Neuronal surface antigen antibodies in limbic encephalitis
Clinical–immunologic associations

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ABSTRACT

Objective: To report the frequency and type of antibodies against neuronal surface antigens (NSA-ab) in limbic encephalitis (LE).

Methods: Analysis of clinical features, neuropathologic findings, and detection of NSA-ab using immunochemistry on rat tissue and neuronal cultures in a series of 45 patients with paraneoplastic (23) or idiopathic (22) LE.

Results: NSA-ab were identified in 29 patients (64%; 12 paraneoplastic, 17 idiopathic). Thirteen patients had voltage-gated potassium channels (VGKC)-ab, 11 novel NSA (nNSA)-ab, and 5 NMDA receptor (NMDAR)-ab. nNSA-ab did not identify a common antigen and were more frequent in paraneoplastic than idiopathic LE (39% vs 9%; \( p = 0.03 \)). When compared with VGKC-ab or NMDAR-ab, the nNSA associated more frequently with intraneuronal antibodies (11% vs 73%; \( p = 0.001 \)). Of 12 patients (9 nNSA-ab, 2 VGKC-ab, 1 NMDAR-ab) with paraneoplastic LE and NSA-ab, concomitant intraneuronal antibodies occurred in 9 (75%). None of these 12 patients improved with immunotherapy. The autopsy of three of them showed neuronal loss, microgliosis, and cytotoxic T cell infiltrates in the hippocampus and amygdala. These findings were compatible with a T-cell mediated neuronal damage. In contrast, 13 of 17 (76%) patients with idiopathic LE and NSA-ab (8 VGKC-ab, 4 NMDAR-ab, 1 nNSA-ab) and 1 of 5 (20%) without antibodies had clinical improvement (\( p = 0.04 \)).

Conclusions: In paraneoplastic limbic encephalitis (LE), novel antibodies against neuronal surface antigens (nNSA-ab) occur frequently, coexist with antibodies against intracellular antigens, and these cases are refractory to immunotherapy. In idiopathic LE, the likelihood of improvement is significantly higher in patients with NSA-ab than in those without antibodies. Neurology® 2008; 71:930–936

GLOSSARY
GAD = glutamic acid decarboxylase; LE = limbic encephalitis; NMDAR = N-methyl-D-aspartate receptor; NSA = neuronal surface antigens; nNSA = novel NSA; SCLC = small-cell lung cancer; VGKC = voltage-gated potassium channels; WBC = white blood cells.

Limbic encephalitis (LE) was initially identified as a paraneoplastic neurologic syndrome characterized by subacute onset of short-term memory loss, seizures, psychiatric changes, and neuroradiological or pathologic evidence of involvement of the amygdala and medial aspect of temporal lobes.\(^1\) Paraneoplastic LE usually associates with onconeural antibodies that help to confirm the diagnosis and guide in the search of the tumor.\(^2\) However, a significant proportion of patients with paraneoplastic LE do not present onconeural antibodies.\(^1\)

Recent studies using new techniques to detect neuronal antibodies against neuronal surface antigens (NSA) identified serum antibodies against voltage-gated potassium channels (VGKC) in a group of LE patients who usually do not develop cancer\(^3\) and anti-NMDA receptor

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antibodies (NMDAR-ab) in young women with ovarian teratoma and an encephalitis that involves neural structures beyond the limbic system.4

In the present study, we analyzed the presence of NSA antibodies (NSA-ab) using neuronal cultures in a series of 45 patients with paraneoplastic or idiopathic LE with the aim to identify new clinical-immunologic associations.

METHODS

Patients. We review all patients with final diagnosis of LE whose serum was sent to our laboratory (Barcelona, Spain) between 2000 and 2007 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.3 LE was considered definite paraneoplastic if a tumor was diagnosed or the serum presented well characterized onconeural antibodies.2 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. LE patients with a shorter follow-up were classified as possible idiopathic LE. The information was obtained from forms filled out by the referring neurologists, telephone interviews, and review of the clinical records. Nineteen (42%) patients were personally seen by at least one of the authors.

Immunologic studies. Onconeural antibodies (Hu, Yo, Ri, CV2, Ma2, amphiphysin, Tr, ZIC4, ANNA3, PCA2) 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.3

NSA-ab were identified by immunocytochemistry of rat hippocampal neuronal cultures as previously described.4 Briefly, live neurons grown on coverslips were incubated with the patients’ serum (dilution 1:400) or CSF (1:10) for 1 hour at 37°C, washed, fixed with 4% paraformaldehyde, and immunoreacted with anti-human IgG Alexa Fluor secondary antibody (Molecular Probes, Eugene, OR). 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.

