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Syndrome and outcome of antibody-negative limbic encephalitis

Francesc Graus, MD, PhD^{1,2}, Domingo Escudero, MD, PhD², Laura Oleaga, MD³, Jordi Bruna, MD⁴, Alberto Villarejo-Galende, MD⁵, Jordi Ballabriga, MD⁶, María Inés Barceló, MD⁷, Francisco Gilo, MD⁸, Stoyan Popkirov, MD⁹, Pavel Stourac, MD¹⁰, and Josep Dalmau, MD, PhD^{1,11,12}

¹Neuroimmunology Program, Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona (Spain)

²Service of Neurology, Hospital Clinic, Barcelona (Spain)

³Department of Radiology, Hospital Clinic, Barcelona (Spain)

⁴Unit of Neuro-Oncology, Hospital de Bellvitge, -Institut Català d'Oncologia(ICO) L'Hospitalet, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Hospitalet del Llobregat (Spain)

⁵Service of Neurology, Hospital 12 de Octubre, Madrid (Spain)

⁶Service of Neurology, Hospital Son Llatzer, Palma de Mallorca (Spain)

⁷Service of Neurology Hospital Son Espases, Palma de Mallorca (Spain)

⁸Service of Neurology, Hospital Nuestra Señora del Rosario, Madrid (Spain)

⁹Department of Neurology, University Hospital Knappschaftskrankenhaus Bochum, Ruhr-University Bochum (Germany)

¹⁰Department of Neurology, Masaryk University and University Hospital Brno (Czech Republic)

¹¹Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona (Spain)

¹²Department of Neurology, University of Pennsylvania, Philadelphia, (USA)

Abstract

Objective—To report the clinical characteristics of 12 patients with limbic encephalitis (LE) who were antibody-negative after a comprehensive immunological study.

Methods—Review of clinical records of 163 patients with LE. Immunohistochemistry on rat brain, cultured neurons, and cell-based assays were used to identify neuronal autoantibodies.

Correspondence: Francesc Graus, MD, PhD. IDIBAPS. Villarroel 170, Barcelona, 08036, Spain. Phone: +34 932275414; Fax: +34 932275783; fgraus@clinic.cat.

DR. DOMINGO ESCUDERO (Orcid ID : 0000-0002-6852-6936)

DR. J. BRUNA (Orcid ID : 0000-0001-6895-5047)

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Patients were included if 1) there was adequate clinical, CSF, and MRI information to classify the syndrome as LE, 2) MRI images were accessible for central review, and 3) serum and CSF were available and confirmed negative for neuronal antibodies.

Results—Twelve (7%)/163 LE patients (median age: 62 years; range: 40–79; 9 [75%] male) without neuronal autoantibodies were identified. The most frequent initial complaints were deficits in short-term memory leading to hospital admission in a few weeks (median time: 2 weeks; range: 0.5–12). In four patients the short-term memory dysfunction remained as isolated symptom during the entire course of the disease. Seizures, drowsiness, and psychiatric problems were unusual. Four patients had solid tumors (1 lung, 1 esophagus, 2 metastatic cervical adenopathies of unknown primary tumor) and 1 chronic lymphocytic leukemia. CSF showed pleocytosis in 7 (58%) with a median of 13 white blood cells/mm³ (range: 9–25). Immunotherapy included corticosteroids, intravenous immunoglobulins, and combinations of both drugs or with rituximab. Clinical improvement occurred in 6 (54%) of 11 assessable patients.

Conclusions—Despite the discovery of new antibodies, 7% of LE remains seronegative. Antibody-negative LE is more frequent in older males and usually develops with predominant or isolated short-term memory loss. Despite the absence of antibodies, patients may have an underlying cancer and respond to immunotherapy.

