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Permalink

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Journal

Neurology, 84(24)

ISSN

0028-3878

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Publication Date

2015-06-16

DOI

10.1212/wnl.0000000000001682

Peer reviewed

Encephalitis and AMPA receptor antibodies

Novel findings in a case series of 22 patients



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ABSTRACT

Objective: We report the clinical features, comorbidities, and outcome of 22 newly identified patients with antibodies to the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA).

Methods: This was a retrospective review of patients diagnosed between May 2009 and March 2014. Immunologic techniques have been reported previously.

Results: Patients' median age was 62 years (range 23–81; 14 female). Four syndromes were identified: 12 (55%) patients presented with distinctive limbic encephalitis (LE), 8 (36%) with limbic dysfunction along with multifocal/diffuse encephalopathy, one with LE preceded by motor deficits, and one with psychosis with bipolar features. Fourteen patients (64%) had a tumor demonstrated pathologically (5 lung, 4 thymoma, 2 breast, 2 ovarian teratoma) or radiologically (1 lung). Additional antibodies occurred in 7 patients (3 onconeural, 1 tumor-related, 2 cell surface, and 1 tumor-related and cell surface), all with neurologic symptoms or tumor reflecting the concurrent autoimmunity. Treatment and outcome were available from 21 patients (median follow-up 72 weeks, range 5–266): 5 had good response to immunotherapy and tumor therapy, 10 partial response, and 6 did not improve. Eventually 5 patients died; all had a tumor or additional paraneoplastic symptoms related to onconeural antibodies. Coexistence of onconeural antibodies predicted a poor outcome ($p = 0.009$).

Conclusion: Anti-AMPA encephalitis usually manifests as LE, can present with other symptoms or psychosis, and is paraneoplastic in 64% of cases. Complete and impressive neurologic improvement can occur, but most patients have partial recovery. Screening for a tumor and onconeural antibodies is important because their detection influences outcome. *Neurology*® 2015;84:2403–2412

GLOSSARY

AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **FLAIR** = fluid-attenuated inversion recovery; **IQR** = interquartile range; **LE** = limbic encephalitis; **mRS** = modified Rankin Scale score; **SCLC** = small cell lung cancer.

The recent characterization of autoimmune synaptic disorders has led to the identification of subtypes of limbic, multifocal, or generalized encephalitis that often respond to immunotherapy. One of the antibodies targets the GluA1 or GluA2 (previously called GluR1 or GluR2) subunits of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), an ionotropic receptor that belongs to the family of glutamate receptors. AMPA mediates most of the fast excitatory synaptic transmission in the brain, and is important for synaptic plasticity, memory, and learning.¹ The initial description of the encephalitis associated with these antibodies was published in 2009 and included 10 patients, all with limbic encephalitis (LE) who had CSF and serum antibodies that reacted with the neuropil of rat brain and the cell surface of cultures of rat hippocampal neurons, leading to precipitate and characterize the target antigens as

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Supplemental data
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From the Service of Neurology (R.H., L.S., A.S., F.G.), Hospital Clínic, Universitat de Barcelona and Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Spain; the Institute of Neurology (R.H.), Medical University of Vienna, Austria; the Department of Neurology (A.v.S., M.J.T.), Erasmus Medical Center, Rotterdam; the Department of Neurology (A.v.S.), Haga Hospital, the Hague, the Netherlands; the Department of Neurology and Institute of Clinical Chemistry (F.L.), University Medical Center Schleswig-Holstein Campus Lübeck, Germany; the Department of Neurology (D.H.), Ochsner Health System, New Orleans, LA; the Memory and Aging Center (M.G., J.G.) and the Department of Neurology (M.P.), University of California, San Francisco; Institució Catalana de Recerca i Estudis Avançats (ICREA) (J.D.), IDIBAPS, Hospital Clínic, Barcelona, Spain; and the Department of Neurology (J.D.), University of Pennsylvania, Philadelphia.

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the GluA1 or GluA2 subunits of the AMPAR.² Recent studies have shown that these antibodies cause a selective decrease in the total surface amount and synaptic localization of GluA1 and GluA2-containing AMPAR through increased internalization and degradation,³ resulting also in a decrease of AMPAR-mediated currents.^{3,4} Since the initial description of this disorder, few cases with similar antibodies have been reported and therefore the clinical manifestations are largely unknown.^{5–8} We report 22 additional patients and describe the clinical presentation, cancer association, response to treatment, comorbidities, prognostic factors, and outcome.

METHODS Patients. Sera or CSF of 10,573 patients with suspected autoimmune encephalitis or paraneoplastic neurologic syndromes (including LE, nonfocal encephalitis, encephalomyelitis, psychiatric disorders, dementia, Morvan syndrome, and cerebellar dysfunction) were included in the studies of antibody screening. The samples were received between May 2009 and March 2014 in the Department of Neurology, University of Pennsylvania; Department of Neurology, Erasmus Medical Center Rotterdam; and the Center of Neuroimmunology at Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), Hospital Clinic, University of Barcelona. Clinical information was obtained by the investigators or from questionnaires completed by the referring physicians and telephone interviews. One patient was previously published as an isolated case report.⁹

Standard protocol approvals, registrations, and patient consents. Informed consent for antibody studies was obtained in all patients. The study was approved by the Institutional Review Boards of the Hospitals of the University of Pennsylvania, Erasmus Medical Center Rotterdam, and University of Barcelona.