Positive samples were further characterized by immunohistochemistry on frozen sections of nonperfused rat brain fixed in paraformaldehyde using an avidin-biotin immunoperoxidase technique as described.4 This immunohistochemical assay is optimized to identify antibodies to cell surface antigens and readily recognize VGKC and NMDAR antibodies.4 To determine if novel NSA (nNSA)-ab targeted similar epitopes, tissue sections preincubated with patient’s serum positive for nNSA-ab were subsequently incubated with biotinylated IgG isolated from the serum of two other nNSA-ab-positive patients. Abrogation of the reactivity indicated both nNSA-ab reacted with the same novel epitopes.4

Positive samples for VGKC antibodies were further confirmed by radioimmunoassay5 and those for NMDAR antibodies by immunocytochemistry on HEK293 cells transfected with plasmids containing rodent NR1, NR2A, or NR2B subunits of the NMDAR as described.4

Neuropathology. Paraffin sections of hippocampus and amygdala from autopsy of four patients with NSA-ab were processed for immunohistological techniques using a panel of antibodies: glial fibrillary acidic protein (GFAP; Dako, Carpinteria, CA; dilution 1:6,000) for astrocytes, CD68 (Novocastra Laboratories, Newcastle upon Tyne, UK; 1:3,000) for microglia, CD20 (Novocastra Laboratories; 1:800) for B-lymphocytes, CD3 (Novocastra Laboratories; 1:60) for T-lymphocytes, CD4 (Novocastra Laboratories; 1:5) for helper T-cells, CD8 (Novocastra Laboratories; 1:10) for suppressor/cytotoxic T-cells, T-cell restricted intracellular antigen 1 (Tia-1; Immunotech, Marseille, France; 1:100) for cytotoxic T-lymphocytes, and complement component 9 (C9) (Novocastra Laboratories; 1:50) as described.7 All sections were evaluated by two neuropathologists blinded to the immunologic status of the patients.

RESULTS The series included 23 paraneoplastic and 22 idiopathic LE (13 were definitive idiopathic LE). NSA-ab were detected in 29 (64%) patients (17 with idiopathic LE). Thirteen patients had VGKC-ab, 11 nNSA-ab, and 5 NMDAR-ab. All paraneoplastic LE patients presented some type of antibody. Isolated NSA-ab were found in 3 patients, onconeural or other antibodies against intraneuronal antigens in 11, and both antibody types in 9 (figure 1). By contrast, 17 patients with idiopathic LE had NSA-ab, 1 patient also had anti-glutamic acid decarboxylase (GAD) antibodies, 5 were seronegative (figure 1).

LE and novel NSA antibodies. nNSA-ab were more frequent in paraneoplastic than in idiopathic LE (9/23 [39%] vs 2/22 [9%]; p = 0.03) and had concomitant intraneuronal antibodies more frequently than VGKC-ab or NMDAR-ab (8/11 [73%] vs 2/18 [11%]; p = 0.001) (figure 1). The clinical and immunologic features of the 11 patients with nNSA-ab are summarized in tables 1 and 2. The median age was 66 years (range: 44 to 81 years) and seven were men. Two patients had definite idiopathic LE and nine paraneoplastic LE associated with small-cell lung cancer (SCLC) in six. Four patients presented concomitant onconeural antibodies (amphiphysin: 2, CV2, Hu, and three antibodies against other intraneuronal antigens: GAD, SOX1,8 and calmodulin-like kinase9 (figure 1). The clinical presentation was similar to that of patients with other NSA-ab (tables e-1 and e-2 on the Neurology® Web site at www.neurology.org) or isolated onconeural antibodies (table e-3). The frequency of hyponatremia (50%) at diagnosis was lower but not significantly different from that seen in idiopathic LE patients with VGKC-ab.3

By definition, all 11 sera with nNSA-ab reacted with neurons in culture.

To ensure (figure 2) that the assay did not identify antibodies against antigens located in the cytoplas-
mic side of the membrane, neurons were immuno-reacted with amphiphysin or GAD-ab-positive serum from patients without LE and the experiments were negative. The immunoreactivity on paraformaldehyde-fixed rat sections of the 11 sera is summarized in table 2. Six sera labeled with variable intensity the neuropil of hippocampus, cerebellum, and cerebral cortex (table 2, figure 2). None of the sera blocked the reactivity in the neuropil of the biotinylated IgG from a patient positive for nNSA-ab (patient 4, table 2). However, two sera blocked, completely (patient 4, table 2) or partially (patient 6, table 2), the biotinylated IgG reactivity of a previously reported patient with treatment-responsive LE and thymic carcinoma (Patient 5, of reference 6).