Keywords

Limbic encephalitis; autoimmune; antibodies; paraneoplastic

Introduction

Limbic encephalitis (LE) is a well characterized neurological syndrome that usually has an autoimmune etiology.¹ Although the term LE is frequently misused to identify any type of paraneoplastic encephalitis or patients with isolated epilepsy and enlarged hippocampus,² recently proposed criteria emphasize the combination of clinical and imaging features for its diagnosis.¹ Symptoms of LE present with a subacute onset, usually in weeks, including confusion, short-term memory loss, behavioral changes, and often seizures. The CSF presents mild to moderate lymphocytic pleocytosis (usually <100 white blood cells (WBC)/mm³) in 60–80% of the patients, and the MRI shows increased FLAIR/T2 signal in the medial aspect of one or both temporal lobes.¹ When bilateral involvement occurs the diagnosis of definite autoimmune LE can be made even in the absence of neuronal antibodies provided that other alternative causes are reasonably excluded.¹

Although the recent characterization of novel antibodies against cell surface and synaptic antigens³ has changed the diagnostic and treatment approach to LE and proved that previously seronegative cases were indeed associated with neuronal autoantibodies, there is no data on the frequency and clinical characteristics of patients with autoimmune LE that remain antibody negative. The recognition of these patients is important in an era that over-relies on antibody testing for the diagnosis of neurological syndromes of autoimmune origin.

In the present study we report the clinical features of 12 patients with autoimmune LE that were antibody-negative after comprehensive immunological investigations.

Methods

Patients

We reviewed the clinical information of 163 patients with clinical and MRI features of LE and whose serum and CSF were sent for antibody testing to the laboratory of Hospital Clinic (Barcelona, Spain) between January 2000 and June 2017. Patients included in the study fulfilled the following criteria: 1) adequate clinical, CSF, EEG, and MRI information to classify the syndrome as LE, 2) MRI studies available for central review by an experienced neuroradiologist, and 3) serum and CSF available for antibody testing which turned out negative for known antibodies and on cultures of live hippocampal neurons (see below). LE was considered paraneoplastic when a tumor was diagnosed within 5 years of onset of neurological symptoms.⁴

Written informed consent for the storage and use of samples for research was obtained from patients or representative family members. The study was approved by the internal review board of the Hospital Clínic, Barcelona, Spain.

Detection of antineuronal antibodies and screening for novel cell surface autoantigens

All serum and CSF samples were examined for onconeural antibodies (Hu, Yo, Ri, CV2 (CRMP5), amphiphysin, Ma1, Ma2, Tr (DNER), Zic4, and SOX1), GAD, AK5, and cell surface antibodies (NMDAR, AMPAR, GABA_AR, GABA_BR, IgLON5, CASPR2, LGI1, DPPX, neurexin 3 α , mGluR1, and mGluR5) using reported techniques.^{3–7} Samples were also examined for antibodies to unknown neuronal antigens using immunohistochemistry on rat brain either post-fixed or perfused with paraformaldehyde and immunofluorescence on cultured live hippocampal neurons and HEK293 cells transfected with the appropriate antigens, as reported.^{5–8}

Results

We identified 12 (7%) antibody-negative patients out of 163 with LE. The remaining 151 LE were antibody-positive (LGI1: 71, GABA_BR: 26, Ma2: 13, AMPAR: 12, Hu: 11, CASPR2: 10, SOX1: 3, AK5:2, mGluR5:1, amphiphysin: 1, neurexin 3 α : 1). Predominant clinical features, response to immunotherapy and outcome at the last visit of the 12 antibody-negative LE patients are summarized in Table 1. Median age was 62 years (range: 40–79 years) and 9 (75%) were male. A tumor was identified in 5 (42%) patients. All but one tumor were diagnosed several months after the onset of LE (Table 1). Other comorbidities were rare; one patient (Patient 6, table 1) had heart transplantation 11 years before the onset of LE and she was on low doses of steroids and mycophenolate at the time of diagnosis. Prodromal symptoms were reported by 6 (50%) patients and included mild flu-like symptoms, nausea and vomiting or diarrhea and in one patient, episodes of high fever during the 5 months preceding the onset of LE (Table 1).