Screening for antineuronal antibodies. Serum and CSF samples were tested for antibodies to intracellular and cell surface antigens using immunohistochemistry on rat brain as previously reported.^{2,10} Samples showing specific tissue staining were further examined with in-house or immunoblot assays for antibodies to onconeural antigens (Hu, Yo, Ri, amphiphysin, Ma1/2, Tr), tumor-associated antigens (SOX1, ZIC4), and non-tumor-associated antigens (GAD65, AK5, Homer3).^{11,12} The identity of the target cell surface or synaptic autoantigens was determined with HEK293 cells expressing LGI1, CASPR2, NMDAR, AMPAR, and GABA(B)R, as reported.^{2,13–16} The type of AMPAR subunit identified by patients' antibodies was investigated using HEK293 cells expressing only the GluA1 or GluA2 subunits of the receptor.² We did not include in these investigations the determination of antibodies using immunoblot of recombinant, denatured AMPAR subunits,⁴ given that these antibodies do not produce the typical neuropil immunostaining of the antibodies studied here and their syndrome association remains to be established.

Review of previously reported cases of tumor-associated anti-AMPA encephalitis. In order to assess the significance of the presence of an underlying tumor or additional paraneoplastic antibodies in the clinical outcome (survival and relapse frequency), we reviewed the current data along with all previously reported oncologic or paraneoplastic cases of anti-AMPA encephalitis.^{2,5,6,8}

Statistical analysis. Age between groups was compared by Mann-Whitney *U* test, time until diagnosis by Student *t* test, and comparison of serum and CSF by McNemar test. For survival, Kaplan-Meier curves were created, using log-rank tests. The association of relapses with type of therapy (aggressive, nonaggressive) was compared with Fisher exact test. Statistical significance was defined as *p* value less than 0.05.

RESULTS Patients. We identified 22 patients with AMPAR antibodies. A summary of the clinical information is shown in tables 1 and 2. The median age was 62 years (interquartile range [IQR] 37.3–70.3 years; range 23–81 years) with no differences between patients with or without tumor (60.5 years, IQR 38.8–70.3, and 64 years, IQR 35–72, respectively; *p* = 0.80). The female:male ratio was 14:8. Fourteen patients (64%) had an underlying tumor; in 13, the tumor was demonstrated pathologically, including 5 small cell lung cancer (SCLC), 4 thymoma, 2 breast cancer, and 2 ovarian teratoma, and in another patient the tumor was demonstrated radiologically (lung cancer). One patient had onconeural antibodies (CRMP5), but no tumor has been identified until now (30 weeks follow-up).

The median time from symptom onset until diagnosis of autoimmune encephalitis was 6.5 weeks (IQR 4–18.3 weeks), and was not different between patients with or without tumor (5.5 weeks [IQR 3.8–8.8] vs 13 weeks [5–52], respectively; *p* = 0.11). In 12 patients, the neurologic symptoms occurred before tumor diagnosis or led to tumor screening (median 5 weeks [IQR 2.3–37.5], range 1.5–56 weeks) and in 2 patients the tumor was identified before developing encephalitis (1 year and 6 months, respectively). The CSF analysis showed lymphocytic pleocytosis in 11/22 patients (median leukocyte count 23 cells/ μ L, range 5–820), and elevated protein concentration in 10/20 (median 71 mg/dL, range 49–425); only 5/22 patients had an elevated protein concentration as an isolated finding (table 1).

Clinical presentation and MRI features. Four clinical presentations were identified: 12 patients (55%) developed symptoms of LE, defined by the presence of short-term memory loss, confusion, and abnormal behavior (table 1, patients 1–12). Two of these patients developed seizures (nos. 5 and 8) and one of them (no. 5) had additional GABA(B)R and SOX1 antibodies. Hyponatremia occurred in 2 patients, both with SCLC. In 11 of the 12 patients, the clinical diagnosis of LE was confirmed by the MRI findings of unilateral (2 patients) or bilateral (9 patients) mesiotemporal increased fluid-attenuated inversion recovery (FLAIR)/T2 signal abnormalities (figure 1, A and B). In patient 6 (table 1), the brain MRI was normal.

Eight patients (table 1, cases 13–20) had diffuse encephalitis with clinical and/or MRI evidence of

