12-13 Maggio 2016
HOTEL ROYAL CONTINENTAL - Napoli

E.C.M.
Educazione Continua in Medicina

14 CREDITI FORMATIVI


# LE ENCEFALITI AUTOIMMUNI

DR PASQUALE PAGLIANO
UOS NEUROLOGIA
OSPEDALE D. COTUGNO - NAPOLI

PRESIDENTE DEL MEETING
C. Di Iorio

COORDINAMENTO SCIENTIFICO
C. Maglione
T. Cafiero
A. Frangiosa
F. Bilotta

# Burden of encephalitis-associated hospitalizations in the United States, 1998–2010

**Table 1** Encephalitis-associated hospitalizations by disease category, United States

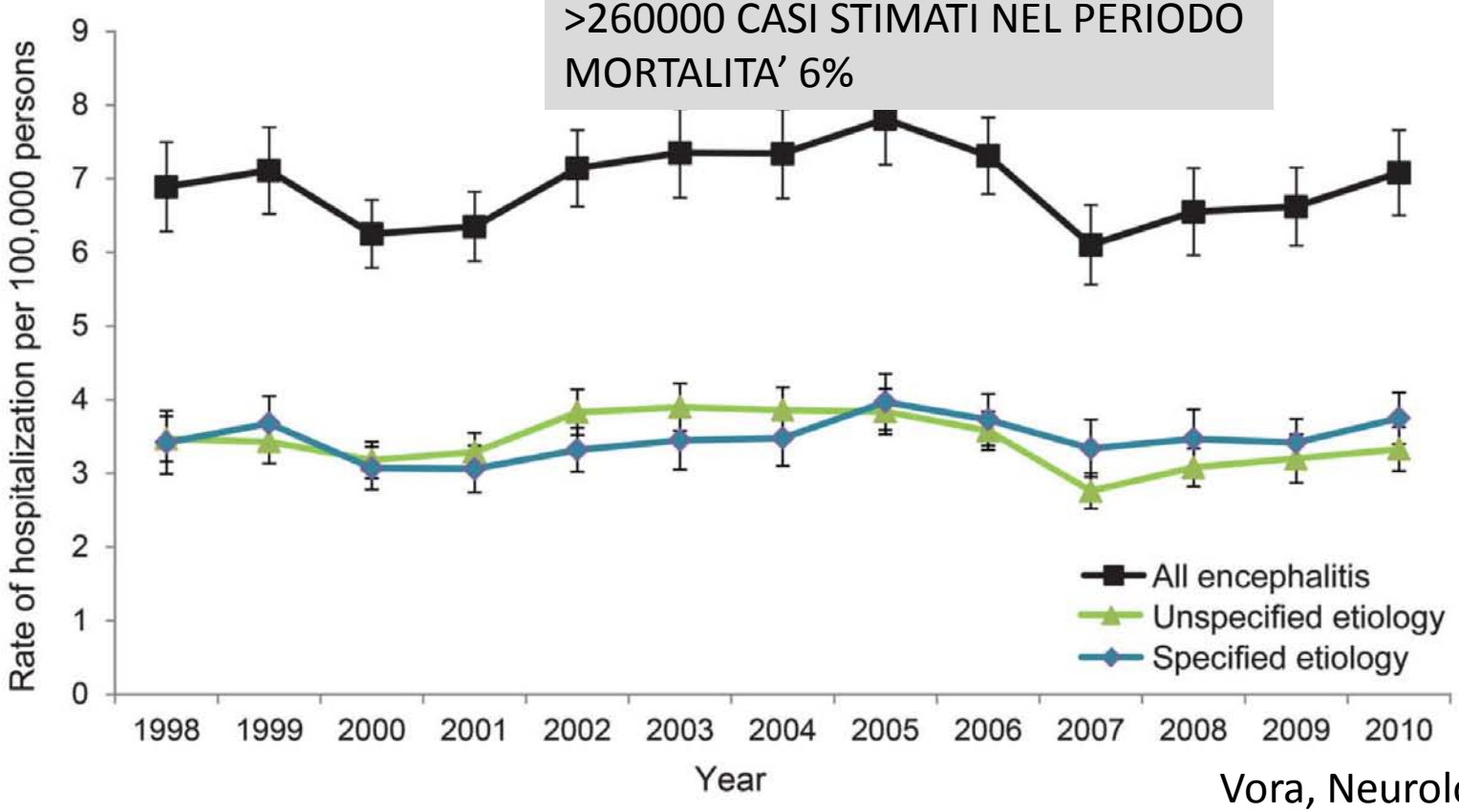
| Encephalitis disease category[a] | No. of hospitalizations, 1998–2010 (SE) | Percent of overall encephalitis-associated hospitalizations, 1998–2010 (95% CI) | Percent of overall encephalitis-associated hospitalizations, 1988–1997[b] |
|---|---|---|---|
| Specified etiology | 132,396 (1,943) | 50.3 (49.6–51.0) | 40.5 |
| Viral | 53,588 (778) | 20.3 (19.9–20.8) | 15.5 |
| Other specified | 48,474 (901) | 18.4 (17.9–18.9) | 5.5 |
| Other infectious | 14,835 (903) | 5.6 (5.0–6.3) | 13.8 |
| Postinfectious | 14,542 (466) | 5.5 (5.2–5.8) | 5.3 |
| Toxic | 1,128 (82) | 0.4 (0.4–0.5) | 0.9 |
| Postimmunization | 555 (56) | 0.2 (0.2–0.3) | <0.1 |
| Unspecified etiology | 130,957 (1,565) | 49.7 (49.0–50.4) | 59.5 |
| Total | 263,352 (3,017) | 100 | 100 |

Vora, Neurology 2014

# Burden of encephalitis-associated hospitalizations in the United States, 1998–2010

**Figure 1** Annual rates of encephalitis-associated hospitalizations, United States, 1998-2010

>260000 CASI STIMATI NEL PERIODO
MORTALITA' 6%




Vora, Neurology 2014

# In Search of Encephalitis Etiologies: Diagnostic Challenges in the California Encephalitis Project, 1998–2000

Carol A. Glaser,[1] Sabrina Gilliam,[1] David Schnurr,[1] Bagher Forghani,[1] Somayeh Honarmand,[1] Nino Khetsuriani,[2] Marc Fischer,[3] Cynthia K. Cossen,[1] and Larry J. Anderson[2]

- 334 pazienti (43% Maschi)
- 206 (62%) ricoverati in ICU
- 251 (75%) febbrili
- 228 (68%) ↑↑ CSF Cells
- 187 (56%) ↑↑ CSF Proteins
- 15 (4%) CSF glucose <40 mg/dl