The most common initial complaints were deficits in short-term memory along with temporal disorientation and confusion that lead to hospital admission in a few weeks (median time 2 weeks; range: 0.5–12). In four (33%) patients the short-term memory dysfunction was the most relevant symptom that remained isolated throughout the course of

the disease. Unlike other types of LE, seizures, drowsiness, or psychiatric problems were unusual. Only 1 (8%) patient had seizures that did not occur at the onset of the disease nor were severe or frequent in number. Two patients complained of visual hallucinations and one developed a Klüver-Bucy syndrome but the remaining 9 (75%) patients did not develop behavior or personality/mood changes like agitation, anxiety, depression or full-blown psychosis.

By definition, brain MRI T2/FLAIR abnormalities involving both hippocampi were found in all patients. In addition, 4 (33%) of them had involvement of the insula, frontoorbital cortex or basal ganglia. CSF pleocytosis (> 5 WBC/mm³) was observed in 7 (58%) patients with a median of 13 WBC/mm³ (range: 9–25). EEG was abnormal in 10 (83%) patients, showing focal or diffuse slowing without associated epileptiform discharges. Only two patients had a normal EEG and no CSF pleocytosis. Other causes of LE were reasonably excluded: PCR for herpes viruses was negative in the CSF, there was no clinical history or laboratory evidence of systemic autoimmune disorders, neurosyphilis or Whipple disease, and anti-thyroid antibodies were negative. Lastly, the follow-up excluded CNS malignancies or neurodegenerative diseases.

Immunotherapy (Table 1) included intravenous corticosteroids or immunoglobulins in all patients either alone (7 patients), combinations of both drugs (3), or with rituximab (2). Clinical improvement occurred in 6 (54%) of 11 assessable patients. Autopsy was granted in patient 9 (table 1) who died from complications of a massive stroke. In the contralesional cerebral hemisphere analysis of the hippocampus disclosed perivascular and parenchymatous infiltrates with neuronal loss and gliosis. Immunohistochemical studies showed numerous CD8+ T cells that were frequently located in close proximity to neurons (Figure 1).

Discussion

This study demonstrates that despite new techniques for antibody detection and the recently identified large repertoire of antibodies against neuronal cell surface antigens there is a subgroup of autoimmune LE that remains antibody-negative.⁹ The frequency of 7% is not very different from that of 11% identified in our previous study in 2008 when we started to identify antibodies against surface antigens in LE.¹⁰ Our findings also support the recent proposed criteria for definite LE which do not require the demonstration of neuronal antibodies provided that patients have a subacute clinical (< 3 months) presentation of short-term memory deficit, seizures, or psychiatric symptoms, bilateral MRI FLAIR/T2 abnormalities predominantly involving the medial temporal lobes, and either CSF pleocytosis (WBC > 5 /mm³) or EEG with epileptic or slow activity involving the temporal lobes.¹

Previous studies on seronegative LE included isolated case reports with incomplete immunological studies, for example published before the description of antibodies closely associated with LE such as GABA_B-receptor antibodies, LE associated with systemic autoimmune disorders, or resulting from immunological adverse effects of immune checkpoint inhibitors.^{11–18}

Although our patients did not have distinctive clinical features compared with reported antibody-positive LE, a few issues must be emphasized. The main clinical presentation was rapid, in a few weeks, and included cognitive dysfunction with prominent short-term memory deficits and disorientation. Drowsiness, seizures, and severe behavioral changes, commonly observed in antibody-positive LE, were rarely described. The frequency of seizures for example is >50% in series of antibody-positive LE a figure much lower than the 8% found in the present study.^{19–21} This clinical presentation is similar to that seen in LE and AK5 antibodies, a non-paraneoplastic LE that occurs in older patients (median age 64 years) and, as in our patients, may present with isolated anterograde amnesia.²² Antibody-negative LE may be paraneoplastic but the associated tumors (Table 1) differ from those commonly seen in antibody-positive LE (e.g., small-cell lung cancer and Hu or GABA_BR antibodies; testicular cancer and Ma2 antibodies). Therefore, the presence of an underlying tumor in 42% of our patients emphasizes the need for tumor screening in LE patients without neuronal autoantibodies.