Table 1 Clinical presentation in patients with AMPAR autoimmune encephalitis

No.	Age, y/sex	Symptom onset until diagnosis, wk	Clinical presentation (initial symptoms)	Other symptoms during course of the disease	Initial MRI	EEG	CSF	Additional antibodies
1	42/F	6	LE	Mild hemiparesis left	Bilateral increased signal in temporal lobe	Epileptiform activity (clinically no seizures)	Normal WBC and protein	—
2	51/F	2	LE	—	Increased signal in left medial temporal lobe	NA	Normal WBC and protein	—
3	59/M	17	LE	—	Bilateral increased signal in temporal lobes	Normal	6 WBC, 50 mg/dL protein	—
4	62/M	7	LE	Hemiparesis, mutism	Bilateral increased signal in temporal lobe and insula	NA	Normal WBC and protein	—
5	63/F	4	LE with seizures	Hyponatremia	Increased signal in medial temporal lobes	NA	Normal WBC, 425 mg/dL protein	GABA(B)R; SOX1
6	70/F	8	LE	—	Normal	Epileptiform activity (clinically no seizures)	Normal WBC, 64 mg/dL protein	—
7	81/F	4	LE	Hyponatremia	Bilateral increased signal in temporal lobe	Focal spike waves; polymorphic delta left frontotemporal	Normal WBC and protein	SOX1
8	33/F	9	LE with seizures	—	Bilateral increased signal in hippocampi and amygdalae	Epileptiform activity	14 WBC, normal protein	—
9	35/M	2	LE	—	Increased signal in medial temporal lobes	Focal activity temporal	23 WBC, proteins NA	—
10	64/F	52	LE	—	Increased signal in left medial temporal lobe	Diffuse slowing and focal abnormalities	5 WBC, normal protein	—
11	72/F	22	LE	Spasticity	Increased signal in medial temporal lobes	General slowing	50 WBC, 49 mg/dL protein	—
12	72/F	13	LE	—	Bilateral increased signal in temporal lobe	Slow (theta) activity	52 WBC, 100 mg/dL protein	—
13	23/M	3	Short-term memory loss, seizures, psychosis	Catatonia, decerebrate posturing right arm	Patchy increased signal in cortex of both hemispheres and basal ganglia	General slowing and epileptiform activity left temporal lobe	23 WBC, normal protein	—
14	25/F	2	Psychosis, confusion, agitation, nonverbal, seizures, dyskinesias	Fever, hypertension, required intubation	Normal	NA	Normal WBC and protein	NMDAR
15	53/F	5	Confusion, bradypsychia, status epilepticus, autonomic dysfunction	—	Increased signal in medial temporal lobes, frontobasal, and caudate	NA	164 WBC, 92 mg/dL protein	CRMP5
16	65/F	52	Short-term memory loss, confusion, abnormal behavior, itching, and involuntary arm movement	Seizures	Hyperintensities in the corpus callosum	Normal	Normal WBC, 71 mg/dL protein	—
17	71/M	5	Somnolent, seizures, disoriented, tremor	—	Abnormality in the hypothalamic region with mass effect on pituitary gland; T2/FLAIR increased signal in the right temporal lobe	Generalized slowing	Normal WBC, elevated protein	NMDAR
18	72/M	6	Short-term memory loss, ataxia, insomnia, psychotic features	Sensory polyneuropathy	Normal	Normal	Normal WBC, 65 mg/dL protein	Amphi
19	62/M	26	Short-term memory loss, confusion, abnormal behavior, psychosis, optic neuropathy	Insomnia, ataxia	Hyperintensities in basal ganglia	Focal activity	33 WBC, 173 mg/dL protein	CRMP5
20	69/M	52	Seizures, short-term memory loss, confusion, psychosis, aphasia	Hyponatremia, fatigue, weakness, ataxia; later Parkinson disease	Increased signal in medial temporal lobes, cortical parietal, cingulum, frontal	Lateralized periodic slowing temporal and hippocampi	Normal WBC and protein	—
21	29/F	11	Left-sided weakness, spasticity	LE, psychosis, dysarthria, tachycardia, hypertension	Increased signal in insula, putamen, and thalamus	Generalized slowing of background, focal slowing in right hemisphere	13 WBC, normal protein	—

Continued

Table 1 Continued

No.	Age, y/sex	Symptom onset until diagnosis, wk	Clinical presentation (initial symptoms)	Other symptoms during course of the disease	Initial MRI	EEG	CSF	Additional antibodies
22	38/F	5	Psychosis with bipolar features	Nystagmus, antipsychotic induced neuroleptic malignant syndrome, fencing posturing, autonomic dysfunction	Normal	Normal	90 WBC, protein NA	—

Abbreviations: AMPAR = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Amphi = amphiphysin antibodies; FLAIR = fluid-attenuated inversion recovery; LE = limbic encephalitis; NA = not available; WBC = white blood cells.

Clinical presentation of LE defined by the presence of short-term memory loss, confusion, and abnormal behavior.

involvement of multiple areas of the CNS (figure 1, C and D). All developed limbic dysfunction along with one or more of the following symptoms: 6 had seizures, 5 prominent psychiatric manifestations, 3 ataxia, 2 abnormal movements, and 1 each optic neuropathy and aphasia. Hyponatremia occurred in one patient without cancer. Two patients in this group had NMDAR antibodies (further described in Immunologic studies).

Another patient (table 1, patient 21) was a 29-year-old woman who first presented with left-sided weakness and spasticity involving face, arm, and leg, and 2 months later developed memory loss, confusion, abnormal behavior, psychiatric symptoms, visual hallucinations, autonomic dysfunction, and dysarthria. The MRI showed increased FLAIR/T2 signal in the right thalamus, bilateral putamen, and cerebellum. Tumor screening revealed an ovarian teratoma but NMDAR antibodies were negative.

The remaining case (patient 22, table 1) was a 38-year-old woman who presented with new-onset psychosis with bipolar features. She was started on antipsychotic medication and 1 week later developed nystagmus and neuroleptic malignant syndrome (rigidity, tonic fencing-like posture, and autonomic instability), requiring intubation for airway protection. The brain MRI was normal, EEG demonstrated moderate generalized slowing, CSF showed 90 leukocytes/mm³, and the tumor screening was negative. Her mental status did not improve and she was lost to follow-up after 5 weeks.