Clinical Infectious Diseases 2003;36:731–42

# CALIFORNIA ENCEPHALITIS PROJECT: QUADRO CLINICO/STRUMENTALE

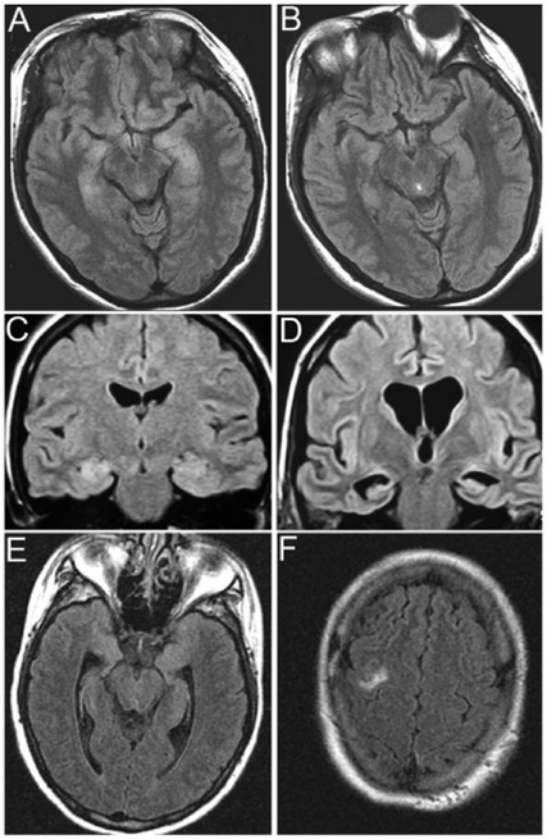
| Characteristic or finding, by type | Etiology group | | | |
|---|---|---|---|---|
| | Infectious[a,b] (*n* = 53) | Noninfectious[b] (*n* = 32) | Unknown[b] (*n* = 208) | *P*[c] |
| Demographic | | | | |
| Female sex | 28 (53) | 14 (44) | 95 (46) | .63 |
| Age, median years (range) | 17 (0–84) | 40 (1–80) | 25 (0–84) | .06[d] |
| Race | | | | .22 |
| White | 33 (62) | 13 (42) | 82 (40) | |
| Hispanic | 11 (21) | 7 (23) | 53 (26) | |
| Black | 3 (6) | 5 (16) | 25 (12) | |
| Asian | 5 (9) | 6 (19) | 38 (19) | |
| Other | 1 (2) | 0 (0) | 6 (3) | |
| Clinical | | | | |
| Duration of illness before admission, median days (range) | 2 (0–91) | 4 (0–75) | 2 (0–91) | .35 |
| ICU admission | 32 (60) | 18 (56) | 130 (64) | .68 |
| Prodrome or concurrent symptom | | | | |
| Fever[e] | 42 (79) | 20 (63) | 155 (75) | .22 |
| Respiratory symptoms | 17 (34) | 9 (29) | 92 (47) | .06[f] |
| Gastrointestinal symptoms | 24 (48) | 17 (55) | 87 (46) | .66 |
| Rash | 9 (18) | 5 (17) | 31 (16) | .98 |
| Neurological finding | | | | |
| Lethargy | 45 (85) | 27 (84) | 161 (82) | .90 |
| Personality change | 30 (58) | 23 (72) | 128 (65) | .39 |
| Extreme irritability | 20 (39) | 11 (36) | 87 (45) | .48 |
| Hallucinations | 7 (14) | 7 (22) | 36 (19) | .60 |
| Stiff neck | 21 (40) | 7 (22) | 67 (34) | .22 |
| Somnolence | 38 (72) | 22 (71) | 149 (76) | .72 |
| Seizures | 24 (45) | 14 (44) | 108 (54) | .37 |
| Coma | 16 (30) | 10 (31) | 64 (32) | .97 |
| Death | 9 (17) | 4 (13) | 37 (18) | .75 |
| Laboratory data | | | | |
| WBC count, cells/mL | | | | .98 |
| <4.5 | 3 (6) | 2 (7) | 15 (8) | |
| 4.5–13.0 | 33 (64) | 19 (61) | 129 (65) | |
| >13.0 | 16 (31) | 10 (32) | 56 (28) | |
| CSF pleocytosis (>5 WBCs/mm$^3$) | 35 (66) | 17 (53) | 145 (71) | .11 |
| Elevated CSF protein level (>45 mg/dL) | 27 (51) | 19 (68) | 120 (61) | .28 |
| Decreased CSF glucose level (<40 mg/dL) | 4 (8) | 2 (7) | 8 (4) | .52 |
| Abnormal MRI findings | 24 (65) | 16 (62) | 83 (52) | .26 |

**Clinical Infectious Diseases 2003; 36:731–42**

# Paraneoplastic Anti–*N*-methyl-D-aspartate Receptor Encephalitis Associated with Ovarian Teratoma

Ann Neurol 2007;61:25–36

Josep Dalmau, MD, PhD,[1] Erdem Tüzün, MD,[1] Hai-yan Wu, PhD,[1] Jaime Masjuan, MD,[2] Jeffrey E. Rossi, BA,[1] Alfredo Voloschin, MD,[3] Joachim M. Baehring, MD,[4] Haruo Shimazaki, MD, PhD,[5] Reiji Koide, MD,[6] Dale King, MD,[7] Warren Mason, MD,[8] Lauren H. Sansing, MD,[1] Marc A. Dichter, MD, PhD,[1] Myrna R. Rosenfeld, MD, PhD,[1] and David R. Lynch, MD, PhD[1]




- 12 pazienti con teratoma ovarico precedentemente sconosciuto
- 10 viral-like presentation
- 12 esordio psichiatrico acuto (allucinazioni, cambiamento di personalità)
- 3 perdita della memoria di breve termine
- 11 crisi parziali o generalizzate
- 10 ventilazione meccanica
- 3 interessamento temporo-mesiale alla RMN

# A clinical approach to diagnosis of autoimmune encephalitis

*Francesc Graus, Maarten J Titulaer, Ramani Balu, Susanne Benseler, Christian G Bien, Tania Cellucci, Irene Cortese, Russell C Dale, Jeffrey M Gelfand, Michael Geschwind, Carol A Glaser, Jerome Honnorat, Romana Höftberger, Takahiro Iizuka, Sarosh R Irani, Eric Lancaster, Frank Leypoldt, Harald Prüss, Alexander Rae-Grant, Markus Reindl, Myrna R Rosenfeld, Kevin Rostásy, Albert Saiz, Arun Venkatesan, Angela Vincent, Klaus-Peter Wandinger, Patrick Waters, Josep Dalmau*

**Panel 1: Diagnostic criteria for possible autoimmune encephalitis**

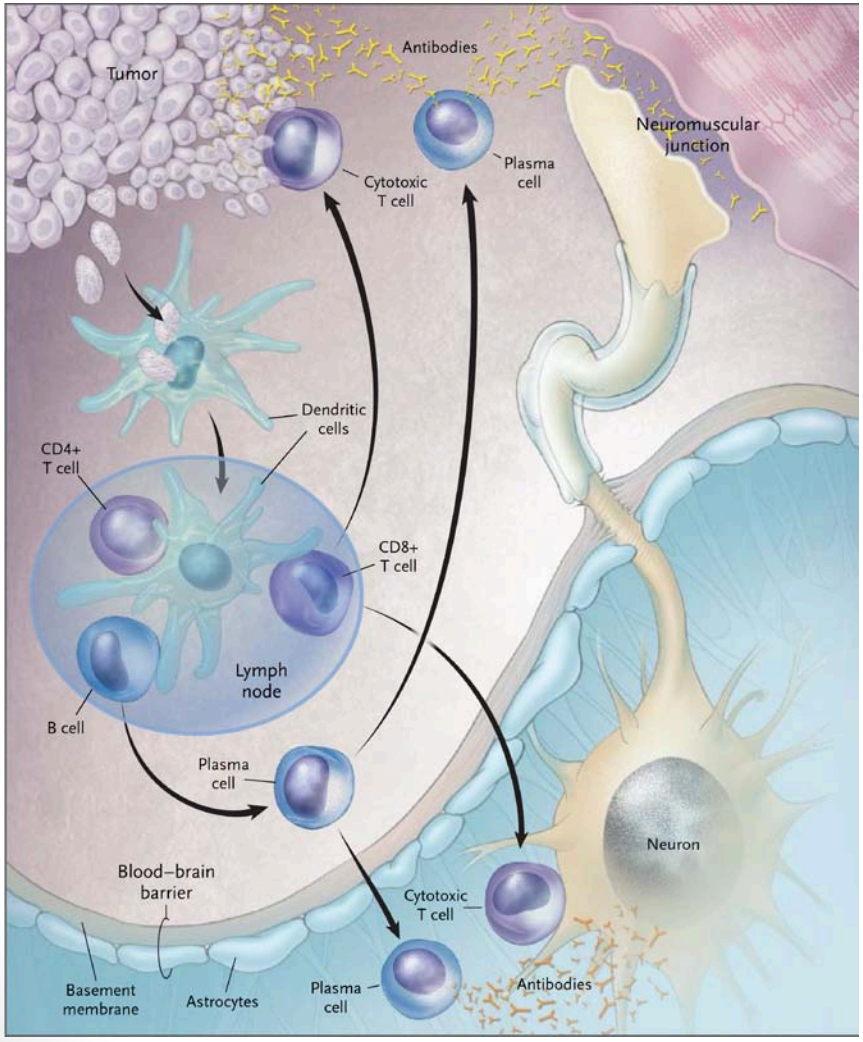
Diagnosis can be made when all three of the following criteria have been met:

1 Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms
2 At least one of the following:
   - New focal CNS findings
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytosis (white blood cell count of more than five cells per $mm^3$)
   - MRI features suggestive of encephalitis†
3 Reasonable exclusion of alternative causes (appendix)

*Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change. †Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

Lancet Neurol 2016

# Encefalite autoimmune Vs Encefalite paraneoplastica




Le encefaliti autoimmuni:

- Possono svilupparsi senza un tumore sottostante
- Gli Ab implicati alterano la struttura e la funzione dell'epitopo target
- Rispondono all'immunoterapia
- Hanno decorso favorevole nel 70-80% dei casi

# ENCEFALITE DA NMDA-R-Ab

- E’ associata alla presenza di Ab diretti contro la sub-unità GluN1 dell’NMDA-R
- Si osserva in giovani adulti e bambini
- Maggiore incidenza tra le donne
- 1% delle ammissioni in ICU in età compresa tra 18 e 35 anni per encefalopatia di origine sconosciuta (Pruss, Neurology 2010)

# A clinical approach to diagnosis of autoimmune encephalitis

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***Panel 4:*** **Diagnostic criteria for anti-NMDA receptor encephalitis**

**Probable anti-NMDA receptor encephalitis***

Diagnosis can be made when all three of the following criteria have been met:

1 Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:
   - Abnormal (psychiatric) behaviour or cognitive dysfunction
   - Speech dysfunction (pressured speech, verbal reduction, mutism)
   - Seizures
   - Movement disorder, dyskinesias, or rigidity/abnormal postures
   - Decreased level of consciousness
   - Autonomic dysfunction or central hypoventilation
2 At least one of the following laboratory study results:
   - Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
   - CSF with pleocytosis or oligoclonal bands
3 Reasonable exclusion of other disorders (appendix)

Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

**Definite anti-NMDA receptor encephalitis***

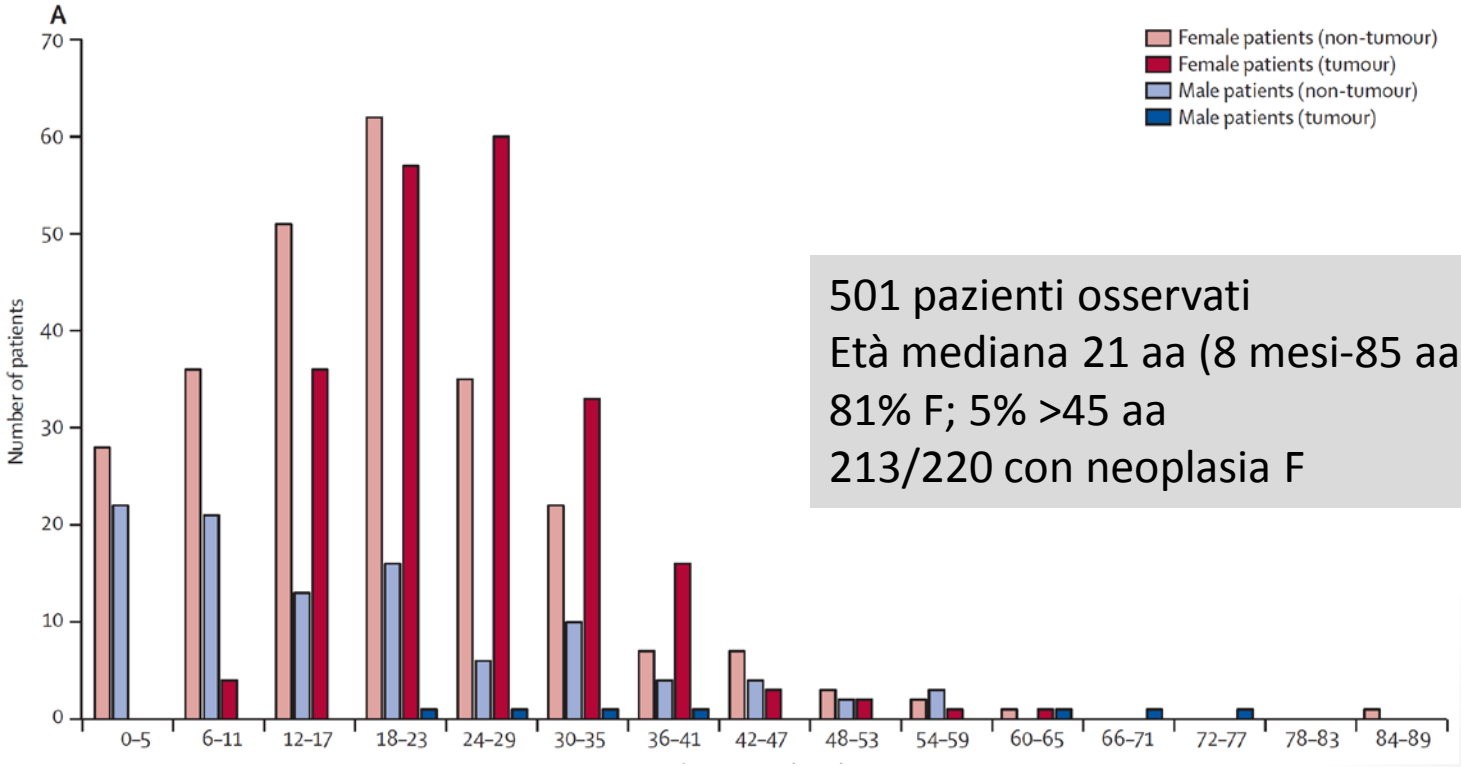
Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies,† after reasonable exclusion of other disorders (appendix)

*Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurological symptoms (post-herpes simplex virus encephalitis). †Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to cell-based assay).

# Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study

*Lancet Neurol* 2013; 12: 157–65

*Maarten J Titulaer, Lindsey McCracken, Iñigo Gabilondo, Thaís Armangué, Carol Glaser, Takahiro Iizuka, Lawrence S Honig, Susanne M Benseler, Izumi Kawachi, Eugenia Martinez-Hernandez, Esther Aguilar, Núria Gresa-Arribas, Nicole Ryan-Florance, Abiguei Torrents, Albert Saiz, Myrna R Rosenfeld, Rita Balice-Gordon, Francesc Graus, Josep Dalmau*




501 pazienti osservati
Età mediana 21 aa (8 mesi-85 aa)
81% F; 5% >45 aa
213/220 con neoplasia F