The term antibody-negative, or seronegative, LE has been used to describe a subgroup of patients with temporal lobe epilepsy and MRI evidence of enlarged amygdala or hippocampus in FLAIR/T2 sequences who did not have neuronal antibodies.² As defined in our series, LE includes a set of clinical and MRI criteria that are almost never fulfilled by patients who present with isolated epilepsy. In fact, we observed that antibody negative LE patients rarely develop seizures as part of the clinical syndrome. An important terminological problem also seems to apply to patients considered to have LE as the trigger of temporal lobe epilepsy with hippocampal sclerosis. Although LE may in some cases lead to hippocampal sclerosis, many of the reported patients had unilateral or chronic, asynchronous involvement of the hippocampi (sometimes months or years apart), presenting with seizures and with clinical features and disease course different from those included in the criteria of LE.^{23,24} In our opinion the use of the term LE in these patients is misleading and we favor the proposed alternative name of temporal lobe epilepsy with amygdala enlargement of autoimmune origin.²⁵

A limitation of our study is that it does not provide a biomarker to confirm that antibody-negative LE is indeed autoimmune and the underlying mechanisms involved. In one of our paraneoplastic patients the neuropathological findings suggested that at least in some cases, the LE could be T-cell mediated as proposed for LE associated with onconeural antibodies.²⁶ On the other hand, immunotherapy was beneficial in 50% of our patients suggesting that potentially undetected antibodies could be responsible for the syndrome. The fact that 75% of the patients were older men raises the possibility that some could have had low titer LGI1 antibodies undetectable by current tests. However, this is unlikely because the clinical profile of patients with anti-LGI1 LE is different, with high frequency of different types of seizures, often preceded by faciobrachial dystonic seizures, and hyponatremia.^{21,27} We cannot rule out the possibility of yet unknown antibodies which may be undetectable with the techniques used here. For example, Lambert-Eaton myasthenic syndrome is caused by antibodies against P/Q type voltage gated calcium channels. These antibodies are determined by radioimmunoassay but they are undetectable by immunohistochemical or immunocytochemical techniques used in our study.²⁸

Overall, the current findings along with the reported clinical and MRI criteria for LE,¹ demonstrate the occurrence of antibody negative LE of possible autoimmune etiology. Importantly, patients with this disorder may have cancer but more than 50% had substantial neurological improvement after immunotherapy. This type of LE is more frequent in older males and usually presents with predominant or isolated short-term memory loss. The task for future studies is to determine whether these patients have autoantibodies that are undetectable with current methods.

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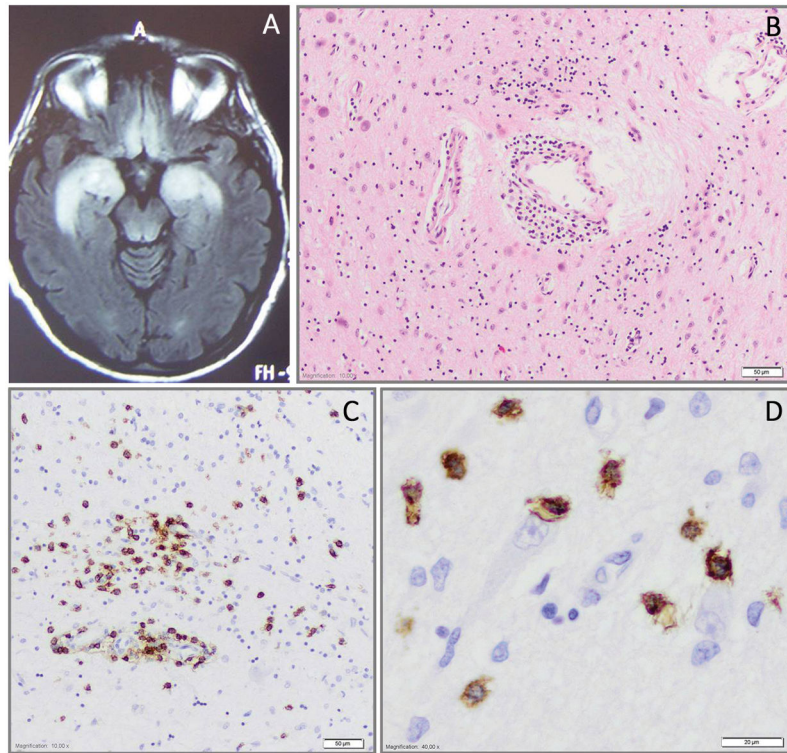