Immunologic studies. All patients' serum or CSF samples showed intense neuropil staining on brain tissue immunohistochemistry and reacted with HEK cells coexpressing GluA1/2 subunits of the AMPAR.² From 5 patients only CSF was available and from another 3 only serum was available; paired samples were available from 14 patients, all CSF were antibody-positive but only 10/14 sera were positive ($p = 0.13$). Four patients had antibodies only against the GluA1 subunit, 7 only against the GluA2

subunit, and 9 against both subunits (figure 2); in 2 cases, the limited amount of sample did not allow for independent subunit assessment. There were no significant differences among clinical presentation, association with a tumor, or prognosis in patients with antibodies recognizing different subunits.

Additional neuronal antibodies were found in 7 patients (3 onconeurointra-cellular, 1 SOX1 [tumor-associated], 2 cell surface/synaptic, and 1 SOX1 and cell surface/synaptic), 6 of them with an associated tumor or cancer (table 2). The 3 patients with onconeurointra-cellular antibodies (2 CRMP5, 1 amphiphysin) developed a clinical phenotype, outcome, or tumor association that were more characteristic of the additional immune response than that of the AMPAR antibody syndrome (tables 1 and 2). Two of the 3 patients with additional antibodies to cell surface/synaptic proteins [1 GABA(B)R, 2 NMDAR] developed syndromes influenced by the additional antibody: the patient with GABA(B)R antibodies had seizures and SCLC, both typical of this autoimmune syndrome, and one patient with NMDAR antibodies developed psychosis, confusion, agitation, decrease of verbal output, seizures, and dyskinesias, all typical of anti-NMDAR encephalitis. In contrast, the second patient with NMDAR antibodies was atypical in many respects, including demographics (71-year-old man), symptoms (somnia, seizures), and tumor (thymic carcinoid). The presentation with somnolence is atypical of NMDAR autoimmunity, and it was likely related to an inflammatory lesion in the hypothalamus (table 1); this case probably represents an overlap syndrome of 2 or more autoimmune disorders.

Treatment and follow-up. Clinical follow-up was available from 21 patients (median 72 weeks, range 5–266). The remaining patient (patient 22) was lost to follow-up shortly after diagnosis. Twenty patients received first-line immunotherapy (steroids, IV immunoglobulins, or plasma exchange) and 5 of them also received second-line immunotherapy

Table 2 Treatment and outcome of patients with AMPAR autoimmune encephalitis

No.	Tumor	Additional antibodies	Symptom onset until start of treatment, wk	Neurologic outcome measuring mRS (compared with mRS at diagnosis)	Immunotherapy or chemotherapy	Treatment response	Follow-up, wk
1	Breast cancer	—	4	2 (5)	Tumor resection, chemotherapy, IVIg	Partial	195
2	SCLC	—	2	1 (3)	Chemotherapy + radiotherapy, steroids	Full	266
3	SCLC	—	11	1 (3)	Chemotherapy + radiotherapy, IVIg	Full	72
4	Malignant thymoma	—	8	1 (5)	Tumor resection, steroids, IVIg	Full	19
5	SCLC	GABA(B)R; SOX1	13	2 (4)	Chemotherapy + radiotherapy	Partial	65, died of cancer
6	SCLC	—	8	2 (3)	Chemotherapy + radiotherapy, steroids	Partial	39, patient died of cancer
7	SCLC	SOX1	4	3 (3)	Chemotherapy, steroids	No	123, patient died of cancer
8	—	—	13	3 (3)	Steroids, plasma exchange, rituximab, cyclophosphamide	No	160
9	—	—	2	2 (3)	Steroids, IVIg, rituximab	Partial	104
10	—	—	52	2 (3)	Steroids, IVIg, plasma exchange	Partial	78
11	—	—	4	3 (5)	Steroids, IVIg	Partial/relapse	25
12	—	—	13	2 (3)	Steroids	Partial	142
13	Thymoma	—	5	3 (5)	Tumor resection, IVIg, steroids, rituximab	Partial	10
14	Ovarian teratoma	NMDAR	2	0 (5)	Tumor resection, steroids, IVIg	Full	50
15	Malignant thymoma	CRMP5	1	5 (4)	Tumor resection, chemotherapy, radiotherapy, steroids, IVIg	No	5, patient died of cancer
16	Breast cancer	—	13	2 (3)	Tumor resection, chemotherapy, radiotherapy, steroids, IVIg, plasma exchange	Partial	260
17	Thymic carcinoid	NMDAR	3	1 (4)	Tumor resection, steroids, plasma exchange	Full	78
18	Lung tumor	Amphi	4	5 (4)	Steroids ^a	No	39, patient died of cancer
19	—	CRMP5	21	4 (3)	Steroids, rituximab	No	30
20	—	—	52	3 (4)	IVIg, plasma exchange	Partial	247
21	Ovarian teratoma	—	8	5 (5)	Tumor resection; steroids, IVIg, plasma exchange, rituximab	No	19
22	—	—	NA	NA (5)	NA	NA	5

Abbreviations: AMPAR = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Amphi = amphiphysin antibodies; IVIg = IV immunoglobulin; mRS = modified Rankin Scale; NA = not available; SCLC = small cell lung cancer.