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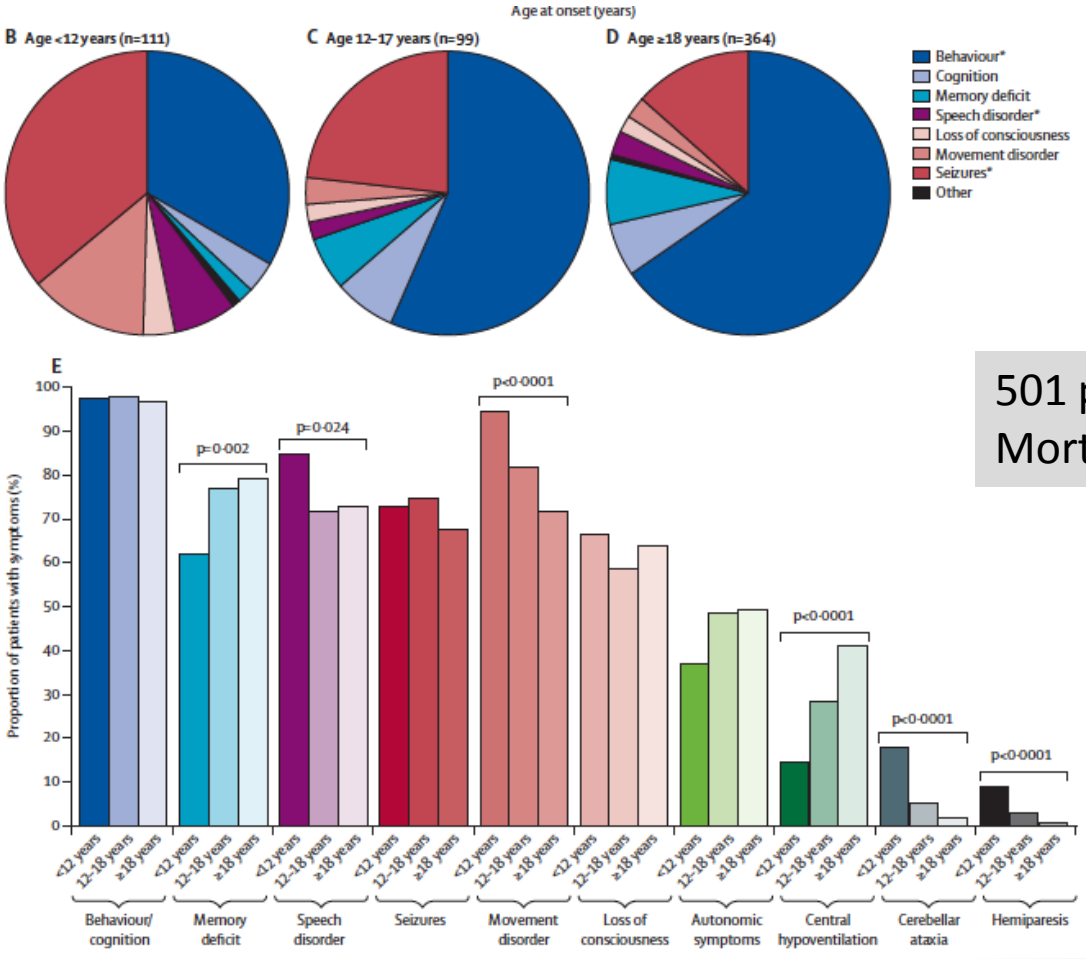
Presenting symptoms

All symptoms




501 pazienti
Mortalità 7%

# The Frequency of Autoimmune *N*-Methyl-D-Aspartate Receptor Encephalitis

**Table 1. Etiologies of Cases ≤30 Years of Age Enrolled in the California Encephalitis Project September 2007–February 2011**

| | Anti-NMDAR (n = 32) | Enterovirus (n = 30) | HSV-1 (n = 7) | VZV (n = 5) | WNV (n = 5) |
|---|---|---|---|---|---|
| Clinical Findings | | | | | |
| Neurologic Symptoms | | | | | |
| Movement disorder, no. (%) | 20 (63%) | 2 (7%) | 0 (0%) | 1 (20%) | 0 (0%) |
| Aphasia, no. (%) | 23 (72%) | 3 (10%) | 2 (29%) | 2 (40%) | 1 (20%) |
| Ataxia, no. (%) | 14 (44%) | 6 (20%) | 1 (14%) | 3 (60%) | 2 (40%) |
| Stiff neck, no. (%) | 2 (6%) | 8 (27%) | 2 (29%) | 0 (0%) | 3 (60%) |
| Autonomic instability, no. (%) | 15 (47%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Cranial nerve abnormality, no. (%) | 3 (9%) | 2 (7%) | 0 (0%) | 0 (0%) | 2 (40%) |
| Psychiatric Symptoms | | | | | |
| Hallucinations, no. (%) | 21 (66%) | 3 (10%) | 0 (0%) | 1 (20%) | 0 (0%) |
| Psychosis, no. (%) | 19 (59%) | 1 (3%) | 0 (0%) | 1 (20%) | 0 (0%) |
| Irritability, no. (%) | 24 (75%) | 6 (20%) | 2 (29%) | 2 (40%) | 2 (40%) |
| General Symptoms | | | | | |
| Fever, no. (%) | 18 (56%) | 18 (60%) | 4 (57%) | 4 (80%) | 5 (100%) |
| GI, no. (%) | 9 (28%) | 11 (37%) | 3 (43%) | 4 (80%) | 0 (0%) |
| URI, no. (%) | 6 (19%) | 8 (27%) | 1 (14%) | 1 (20%) | 0 (0%) |
| Rash, no. (%) | 7 (22%) | 2 (7%) | 1 (14%) | 3 (60%) | 0 (0%) |
| Severe headache, no. (%) | 12 (38%) | 15 (50%) | 2 (29%) | 4 (80%) | 3 (60%) |
| Intubation, no. (%) | 13 (41%) | 7 (23%) | 1 (14%) | 1 (20%) | 2 (40%) |
| ICU admission, no. (%) | 17 (53%) | 13 (43%) | 6 (86%) | 1 (20%) | 3 (60%) |
| Seizures, no. (%) | 22 (69%) | 14 (47%) | 2 (29%) | 1 (20%) | 1 (20%) |

**Mary S. Gable** CID 2012:54

# The Frequency of Autoimmune *N*-Methyl-D-Aspartate Receptor Encephalitis

**Table 1. Etiologies of Cases ≤30 Years of Age Enrolled in the California Encephalitis Project September 2007–February 2011**

| | Anti-NMDAR (n = 32) | Enterovirus (n = 30) | HSV-1 (n = 7) | VZV (n = 5) | WNV (n = 5) |
|---|---|---|---|---|---|
| Neuroimaging and EEG[a] | | | | | |
| MRI | | | | | |
| Abnormal, no. (%) | 13/28 (46%) | 8/20 (40%) | 6/6 (100%) | 3/3 (100%) | 3/5 (60%) |
| Temporal lobe, no. (%) | 4/28 (14%) | 1/20 (5%) | 6/6 (100%) | 0/3 (0%) | 0/5 (0%) |
| White matter involvement, no. (%) | 3/28 (11%) | 1/20 (5%) | 1/6 (17%) | 0/3 (0%) | 1/5 (20%) |
| EEG | | | | | |
| Abnormal, no. (%) | 21/24 (88%) | 6/11 (55%) | 3/4 (75%) | 0/0 (0%) | 3/4 (75%) |
| Slowing, no. (%) | 9/24 (38%) | 3/11 (27%) | 2/4 (50%) | 0/0 (0%) | 3/4 (75%) |
| Epileptiform activity, no. (%) | 6/24 (25%) | 1/11 (9%) | 1/4 (25%) | 0/0 (0%) | 0/4 (0%) |
| Laboratory | | | | | |
| CSF median values (range) | | | | | |
| WBC count, cells/mm$^3$ | 23 (0–252) | 70 (1–2655) | 78 (3–540) | 167 (43–705) | 189 (17–645) |
| Protein level, mg/dL | 24 (10–67) | 34 (10–131) | 52 (6–126) | 70 (30–119) | 65 (48–179) |
| Glucose level, mg/dL | 64 (35–92) | 64 (42–122) | 55 (34–79) | 56 (40–58) | 59 (39–63) |

# Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study

*Nuria Gresa-Arribas*, Maarten J Titulaer*, Abiguei Torrents, Esther Aguilar, Lindsey McCracken, Frank Leypoldt, Amy J Gleichman, Rita Balice-Gordon, Myrna R Rosenfeld, David Lynch, Francesc Graus, Josep Dalmau*

