subunits of the $GABA_BR$ (figure 1). All positive samples immunoreacted in vivo with primary cultures of hippocampal neurons (figure 2). $GABA_BR$-ab were positive in both serum and CSF in the 5 patients from whom paired samples were available. Median titer of $GABA_BR$-ab was 1/120 (range 40–2,000) in serum and 1/60 (range 20–640) in the CSF.

We found $GABA_BR$-ab in 10 patients with LE. Positive $GABA_BR$-ab were identified more frequently in the group of paraneoplastic LE without onconeural antibodies (previously considered "seronegative") (table 1). Seven (39%) of the 18 patients were $GABA_BR$-ab-positive and all had SCLC. In total, positive $GABA_BR$-ab were identified in 7 (70%) of the 10 patients with LE and SCLC without onconeural antibodies. The other 3 patients were positive for AMPAR-ab. We previously demonstrated that 9 (39%) of 23 patients with paraneoplastic LE had concomitant onconeural or other antibodies against intraneuronal antigens, and antibodies against unidentified neuronal surface antigens.[6] In this study, we analyzed 33 patients with LE and onconeural antibodies, and only one, with Hu-ab and SCLC, tested positive for $GABA_BR$-ab. However, 4 of the 7 patients with LE with $GABA_BR$-ab without onconeural antibodies presented antibodies against intracellular antigens (table 2). Two patients had GAD-ab (one also SOX1-ab), one Hu-ab, and, in 2 cases previously reported, one had brain serine/threonine kinase (BRSK)2-ab and the other SOX1 and VGKC-ab.[9,10]

No tumor was identified in the remaining 2 $GABA_BR$-ab-positive patients but the follow-up is too short to classify them as definite idiopathic LE. In the group of 10 patients with LE and GAD-ab, the coincidence of $GABA_BR$-ab and GAD-ab occurred in 2 patients with SCLC whereas the other 3 patients with paraneoplastic LE associated with other tumors (thymoma 2, lymphoma) were $GABA_BR$-ab-negative. None of the 5 patients with idiopathic LE and GAD-ab were positive for $GABA_BR$-ab (table 1).

A summary of the clinical features of the $GABA_BR$-ab-positive patients is presented in table 2. Nine of the 10 patients with $GABA_BR$-ab and LE were men. Median age was 60 years (range 47–70 years). Seizures were the predominant and presenting symptom in 8 patients and 2 required admission to the intensive care unit for control of the seizures. All patients also presented confusion, disorientation, memory loss, or behavior changes consistent with encephalitis predominantly involving the limbic system. The CSF disclosed mild lymphocyte pleocytosis in 4 patients. Brain MRI showed increased fluid-attenuated inversion recovery signal in one or both hippocampus and amygdala in 7 patients. In 4 of them the initial brain MRI was reported normal.

Table 1 Frequency of $GABA_BR$-ab in 147 patients with limbic encephalitis or GAD-ab–associated neurologic syndromes

Syndrome	No. of patients	$GABA_BR$-ab positive (%)	Comments on positive cases
Paraneoplastic LE	51	8 (16)	
With onconeural ab[a]	33	1 (3)	Hu-ab with SCLC
Without onconeural ab[b]	18	7 (39)	All SCLC, GAD-ab: 2
Idiopathic LE[c]	19	2 (14)	Short follow-up
GAD-ab–positive, non-LE	77	1 (1)	
Stiff-person syndrome	29	0 (0)	
Cerebellar ataxia	28	0 (0)	
Epilepsy	14	0 (0)	
Paraneoplastic	6	1 (17)	Cerebellar ataxia

Abbreviations: $GABA_BR$-ab = γ-aminobutyric acid-B receptor antibodies; LE = limbic encephalitis; SCLC = small-cell lung carcinoma.
[a] Hu-ab (26), Ma2-ab (4), amphiphysin-ab (3). Lung cancer in 18 patients.
[b] GAD-ab in 5 patients. Lung cancer in 11 patients (SCLC 10, non-SCLC 1).
[c] GAD-ab in 5 patients. Definite idiopathic (≥3 years of follow-up without cancer) LE, 7 patients.