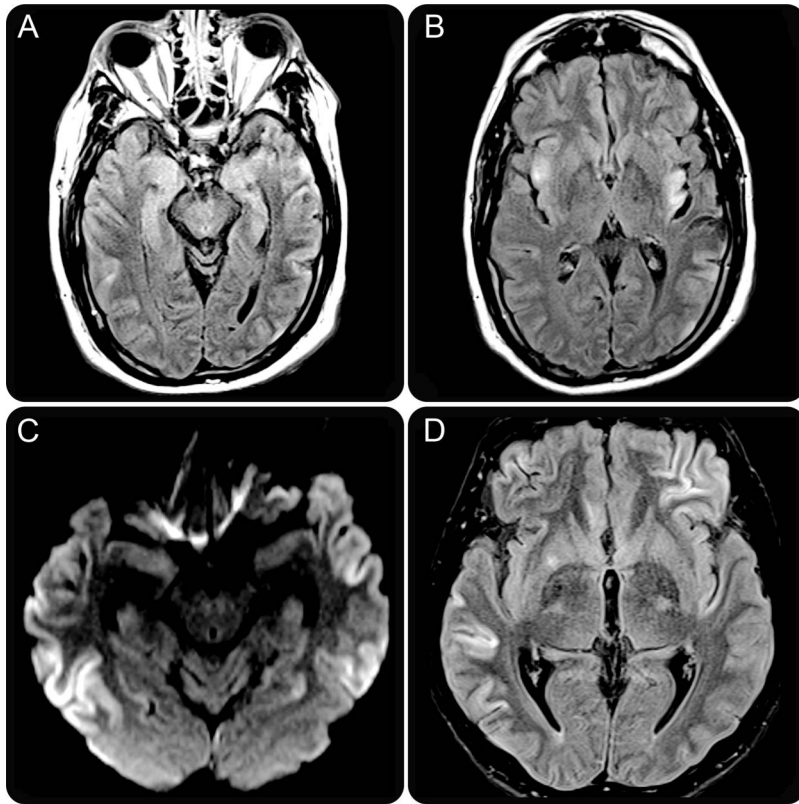
Treatment response was defined by decrease of at least 1 score in the mRS with an mRS at the last follow-up ≤ 3 . At the last follow-up, all patients with good response had mRS of 0-1, and all cases with partial response had mRS of 2-3.

^aThe patient died before tumor diagnosis was confirmed.

(rituximab, cyclophosphamide) (table 2). Thirteen patients had one or more of the following oncologic treatments: 7 tumor resection, 8 chemotherapy, and 6 radiation therapy (table 2). Five patients showed good neurologic response to immunotherapy or oncologic therapy with a modified Rankin Scale (mRS) score between 0 and 1 at the last follow-up; 10 patients had

partial response with an mRS score between 2 and 3, and 6 patients had poor or no response to treatment (table 2). One of the patients with partial response (patient 11, table 2) relapsed 2 months later; this patient was lost to follow-up after relapse. Of the 6 patients with poor or no response to treatment, 4 had a malignant tumor or additional antibodies (1 SOX1,

Figure 1 Brain MRI findings of anti-AMPA receptor encephalitis



Brain MRI obtained 6 weeks after symptom onset (patient 4, table 1) shows increased T2/fluid-attenuated inversion recovery (FLAIR) signal abnormalities involving medial temporal lobes (A) and insular cortex (B). In addition, the frontal and parieto-occipital cortex and caudate show mild focal hyperintensity (B). Diffusion-weighted images of patient 13 (table 1) show widespread involvement of the temporal cortex (C). Similar abnormalities are shown on FLAIR sequences involving the left frontal and right temporal cortex as well as the right putamen (D). AMPAR = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

1 amphiphysin, and 2 CRMP5) with superimposed paraneoplastic symptoms (see details in appendix e-1 on the *Neurology*[®] Web site at Neurology.org).

There was no significant change in survival for patients with or without a tumor (median 123 weeks vs not met, all 6 without tumor still alive; $p = 0.086$; figure 3A; the patient with onconeural CRMP5 antibodies but without tumor was excluded from this as well as from the following analysis). On the other hand, the median survival of the 4 patients with tumor and onconeural or SOX1 antibodies (cases 5, 7, 15, and 18) was 52 weeks (range 5–123 weeks; all died), while that of the 10 patients with tumor but without additional onconeural antibodies was not met (median follow-up 61 weeks, range 10–266 weeks; 9 of 10 alive at last follow-up; $p = 0.009$; figure 3B).

In order to further assess the significance of the presence of an underlying tumor and onconeural antibodies in patient outcome, we reviewed the data of all oncologic cases of the current study together with those previously reported.^{2,5,6,8} Of 24 patients identified, 7 had onconeural, GAD65, or SOX1