**LE and VGKC antibodies.** Eleven of the 13 patients with VGKC antibodies presented an idiopathic LE (table e-1). The clinical features were in line with previously reported series of VGKC antibody-associated LE. The other two patients had a paraneoplastic LE and both also had a concomitant intraneuronal antibody against SOX1 and amphiphysin. The first patient, previously reported, was a 47-year-old man with a steroid-responsive LE who had a relapsing course associated with a SCLC. The second patient was a 66-year-old woman with a LE

### Table 1

Clinical features of patients with limbic encephalitis (LE) and novel neuronal surface antigens (NSA) antibodies

| Patient | Age, y/sex | Cancer | Presenting symptoms* | MRI temporal lesions | CSF pleocytosis | Hyponatremia |
|---------|------------|--------|---------------------|---------------------|----------------|-------------|
| 1       | 77/M       | SCLC   | Memory impairment, behavior change | Bilateral           | No             | No          |
| 2       | 72/M       | Bladder | Memory impairment, behavior change | Normal             | No             | Yes         |
| 3       | 70/M       | SCLC   | Seizures, memory impairment | Normal†             | No             | Yes         |
| 4       | 44/F       | Thymoma| Behavior change, confusion | Not done†           | Yes (15 WBC)  | No          |
| 5       | 66/F       | Pancreas | Behavior change, memory impairment | Right              | No             | Yes         |
| 6       | 81/F       | SCLC   | Memory impairment | Bilateral           | No             | Yes         |
| 7       | 69/M       | SCLC   | Seizures, memory impairment | Left               | NA             | No          |
| 8       | 58/M       | SCLC   | Seizures, memory impairment | Bilateral           | Yes (15 WBC)  | Yes         |
| 9       | 60/M       | SCLC   | Status epilepticus | Left               | Yes‡           | NA          |
| 10      | 45/M       | None§  | Memory impairment | Right              | No             | No          |
| 11      | 49/F       | None§  | Memory impairment, seizures | Bilateral           | No             | No          |

*Predominant symptom listed first.
*LE confirmed at autopsy.
*Number of WBC unknown.
§Idiopathic LE.
SCLC = small-cell lung cancer; WBC = white blood cells; NA = not available.
associated with amphiphysin and VGKC antibodies who made a progressive course despite immunosuppressor therapy. Mammography showed a lesion compatible with a breast cancer. Because of the clinical situation, the family refused any further studies. The neuropathologic study is described below.

**LE and NMDAR antibodies.** Five patients had NMDAR antibodies (table e-2). Three were women;
age range, 20 to 32 years. Two patients presented with the classic syndrome associated with these antibodies and one with isolated status epilepticus.

Two patients were men aged 53 and 76 years. The first patient improved after steroid treatment and no tumor has been found after a follow-up of 12 months. The second patient had a subacute onset of memory loss and confusion that evolved to diffuse encephalopathy, severe hyponatremia, and death in 2 weeks. Routine blood and CSF analysis and cranial MRI were normal. EEG showed generalized slowing without epileptic features. The autopsy study demonstrated a SCLC with mediastinal and hepatic metastasis. The neuropathologic study is described below.

Seronegative LE. Five patients with idiopathic LE (definite in three) did not present any intraneuronal or NSA-ab in the serum or CSF (three samples studied). The median age was 64 years (range: 40 to 67 years) and three were men. There was no previous history of autoimmune disorders. Two patients had a prodromic syndrome with fever and malaise. The LE presented with an acute, in days, memory deficit and confusion. None had seizures. CSF pleocytosis was observed in three patients and hyponatremia in one.

Neuropathology. A postmortem study of the brain was performed in four patients with NSA-ab. Three of them, with nNSA-ab (patients 1 and 4 of table 1) or VGKC-ab (patient 12 of table e-1), had a concomitant onconeural antibody. The fourth patient presented isolated NMDAR-ab and SCLC (patient 5 of table e-2). Death occurred less than 2 months since the onset of the LE in three patients and two patients did not receive any immunotherapy. The hippocampus and amygdala of the four patients exhibited variable grades of neuronal loss, astrogliosis, microglial hyperplasia and activation, and inflammatory infiltrates of B (mainly perivascular) and T cells (perivascular and parenchymal). The hippocampus of the patient with isolated NMDAR-ab showed less severe neuronal loss and gliosis compared with the other three patients. Tia-1-immunoreactive T-cells were present in the samples of the three patients with concomitant onconeural and NSA-ab but not in the hippocampus of the patient with NMDAR-ab (figure 3). Complement deposits were not observed in the brain tissue of the four patients.