Table 2 Clinical features and outcome of patients with positive $GABA_BR$-ab

Case	Age, y/sex	Cancer	Presenting symptoms[a]	MRI temporal lesions	CSF pleocytosis (WBC)	Other antineuronal-ab	Treatment	Outcome
1	60/M	SCLC	Status epilepticus	Left	Yes (unknown)	None	Steroids, IVIg	Partial control of seizures (dead from ICU complications)
2	57/F	SCLC	Seizures, behavior change	Bilateral	No	None	Steroids, IVIg	Complete recovery[b]
3	66/M	SCLC	Seizures, confusion	Normal	Yes (18)	GAD	Steroids, IVIg	Not available (short follow-up)
4[c]	47/M	SCLC	Seizures, behavior change, memory impairment	Bilateral	Yes (20)	SOX1, VGKC	Steroids, IVIg, chemotherapy	Partial recovery, relapsing course (dead from cancer progression)
5[d]	69/M	SCLC	Seizures, memory impairment, confusion	Left	Traumatic	None	Chemotherapy	Partial response; dead from cancer-related treatment (3 mo)
6[b]	70/M	SCLC	Seizures, memory impairment, confusion	Normal	No	GAD, SOX1	Steroids, IVIg, chemotherapy	No response; dead from cancer-related treatment (2 mo)
7	58/M	SCLC	Seizures, memory impairment	Bilateral	Yes (15)	Hu	Steroids, IVIg, chemotherapy	No response (dead from LE)
8[a]	61/M	SCLC	Memory impairment	Bilateral	No	BRSK2	None	No response; lost when tumor was diagnosed 9 mo later
9	61/M	No	Confusion, seizures, behavior change	Normal	No	None	IVIg	Partial improvement; severe ICU neuropathy
10	50/M	No	Seizures, behavior and memory impairment	Bilateral	No	None	Antiepileptics only	Complete recovery
11	57/F	Carcinoid of thymus	Subacute cerebellar ataxia	Normal	No	GAD	Steroids	Complete recovery

Abbreviations: BRSK2 = brain serine/threonine kinase 2; $GABA_BR$-ab = γ-aminobutyric acid-B receptor antibodies; GAD = glutamic acid decarboxylase; IVIg = IV immunoglobulin; SCLC = small-cell lung cancer; WBC = white blood cells.

[a] Predominant symptom listed first.

[b] Recovery before the start of chemotherapy.

[c] Patients previously reported in references [10] and [9].

[d] Included in the initial series of GABAR-ab.[4]

Only one patient had hyponatremia. Seven patients were treated with steroids, IV immunoglobulins, or combination of both drugs. Three of the 8 patients with SCLC were also treated with chemotherapy. Only 2 patients made a complete recovery (one without cancer) and none of them had concurrent antineuronal antibodies. Partial responses to the indicated treatments were achieved in 4 with a relapse in one of them.

$GABA_BR$-ab were not detected in 71 patients with GAD-ab and nonparaneoplastic SPS, cerebellar ataxia, or epilepsy. In contrast, one of the 6 patients with paraneoplastic neurologic syndromes and GAD-ab was $GABA_BR$-ab positive (table 1). She was a 57-year-old woman with a known anaplastic carcinoid of the thymus and bone metastases. She developed nausea, vomiting, gait instability, and diplopia. Neurologic examination disclosed a normal mental status, bilateral horizontal nystagmus, and cerebellar gait ataxia. The patient was treated with oral steroids and the symptoms slowly resolved over the ensuing 3 months.

The other 5 GAD-ab-positive patients without $GABA_BR$-ab presented with paraneoplastic encephalomyelitis associated with pancreatic cancer[11] and cerebellar ataxia with breast cancer (2 patients), non-SCLC, and neuroendocrine thymic carcinoma.[12]

To see if $GABA_BR$-ab associate with other cases of paraneoplastic cerebellar degeneration (PCD), we analyzed the serum or CSF of a series of 45 patients with PCD and lung cancer (35 with SCLC). The majority (73%) were included in a previous study.[13] These patients had Hu-ab (15%) or voltage-gated calcium channel antibodies (50%). However, all were negative for $GABA_BR$-ab.

DISCUSSION The current study expands our knowledge of the profile of symptoms and immunologic associations of $GABA_BR$-ab. We found that $GABA_BR$-ab are the most common antibodies identified in patients with SCLC and LE previously considered "seronegative." Although the occurrence of $GABA_BR$-ab and GAD-ab was observed in an initial series of 15 patients,[4] when we tested a larger series of patients with several

types of neurologic syndromes associated with GAD-ab, $GABA_BR$-ab were only identified in those who had a paraneoplastic syndrome.