Figure 1. Brain MRI and neuropathological findings in a patient with antibody-negative LE and adenocarcinoma of the lung. Panel A, axial FLAIR showing high signal intensity in both hippocampi and gyrus recti. Panel B, hematoxylin and eosin staining of hippocampus demonstrating perivascular and parenchymatous inflammatory infiltrates. Immunohistochemical analysis showed many CD8+ T cells in the parenchyma (Panel C) and in close apposition with neurons (Panel D). Panels C and D lightly counterstained with hematoxylin. Positive CD8 T cells are stained brown.

Table 1

Clinical features of 12 patients with antibody-negative limbic encephalitis

Patient # Age/sex	Tumor (delay in months)	Prodromal symptoms	Main symptoms	Seizures	CSF WBC	Treatment	Outcome, last follow-up (months)
1. 65/M	None	No	Memory loss evolving to Klüver-Bucy syndrome	No	0	Intravenous steroids	^b Sudden death (1)
2. 40/F	None	Low-grade fever	Isolated short-term memory loss	No	10	Intravenous steroids	Partial improvement. Independent for ADL. (151)
3. 59/M	None	Gastro-enteritis	Isolated short-term memory loss	No	0	Intravenous steroids and immunoglobulins	No improvement. Severe cognitive deficits. (168)
4. 69/M	^a H&N (6)	Fever episodes	Short-term memory loss, drowsiness and confusion	No	3	Intravenous steroids and chemotherapy	Improved. Independent for ADL. (24)
5. 41/M	None	Fever and headache	Short-term memory loss, agitated, visual hallucinations	Yes	21	Intravenous steroids	Improved. Independent for ADL. (6)
6. 79/F	Esophagus (-19)	Gastro-enteritis	Short-term memory loss and confusion	No	11	Intravenous steroids and rituximab	No improvement. Died from sepsis (6)
7. 65/M	CLL (1)	No	Short-term memory loss and confusion	No	9	Intravenous steroids and rituximab	No improvement. Died from the CLL (6)
8. 59/M	^a H&N (6)	No	Short-term memory loss, apatic, visual hallucinations	No	13	Intravenous immunoglobulins	Partial improvement. Dependent for ADL. Died from pneumonia (60)
9. 54/M	NSCLC (6)	Low-grade fever	Short-term memory loss, hypersomnia	No	20	Intravenous steroids and immunoglobulins, chemotherapy	No improvement. Died from stroke (18)
10. 66/M	None	No	Short-term memory loss, child-like behavior	No	25	Intravenous steroids	Improved. Independent for ADL. (31)
11. 45/M	None	No	Isolated short-term memory loss	No	0	Oral steroids	No improvement. Dependent for ADL. (120)
12. 67/F	None	No	Isolated short-term memory loss	No	0	Intravenous steroids and immunoglobulins	Partial improvement. Dependent for ADL. (84)

ADL: activities of daily living; CLL: Chronic lymphocytic leukemia; H & N: Head and neck; NSCLC: Non-small cell lung cancer; WBC: White blood cells.

^a metastatic squamous cell carcinoma in cervical lymph node, primary tumor unknown.^b Patient had a severe aortic stenosis