Treatment and outcome. The clinical outcome is summarized in table 2 and tables e-1 to e-3. A clinical response, defined by complete recovery of the neurologic deficits or mild residual memory that did not interfere with normal daily activities, was observed in 13 (76%) of 17 patients with NSA-ab but

Figure 3 Photomicrographs of the hippocampus of the patient with isolated NMDAR-ab (A, B) and the patient with amphiysin and nNSA-ab (C, D)

There is mild neuronal loss in the pyramidal layer of the first patient (A), in contrast with the severe loss observed in the hippocampus of the patient with amphiysin and nNSA-ab (C). Both hippocampi presented perivascular and parenchymatous infiltrates of CD3+ cells (T-cells) (B, D). However, Tia-1+ cells (cytotoxic T-cells) in close apposition with neurons were only observed in the hippocampus of the patient with amphiysin and nNSA-ab (D, insert). Bar = 100 μm (A and C), 15 μm (B, D, and insert).
DISCUSSION

This study identified NSA-ab in 64% of patients with LE. The combined results of immunocytochemistry on cultures of rat hippocampal neurons,6 and the standard detection of antibodies against intraneuronal antigens;2 demonstrated antibodies with a potential pathogenic role or markers of the underlying cancer in 89% of the patients. Only 5 (11%) patients, all with idiopathic LE, were antibody negative.

nNSA-ab were more frequently detected in patients with paraneoplastic LE, usually associated with SCLC, and the majority of them also presented antibodies against intraneuronal antigens. The immunochemical studies and competitive inhibition assays suggest that nNSA-ab are heterogeneous and probably target different membrane antigens. However, the two sera that completely blocked the neuropil immunoreactivity of each other presented a thymic tumor suggesting that LE associated with thymic neoplasms may be associated with a common nNSA-ab.6

Although LE with NSA-ab usually have a good prognosis,13 our study shows that the outcome of paraneoplastic LE with nNSA-ab is poor. Several reasons could account for this evolution. Only four of the nine patients received tumor therapy, which is critical to improve the paraneoplastic syndrome.14 Four patients had an associated onconeuronal antibody and the autopsy in three of them disclosed pathologic features compatible with a T-cell driven immune response that could be the cause of irreversible deficits.15 The lack of improvement of the other five patients (one was not treated) is less clear. In absence of pathologic studies, we can only speculate that the immune response included a T-cell response or that the antibodies caused an irreversible neuronal damage as suggested in two patients with encephalitis and NMDAR-ab.4

Although VGKC-ab often associates with idiopathic LE,16 our study confirms that these patients may have a tumor, usually thymoma17 or SCLC.11 Our two patients with paraneoplastic LE and VGKC-ab also had intraneuronal antibodies, SOX1-ab (previously called anti-glial nuclear antibody or AGNA),18 and amphiphysin-ab. In a previous study, VGKC-ab were identified in 3 (5%) of 63 patients with paraneoplastic neurologic syndromes and amphiphysin-ab. Two of them had LE and an encephalopathy that was not further characterized.19 We found NSA-ab in three of the four patients with paraneoplastic LE and amphiphysin-ab compared to one of 10 patients with other onconeuronal antibodies. Although the numbers are small, future studies will be important to confirm this association that may have clinical and research implications. For example, passive transfer experiments using IgG from sera positive for amphiphysin-ab could show discordant results depending on the presence or absence of concomitant NSA-ab.20

Antibodies to NMDAR were initially reported in young women with encephalitis and ovarian teratoma.4 The current series emphasizes several known characteristics of the disorder, such as the frequent response to treatment and possible occurrence without tumor association.2 A novel finding is the association with SCLC in one patient, a unique feature among 99 patients with anti-NMDAR encephalitis (Dalmau, data not published).

Five patients with idiopathic LE were seronegative. The acute onset of symptoms and the presence of CSF pleocytosis in three patients suggest the disorder could be immune mediated. None of the patients presented with seizures, which may cause hippocampal edema and MRI T2 abnormalities identical to those caused by the inflammatory process associated with LE.21 Previous work demonstrated that definitive LE may present with acute onset of seizures or status epilepticus.22 However, it can be impossible to diagnose autoimmune LE vs other disorders in patients presenting with seizures and the indicated MRI changes unless there is evidence of a systemic tumor, presence of onconeuronal antibodies, or demonstration of inflammatory infiltrates in the brain biopsy.22 Without these clues, the diagnosis of idiopathic, antibody-negative LE is uncertain, particularly when the MRI changes occur late in the evolution of the disorder.23

Data from this series and previous studies performed in a center with different referral patterns13 highlight the frequency (89% and 92%) of immune responses in patients with LE defined by rigorous clinical criteria. These findings should be considered when making clinical decisions. For example, the absence of onconeuronal or VGKC antibodies does not necessarily imply that the disorder is not immune mediated or will not respond to immunotherapy.23 Sera and CSF of these patients should be further
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