At the time of the initial description of Hu-ab as markers of neurologic syndromes associated with SCLC, we observed that up to 50% of patients with LE were "seronegative." The syndrome of these patients was highly restricted to the limbic system and seemed to improve more often after treatment of the cancer than that of patients with Hu-ab.[14] In the current study, 7 of 10 (70%) patients with LE, SCLC without onconeural antibodies had $GABA_BR$-ab. The other 3 patients were positive for AMPAR-ab.[3,15] Taken together, all patients with LE and SCLC previously considered seronegative for onconeural antibodies had antibodies against synaptic receptors. Although the series is small, the association between AMPAR-ab and SCLC seems to be less robust than that of $GABA_BR$-ab. Review of published cases and the current series shows that all 11 patients with paraneoplastic LE with $GABA_BR$-ab had SCLC (in one case a neuroendocrine tumor of the lung)[4] whereas only 7 of 13 patients with AMPAR-ab had SCLC. Other tumors associated with AMPAR-ab were benign or malignant thymomas, non-SCLC, and breast cancer.[3,15,16]

We previously reported the occurrence of SCLC-associated onconeural antibodies (Hu, amphiphysin, CV2) and antibodies to unidentified neuronal surface proteins in 4 of 11 (36%) patients with paraneoplastic LE.[6] In the current study we show that Hu-ab and $GABA_BR$-ab only occurred in 1 of 33 patients, suggesting that this specific association is uncommon. In contrast, we confirm that 40% of these patients had antibodies that are markers of the underlying SCLC (SOX1,[17] BRSK2[9]) or directed against VGKC or GAD.[4]

As reported, the clinical profile of patients with LE and $GABA_BR$-ab is not substantially different from that seen in other autoimmune LE. The high frequency of seizures was noted in the previous study and could be explained by the role of $GABA_B$ receptors in the development of seizures.[18] Since almost 50% of patients with all types of LE[19] and the majority of cases with GAD antibodies develop seizures,[8,20] this symptom does not predict that the underlying autoimmunity is against $GABA_BR$.

The clinical outcome of our patients was not as good as expected from an antibody-mediated encephalitis.[21] However, many patients did not receive tumor treatment or died shortly from complications of the treatment, an important requirement for potential control of the neurologic dysfunction.[2,22] One of the patients without cancer (patient 10) was treated only with antiepileptics and made a complete recovery. His follow-up is too short and we cannot rule out the possibility of future neurologic relapses. Complete recovery in the absence of immunotherapy has been reported in patients with anti-NMDAR encephalitis and emphasizes the concept that autoimmune synaptic encephalitides are underdiagnosed.[23]

In this study, all patients with concurrent $GABA_BR$-ab and GAD-ab had a paraneoplastic neurologic disorder. In the initial series, 2 of the 8 patients with idiopathic LE encephalitis had additional GAD-ab.[4] We did not find $GABA_BR$-ab in patients with LE or isolated epilepsy with GAD-ab except in the 2 patients with SCLC. Our 5 patients with idiopathic LE and GAD-ab were women with a median age of 29 years and 4 presented with seizures. This profile is similar to that recently reported in a series of 9 patients.[20] One of the 2 patients with concurrent $GABA_BR$-ab and GAD-ab and idiopathic LE previously reported also had this phenotype. To determine how often both antibodies coincide in patients with idiopathic LE, we suggest routinely looking for $GABA_BR$-ab in all patients with LE suspected to be related to GAD-ab.

The only patient with GAD-ab and $GABA_BR$-ab without LE had a reversible cerebellar ataxia associated with carcinoid of the thymus. $GABA_BR$-ab titers were similar to those of patients with LE. $GABA_B$ receptors are widely expressed in the brain with the highest levels in the hippocampus, thalamus, and cerebellum.[24] Therefore it is plausible that some patients with $GABA_BR$-ab may develop cerebellar rather than hippocampal dysfunction. Low titers of $GABA_BR$-ab have previously been reported in a patient with nonparaneoplastic cerebellar ataxia and GAD-ab.[4] However, we did not find any case in our series of patients with nonparaneoplastic cerebellar ataxia with GAD-ab[8] or with paraneoplastic cerebellar degeneration and lung cancer,[13] suggesting that $GABA_BR$ autoimmunity rarely causes cerebellar dysfunction.

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DISCLOSURE

Dr. Boronat, Dr. Sabater, and Dr. Saiz report no disclosures. Dr. Dalmau has received royalties from a patent re: Ma2 autoantibody test and has patents pending re: NMDA and $GABA_B$ receptor autoantibody tests (license fee payments received from EUROIMMUN AG); and receives research support from funding from EUROIMMUN AG and the NIH/NCI. Dr. Graus serves on the editorial board of *Lancet Neurology* and has received research support from Fondo Investigaciones Santitarias.

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