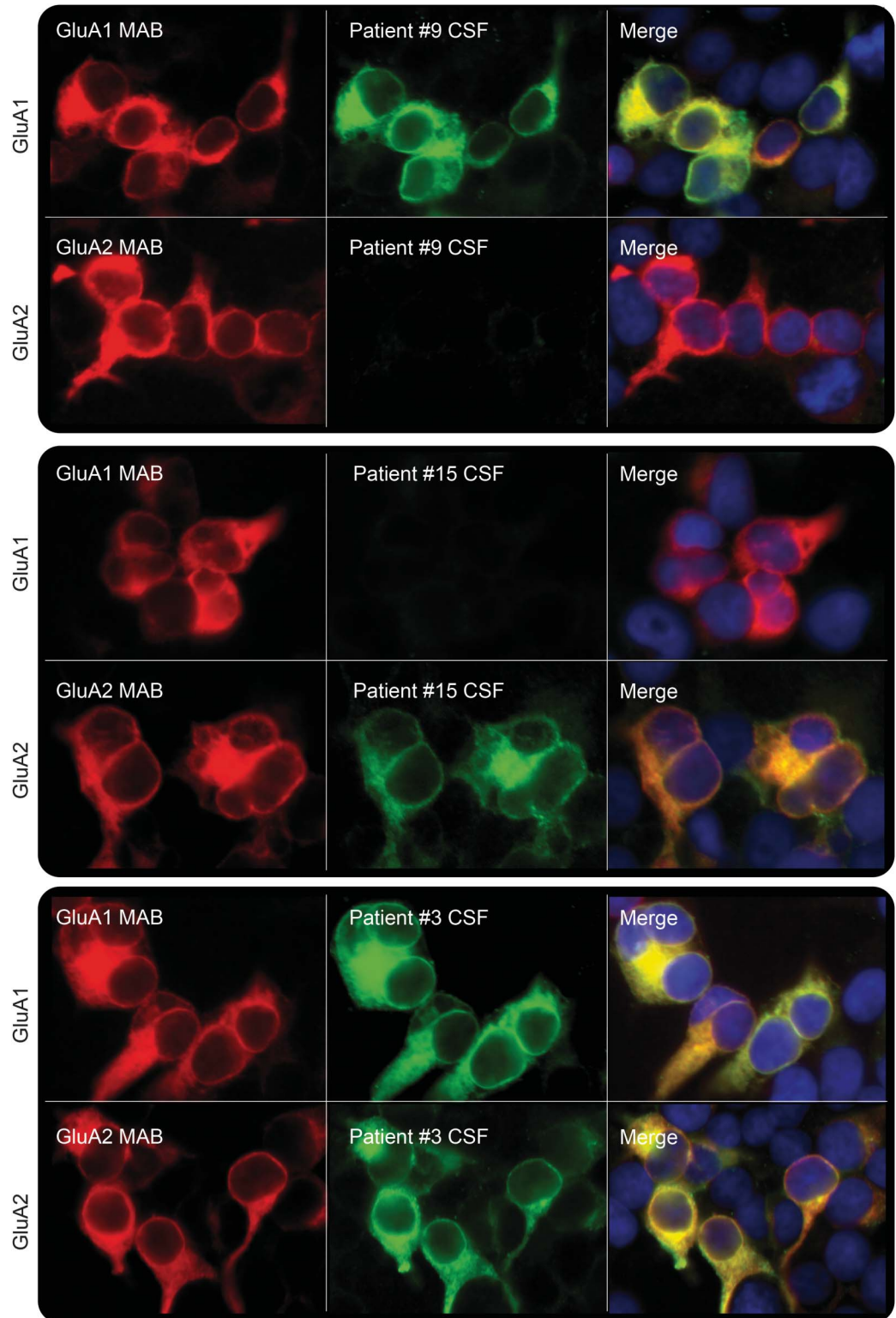
antibodies and 17 had no additional antibodies. Six out of 7 patients with paraneoplastic syndromes and additional antibodies have died (median survival 65 weeks); in contrast, 15 of 17 patients with tumor but without additional onconeural antibodies were alive (median survival not met; median follow-up 60 weeks, range 10–516 weeks; $p = 0.003$). Eleven out of 13 patients without tumor are alive (median follow-up 104 weeks; range 25–390), which was not significant compared to patients with tumor ($p = 0.079$; figure 3C).

To determine whether clinical relapses were associated with less aggressive therapy, we reviewed the data of 21 patients of the current study and those of 16 previously reported cases for which information was available.^{2,5,6,8} Overall, relapses occurred in 6/37 patients (16%, 1 case in the current study). While 0/19 patients who received aggressive therapy (chemotherapy or rituximab) had relapses, 6/18 who did not receive aggressive therapy had relapses ($p = 0.008$).

DISCUSSION We report 22 newly identified patients with anti-AMPA receptor encephalitis and provide several clinically relevant findings, including (1) the frequent presentation of the disorder as LE, sometimes with prominent psychiatric features, psychosis, or hyponatremia that can mislead the initial diagnosis; (2) the presence of an underlying tumor in 64% of the patients; (3) the coexistence of onconeural and cell surface autoantibodies in 32% of the patients, all with symptoms or tumors that reflect the concurrent autoimmunity; and (4) the frequent but limited response to treatment, with long-term outcome influenced by the presence of onconeural antibodies and related paraneoplastic symptoms or tumors.