***Lancet Neurol* 2014**

| | CSF | | Serum | | p value* | Serum (non-tumour) | | Serum (tumour) | | p value† |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | % (95% CI) | n | % (95% CI) | | n | % (95% CI) | n | % (95% CI) | |
| **Sensitivity** | | | | | | | | | | |
| Number of patients | 250 | -- | 250 | -- | -- | 153 | -- | 97 | -- | -- |
| Both tests positive | 250 | 100% (98·5–100) | 214 | 85·6% (80·7–89·4) | <0·0001 | 123 | 80·4% (73·4–85·9) | 91 | 93·8% (87·2–97·1) | 0·0029 |
| IHC positive | 250 | 100% (98·5–100) | 229 | 91·6% (87·5–94·7) | 0·0095‡ | 135 | 88·2% (82·1–92·9) | 94 | 96·9% (91·2–99·4) | 0·018 |
| CBA positive | 250 | 100% (98·5–100) | 217 | 86·8% (82·0–90·7) | -- | 125 | 81·7% (74·7–87·5) | 92 | 94·8% (88·4–98·3) | 0·0055 |
| **Specificity** | | | | | | | | | | |
| Number of controls§ | 100 | -- | 100 | -- | -- | -- | -- | -- | -- | -- |
| Both tests negative | 100 | 100% (96·3–100) | 100 | 100% (96·3–100) | 1·00 | -- | -- | -- | -- | -- |

IHC=immunohistochemistry; CBA cell-based assay; *McNemar's test . †Fisher's exact test. ‡Comparison of serum immunohistochemistry sensitivity versus serum cell-based assay sensitivity. §The 100 control patients with suspected encephalitis included two patients with antibodies for LGI1 (leucine-rich glioma inactivated 1), one for amphiphysin, one for GAD (glutamic acid decarboxylase), and one for DPPX (dipeptidyl-peptidase-like protein-6).

***Table 1:*** **Sensitivity and specificity of NMDAR antibodies tests in serum and CSF**

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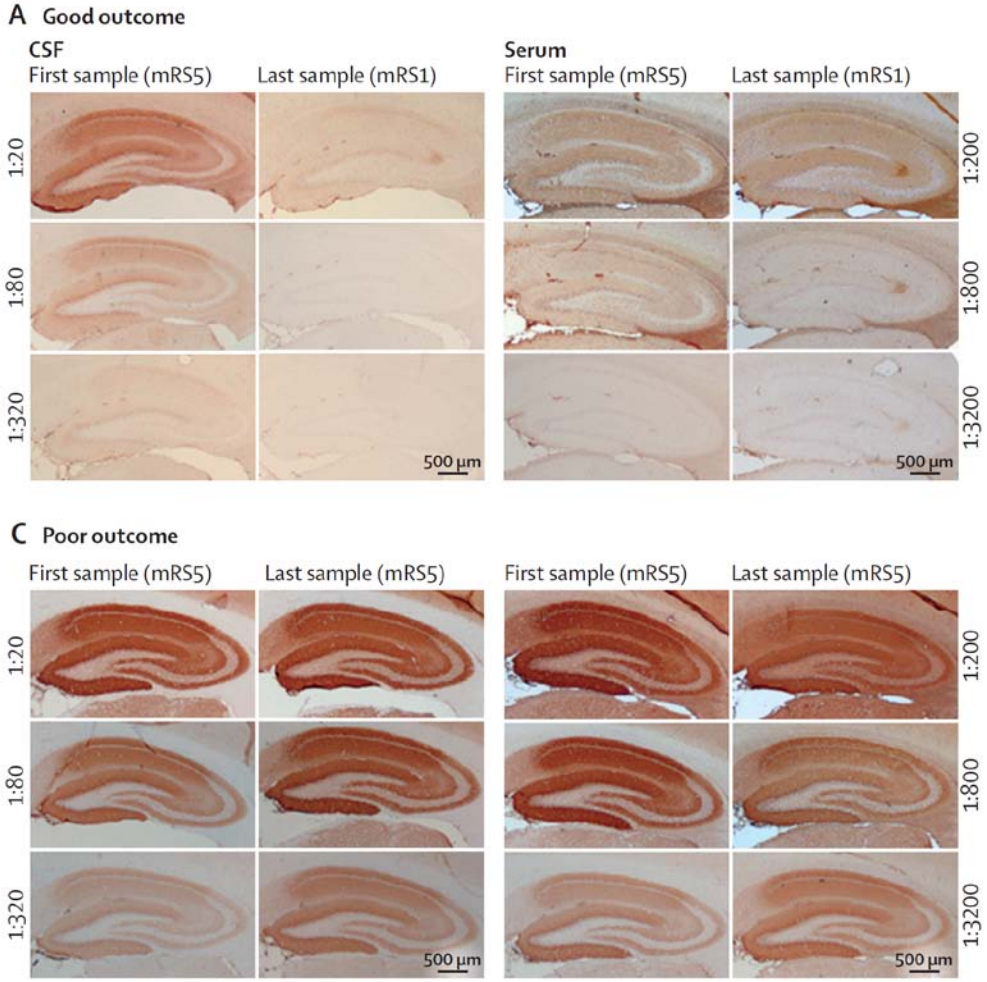
***Lancet Neurol* 2014**



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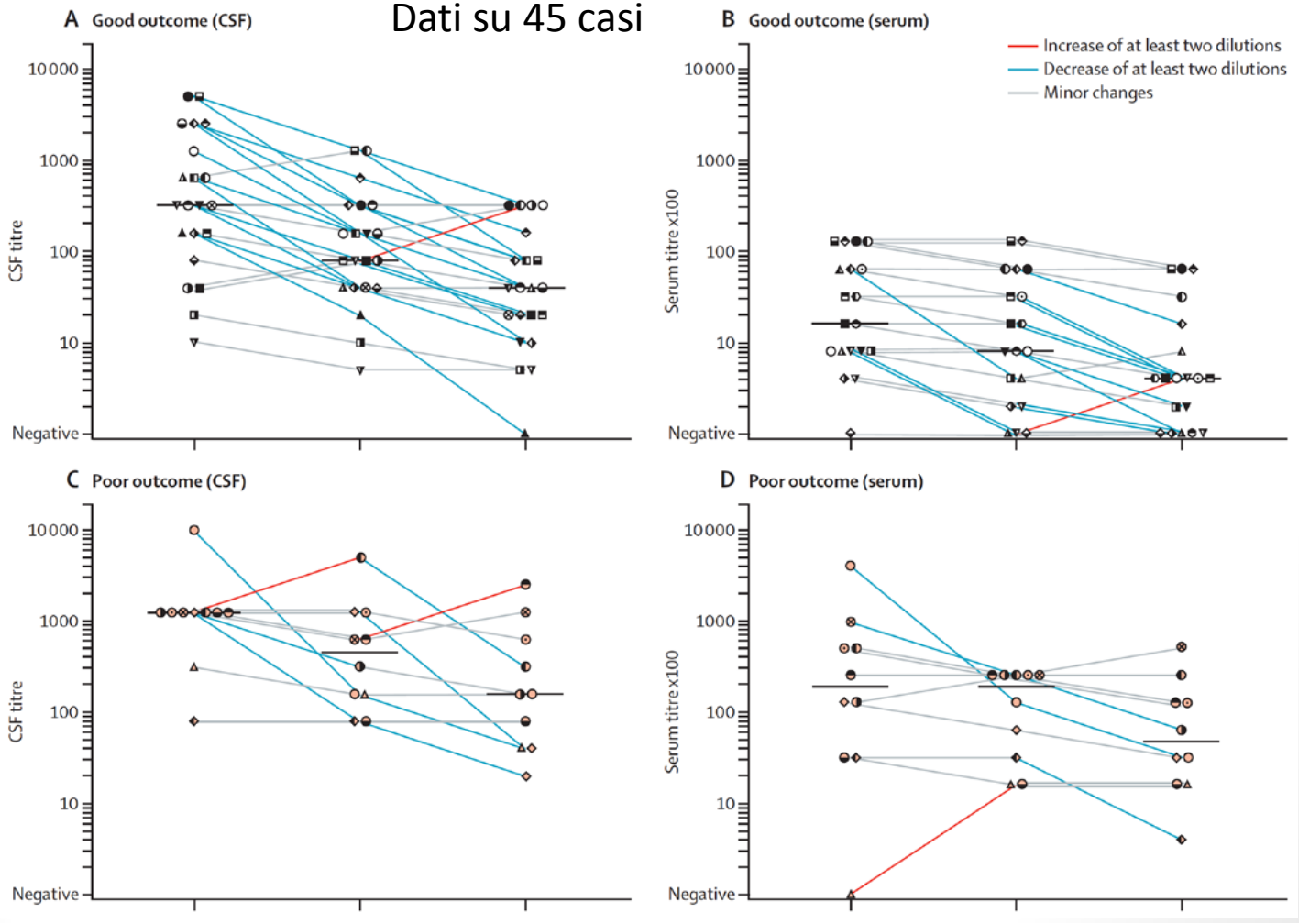
***Lancet Neurol* 2014**

Dati su 45 casi



# Extreme delta brush

## A unique EEG pattern in adults with anti-NMDA receptor encephalitis

Figure 2 Continuous EEG recording in a 19-year-old man with anti-NMDA receptor encephalitis associated with dyskinesias, seizures, and coma

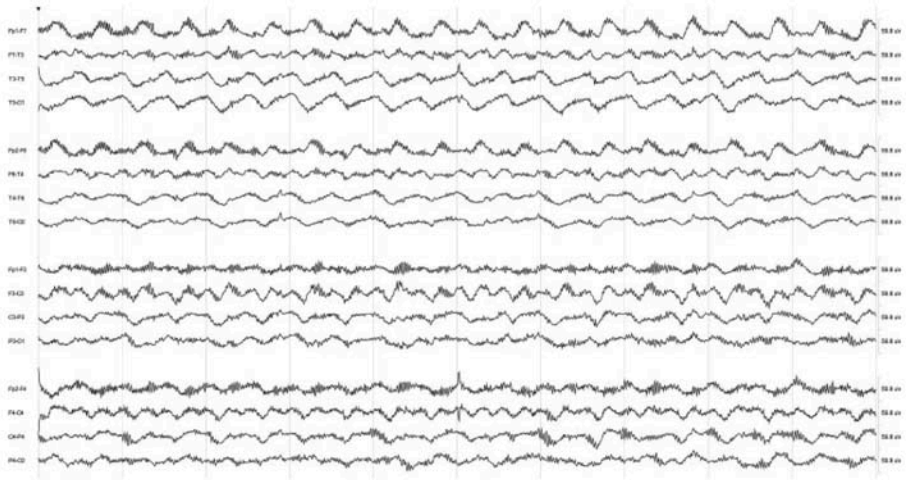
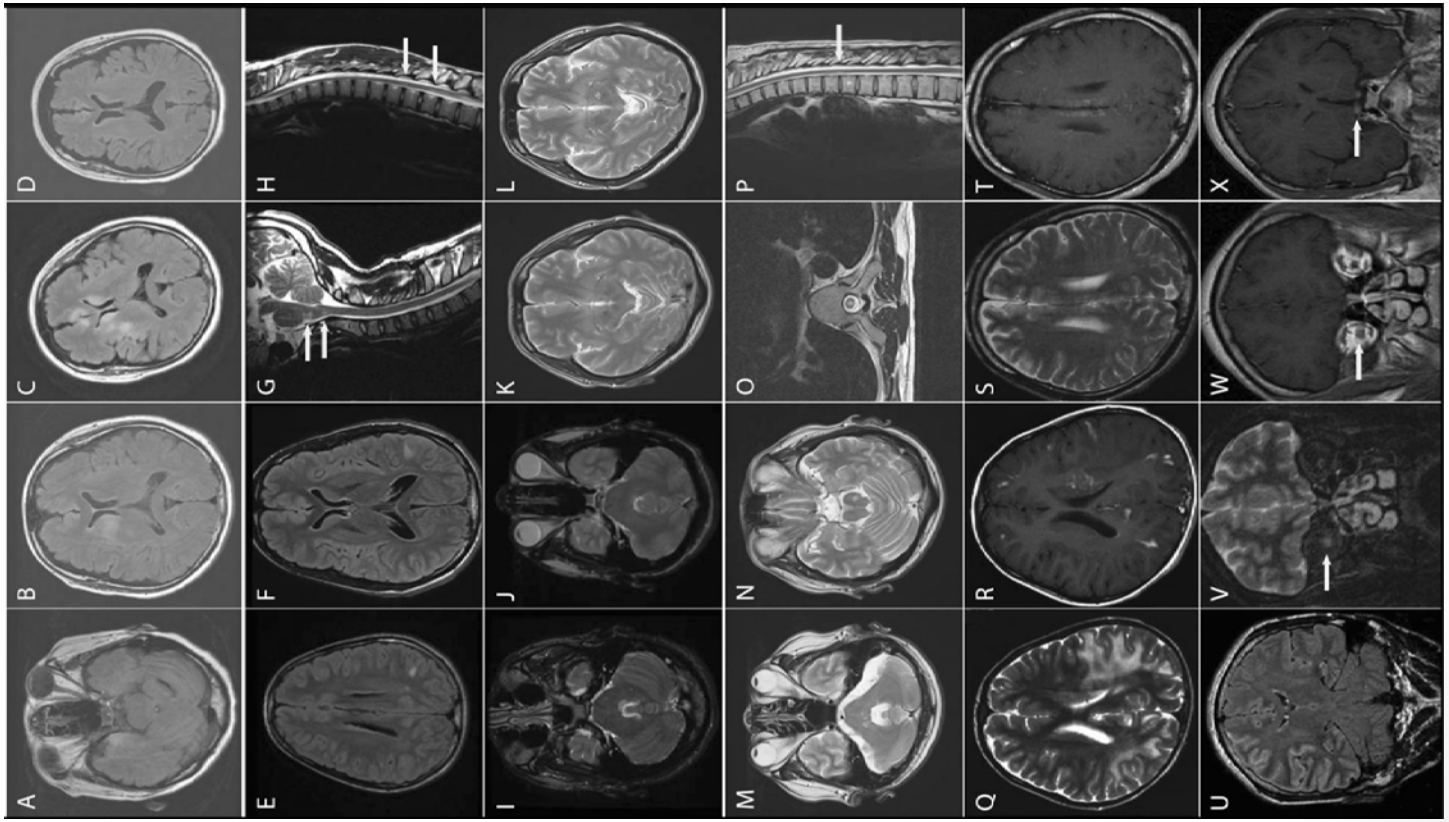


Table 1 Summary of cEEG findings

| EEG findings | No. | % |
|---|---|---|
| Normal EEG | 2 | 8.7 |
| Mild polymorphic diffuse slowing | 2 | 8.7 |
| Moderate polymorphic diffuse slowing | 10 | 43.5 |
| Severe polymorphic diffuse slowing | 9 | 39.1 |
| Focal slowing | 8 | 34.8 |
| Hemispheric | 5 | 21.7 |
| Frontal | 6 | 26.1 |
| Central | 4 | 17.4 |
| Temporal | 6 | 26.1 |
| Parietal | 4 | 17.4 |
| Occipital | 4 | 17.4 |
| Other | 4 | 17.4 |
| Generalized rhythmic delta frequency activity without extreme delta brush | 4 | 17.4 |
| Excess beta frequency activity without extreme delta brush | 5 | 21.7 |
| Electrographic seizures | 14 | 60.1 |
| Left | 0 | 0 |
| Right | 6 | 42.9 |
| Bilateral/generalized | 4 | 28.6 |
| Unknown | 4 | 28.6 |
| Electrographic seizures without clinical correlate | 9 | 39.1 |
| Clinical seizures | 14 | 60.9 |
| Extreme delta brush | 7 | 30.4 |