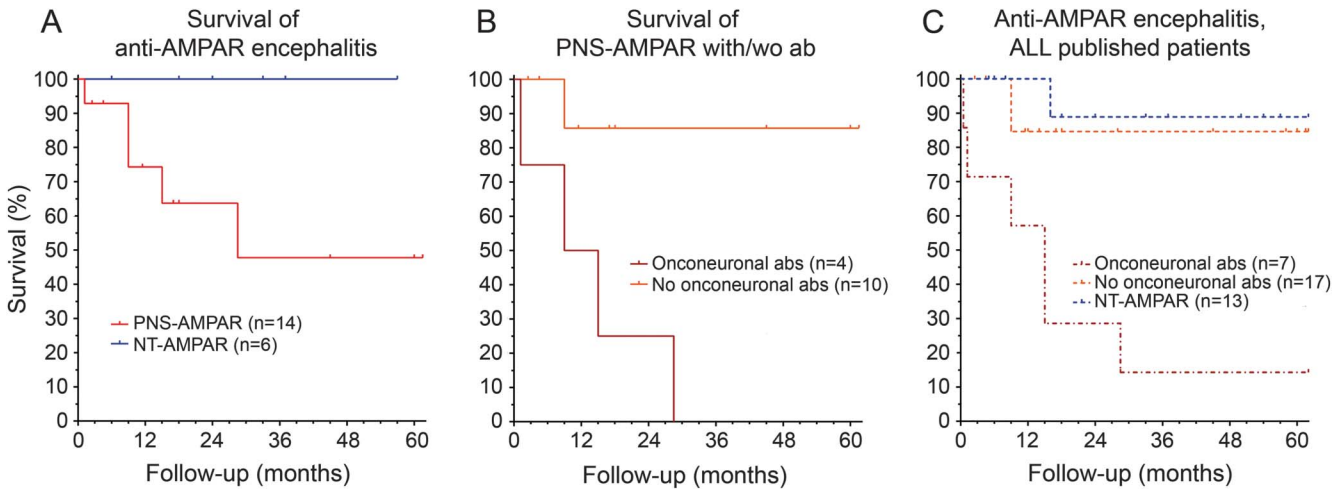
The term LE refers to an inflammatory process of the brain restricted clinically or radiologically to the limbic system, which includes the medial temporal lobes and frontobasal and cingular regions. Despite a well-defined syndrome, it is frequently poorly recognized, misnaming as LE any type of autoimmune or paraneoplastic process above the foramen magnum. Among the many antigens of paraneoplastic and autoimmune encephalitis, there are 3 that typically associate with LE, including LGI1, GABA(B)R, and AMPAR.^{2,13,16–18} At least 60% of the patients with any of these disorders develop a typical clinical or radiologic picture of LE, with additional symptoms or associations that can suggest the antigen. For example, while LE with LGI1 antibodies frequently associates with hyponatremia but almost never SCLC,¹³ LE with GABA(B)R frequently occurs with early and prominent seizures and 50%–60% of the patients have SCLC.^{16,18} Recognition of each autoantigen is important because all 3 disorders are

Figure 2 Reactivity of patients' antibodies with GluA1 or GluA2 subunits of AMPAR



Patients' antibodies were identified on HEK293 cells transfected with GluA1 or GluA2 subunits of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA). Examples of patients with antibodies targeting only GluA1 (patient 9), or GluA2 (patient 15), or both subunits (patient 3) are shown. Patients' antibodies are shown with green fluorescence; commercial monoclonal antibodies against GluA1 or GluA2 are shown with red fluorescence; the blue nuclear staining is shown with 4',6-diamidino-2-phenylindole (DAPI). All panels: $\times 400$.

Figure 3 Survival of patients with paraneoplastic or idiopathic anti-AMPA receptor encephalitis



(A) Kaplan-Meier survival curves for patients with paraneoplastic anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) encephalitis (with or without onconeural antibodies, red) and patients with idiopathic anti-AMPA receptor encephalitis (blue). (B) Kaplan-Meier survival curves for 4 patients with paraneoplastic anti-AMPA receptor encephalitis plus additional onconeural antibodies (dark red) and 10 patients with paraneoplastic anti-AMPA receptor encephalitis without onconeural antibodies (orange). (C) Kaplan-Meier survival curves for all assessable reported patients with paraneoplastic anti-AMPA receptor encephalitis and onconeural antibodies (dark red), paraneoplastic anti-AMPA receptor encephalitis without onconeural antibodies (orange), and idiopathic anti-AMPA receptor encephalitis (blue).^{2,5,6,8}

potentially treatable but for the appropriate treatment one should consider the associated comorbidities or tumors (further discussed later). Our findings show that LE with hyponatremia not only occurs in patients with LGI1, but also in some patients with antibodies to AMPAR or GABA(B)R, either as part of SCLC-related syndrome of inappropriate antidiuretic hormone secretion (which was not further investigated in 2 of our patients) or as a primary effect of the immune response (one patient did not have cancer).

In the initial report of 10 patients with anti-AMPA receptor encephalitis, the main findings were that all developed LE, 7 had a tumor (lung, breast, or thymoma), and the disorder frequently responded to treatment but had tendency to relapse. The current data confirm some of these findings and expand on others. Ten of the current patients did not initially present with classical LE, although most of them had limbic dysfunction concurrent or heralded by other symptoms. Importantly, 6 of these patients had prominent psychiatric symptoms, one of them manifesting as pure psychosis for 1 week before developing a neuroleptic malignant syndrome induced by treatment along with mild additional neurologic symptoms. The presentation of anti-AMPA receptor encephalitis as pure psychosis (without additional neurologic symptoms) has been previously reported in 2 cases,⁶ indicating that this type of encephalitis should be included in the differential diagnosis of autoimmune psychosis.

The histologic types of tumors were similar to those previously reported in anti-AMPA receptor encephalitis,² but 2 patients had ovarian teratoma (one without

evidence of NMDAR antibodies), an association not previously reported. We do not know why patients in the current study had fewer neurologic relapses than those in previous studies (1/21 vs 5/16)^{2,5,6,8}; however, the approach to therapy may be a reason. Indeed, when considering all current and previous cases for which treatment information is available ($n = 37$), all clinical relapses were in the group who did not receive aggressive therapy (6 of 18 patients, $p = 0.008$). Aggressive treatment has been associated with lower relapse risk in anti-NMDAR encephalitis.¹⁹ Another possible explanation could be a diagnosis bias: at the time of the initial study, patients with monophasic disease were often not sent for antibody testing and were missed, resulting in an overrepresentation of relapsing patients.