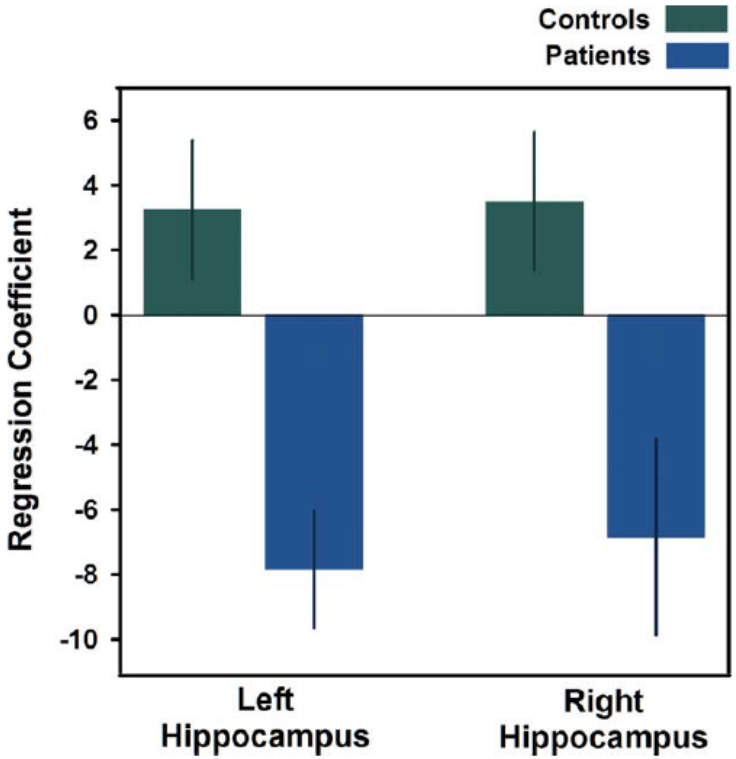
Schmitt SE, Neurology 2002

# ENCEFALITE DA NMDA-R-Ab: IMAGING

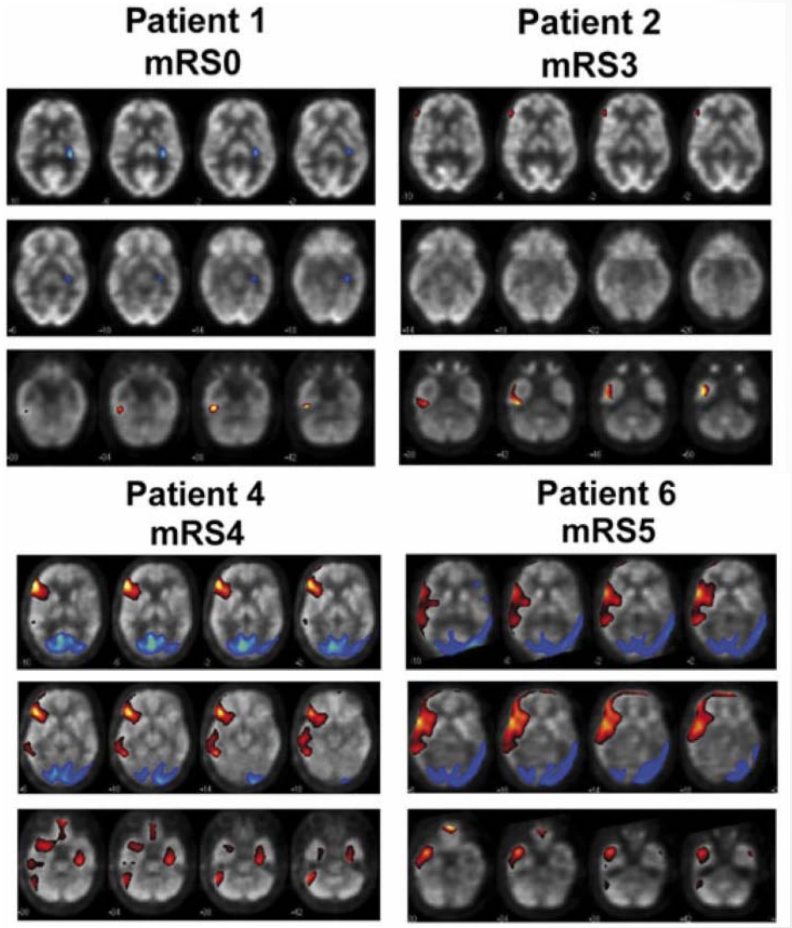



Titulauer MJ Annals Neurology 2014

# ENCEFALITE DA NMDA-R-Ab: IMAGING

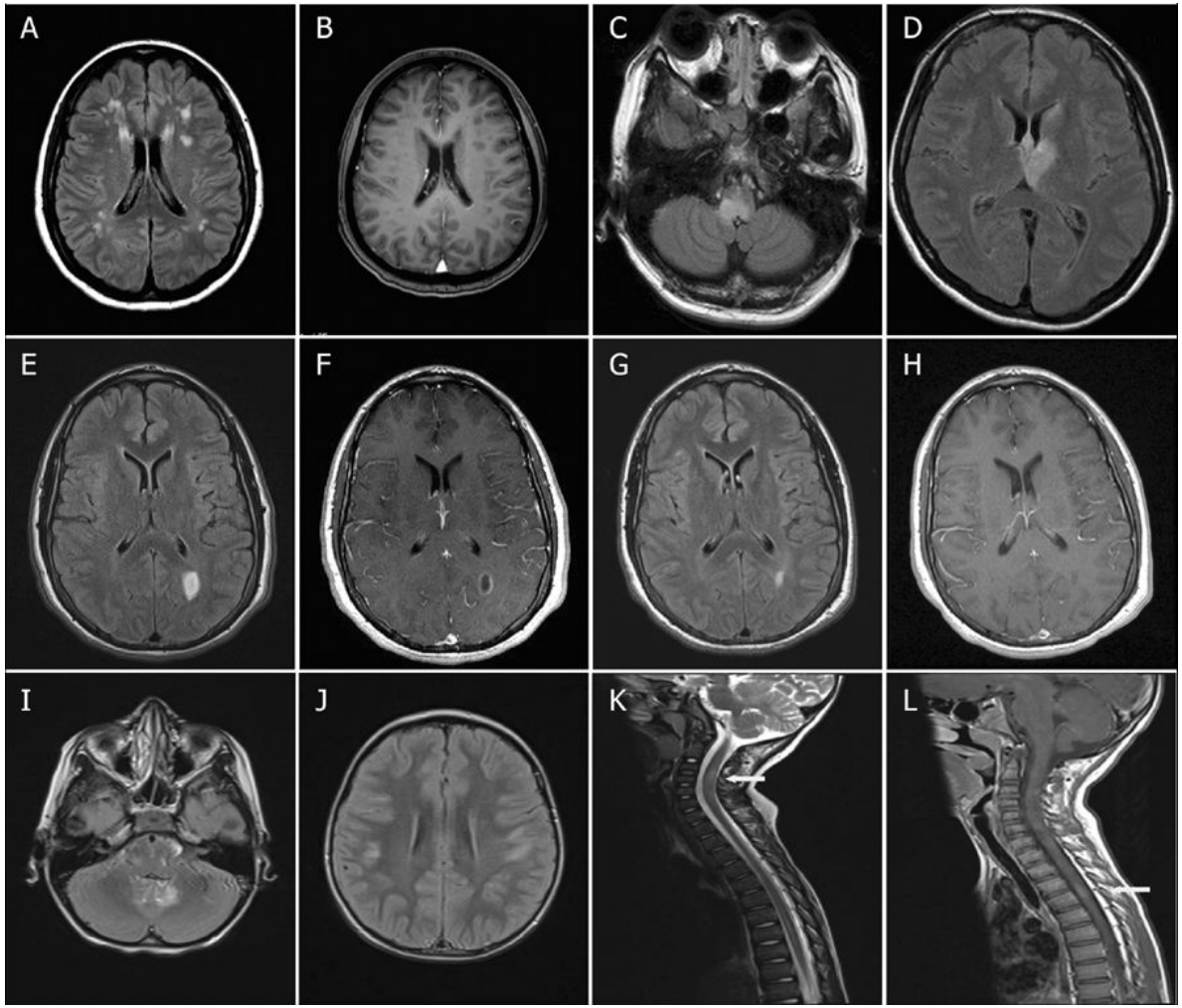



Finke, Ann Neurol 2013



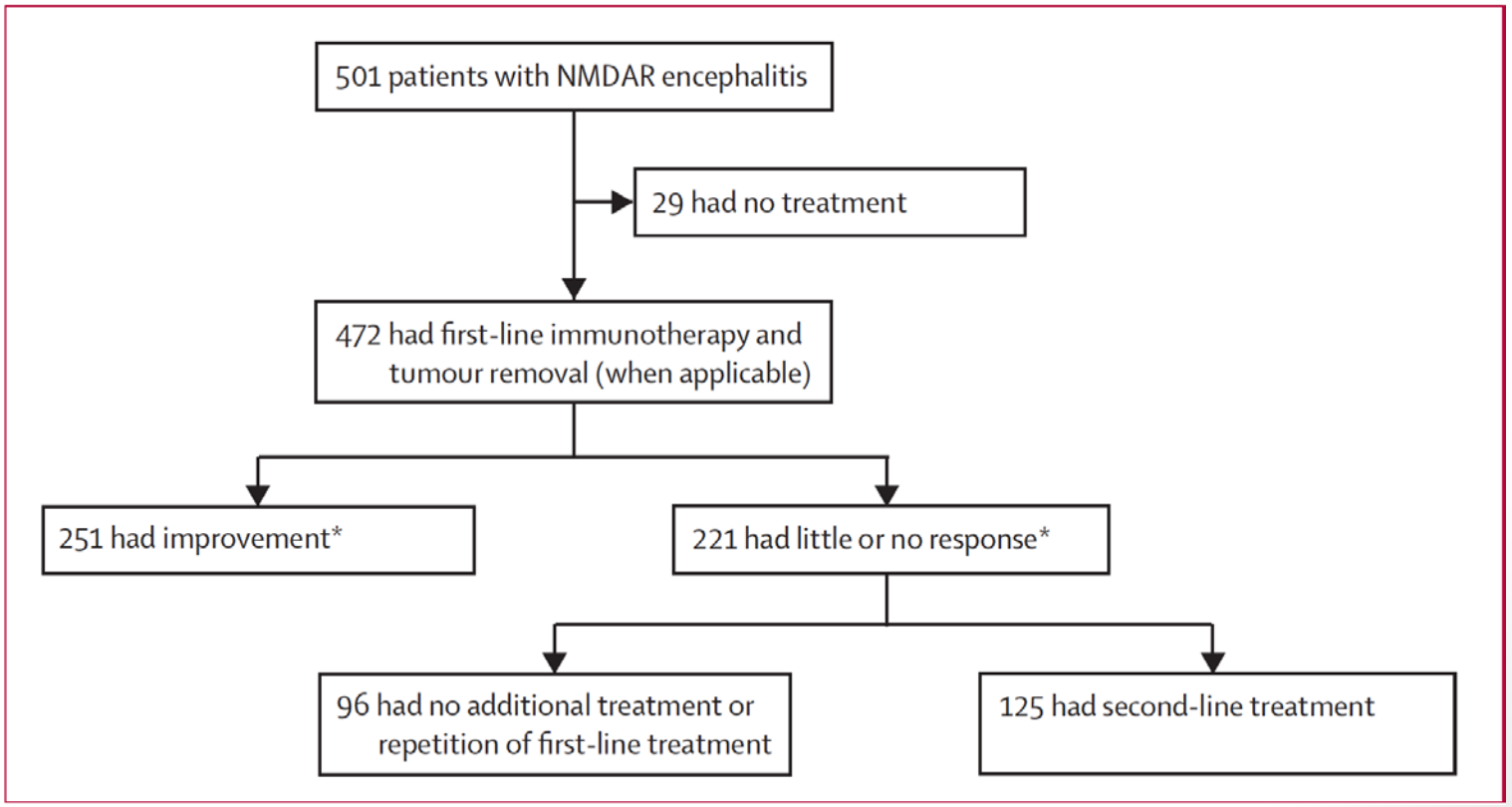

Leypoldt JNNP 2012

# ENCEFALITE DA NMDA-R-Ab: OVERLAP CON ADEM



# Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study

*Maarten J Titulaer, Lindsey McCracken, Iñigo Gabilondo, Thaís Armangué, Carol Glaser, Takahiro Iizuka, Lawrence S Honig, Susanne M Benseler, Izumi Kawachi, Eugenia Martinez-Hernandez, Esther Aguilar, Núria Gresa-Arribas, Nicole Ryan-Florance, Abiguei Torrents, Albert Saiz, Myrna R Rosenfeld, Rita Balice-Gordon, Francesc Graus, Josep Dalmau*




Titulaer, Lancet Neurol 2013

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| | Non-tumour (n=304) | Tumour (n=197) | All (N=501) | p value* |
|---|---|---|---|---|
| Median time from symptom onset until treatment in days (IQR) | 21 (14–49) | 21 (14–42) | 21 (14–46) | 0·090 |
| First-line immunotherapy | 283 (93%) | 179 (91%) | 462 (92%) | 0·40 |
| Steroids | 265 (87%) | 156 (79%) | 421 (84%) | 0·024 |
| Intravenous immunoglobulins | 221 (73%) | 125 (63%) | 346 (69%) | 0·030 |
| Plasmapheresis | 80 (26%) | 83 (42%) | 163 (33%) | 0·0003 |
| Second-line immunotherapy† | 93 (31%) | 41 (21%) | 134 (27%) | 0·017 |
| Rituximab | 71 (23%) | 30 (15%) | 101 (20%) | 0·030 |
| Cyclophosphamide | 50 (16%) | 31 (16%) | 81 (16%) | 0·90 |
| Other immunotherapy‡ | 23 (8%) | 8 (4%) | 31 (6%) | 0·13 |
| Median time from symptom onset until tumour removal in months (IQR, range) | .. | 1·4 (0·7–2·6, –13 to 177) | .. | |
| Surgery§ | 14 (5%) | 189 (96%) | .. | <0·0001 |
| During initial episode | 14 (5%) | 169 (86%) | .. | |