Overall, 71% of the patients responded to immunotherapy or treatment of the tumor, most of them showing a partial neurologic response (48%). These data suggest that patients with AMPAR antibodies have less substantial recoveries than those with other types of autoimmune encephalitis [NMDAR, LGI1, or GABA(B)R]. Despite this, substantial and sometimes unexpected recoveries do occur, but require aggressive therapy. An example is patient 13, who presented with severe encephalitis, refractory seizures, and a large thymoma, but his Karnofsky Performance Status was considered too low (30/100) for treatment. The patient was transferred to our institution (Hospital Clinic, Barcelona) under pharmacologically induced coma and mechanical ventilation. The brain MRI showed changes suggestive of widespread

cortical damage (figure 2). He underwent intensive immunotherapy and tumor removal, and currently is at home, free of seizures, and rapidly improving. This case suggests caution in clinically assessing autoimmune encephalitis using Karnofsky or similar neurologic scales for treatment decisions.

The presence of concurrent antibodies, mainly onconeural (CRMP5, amphiphysin) or tumor biomarkers linked to paraneoplastic autoimmunity (e.g., SOX1), is associated with additional paraneoplastic symptoms and a poorer prognosis. The 5 patients who died had one or more of these features along with an underlying tumor. These findings along with the review of previously reported cases with tumor (either with or without an additional paraneoplastic neurologic autoimmunity)^{2,5,6,8} suggest that the presence of an additional paraneoplastic autoimmunity is the main prognostic factor for a poor outcome. Indeed, the survival of patients with tumor but without additional paraneoplastic autoimmunity was similar to that of patients without tumor, but the survival of patients with tumor and additional paraneoplastic autoimmunity was significantly worse than that of the other subgroups. Similar comorbidities linked to a poor prognosis have been reported in patients with anti-GABA(B)R encephalitis, a disorder that frequently occurs with SCLC and may associate with concurrent paraneoplastic immune responses (e.g., amphiphysin, Ri, SOX1).¹⁸

This and previous studies suggest an interesting molecular link between the symptoms of LE and the effects of LGI1 and AMPAR antibodies. Indeed, LGI1 is a secreted neuronal protein that forms a trans-synaptic complex interacting at the postsynapse with ADAM22 and AMPAR and at the presynapse with ADAM23 and the shaker potassium channel Kv1.²⁰ There is evidence that LGI1 antibodies prevent the binding of LGI1 to ADAM22 and by unclear mechanisms result in a decrease of AMPAR (the effects on the presynapse have not been determined).²¹ On the other hand, the antibodies of patients with anti-AMPA encephalitis bind directly to the GluA1/2 subunits, causing a decrease of the levels of receptors by antibody-mediated internalization.² Therefore, 2 seemingly different immune responses against different synaptic proteins result in a common downstream effect (decrease of postsynaptic AMPAR clusters), providing a potential explanation for the frequent association of both disorders with classical LE.

The current findings taken together with those of previous studies have several practical implications. First, in patients with classic LE with or without tumor association, determination of AMPAR antibodies should be considered. These antibodies may also occur in patients with multifocal encephalitis

usually involving the limbic system, and less frequently can present as pure psychosis. Second, detection of GluA1/2 AMPAR antibodies should lead to an extensive screening, including underlying tumors, classical paraneoplastic antibodies, and other cell surface antibodies. Third, prompt treatment of the tumor and immunotherapy are important, because the disorder is potentially reversible, but the outcome seems related to the presence of concurrent paraneoplastic autoimmunity linked to an underlying tumor.

AUTHOR CONTRIBUTIONS

Design/conceptualization of the study: R.H., M.T., F.G., J.D.; analysis/interpretation of the data: R.H., A.v.S., F.L., M.G., J.G., M.P., D.H., L.S., A.S., M.T., F.G., J.D.; statistical analysis: M.T.; drafting/revising the manuscript: R.H., F.L., M.T., F.G., J.D. All authors give final approval of the version to be published.

ACKNOWLEDGMENT

The authors thank Mercè Alba, Eva Caballero, Esther Aguilar, and Esther Hulsenboom for technical support.

STUDY FUNDING

Supported in part by grant PI12/00611 from the Fondo de Investigaciones Sanitarias, Madrid, Spain (F.G.), NIH RO1NS077851 (J.D.), RO1MH094741 (J.D.), Instituto Carlos III (FIS, Spain, 14/00203, J.D.), and Fundació la Marató de TV3 (J.D.). J.D. receives royalties from Athena Diagnostics for a patent for the use of Ma2 as autoantibody test, and licensing fees from Euroimmun for a patent for the use of NMDAR as autoantibody test. M.T. was supported by an ErasmusMC fellowship, by the Netherlands Organisation for Scientific Research (NWO, Veni incentive), and by the Dutch Epilepsy Foundation, project number 14-19.

DISCLOSURE

R. Höftberger, A. van Sonderen, F. Leypoldt, D. Houghton, M. Geschwind, J. Gelfand, M. Paredes, L. Sabater, A. Saiz, and F. Graus report no disclosures relevant to the manuscript. M. Titulaer received a travel grant for lecturing in India from Sun Pharma. J. Dalmau has a research grant from Euroimmun, and receives royalties from patents for the use of Ma2, GABA(B)R, and NMDAR as autoantibody tests. Go to Neurology.org for full disclosures.

Received October 20, 2014. Accepted in final form December 29, 2014.

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