| At relapse | 0 | 7 (4%) | .. | |
| After recovery | 0 | 13 (7%) | .. | |
| Failure of first-line immunotherapy¶ | | | | |
| Yes | 145 (48%) | 76 (39%) | 221 (44%) | 0·069 |
| No | 138 (45%) | 103 (52%) | 241 (48%) | |
| Surgery with no immunotherapy | 1 (<0·5%) | 9 (5%) | 10 (2%) | |
| No treatment | 20 (7%) | 9 (5%) | 29 (6%) | |

Titulaer, Lancet Neurol 2013

# ENCEFALITE LIMBICA AUTOIMMUNE

- Clinica
  - Rapido sviluppo di stato confusionale
  - Perdita della memoria di breve termine
  - Convulsioni

- Caratteristiche liquorali
  - Pleocitosi linfocitaria
  - IgG Index elevato o presenza di BOC

- Caratteristiche all'imaging
  - Aumento del segnale temporale bilaterale in FLAIR

# ENCEFALITE LIMBICA AUTOIMMUNE

***Panel 2:* Diagnostic criteria for definite autoimmune limbic encephalitis**

Diagnosis can be made when all four* of the following criteria have been met:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes†
3. At least one of the following:
   - CSF pleocytosis (white blood cell count of more than five cells per $mm^3$)
   - EEG with epileptic or slow-wave activity involving the temporal lobes
4. Reasonable exclusion of alternative causes (appendix)

*If one of the first three criteria is not met, a diagnosis of definite limbic encephalitis can be made only with the detection of antibodies against cell-surface, synaptic, or onconeural proteins. †$^{18}$Fluorodeoxyglucose ($^{18}$F-FDG) PET can be used to fulfil this criterion. Results from studies from the past 5 years suggest that $^{18}$F-FDG-PET imaging might be more sensitive than MRI to show an increase in FDG uptake in normal-appearing medial temporal lobes.[44,45]

Grauss, Lancet Neurol 2016

# ANTICORPI NELLA DIAGNOSI DI ENCEFALITE LIMBICA

| | Syndrome | Diagnostic assay | Frequency of cancer | Main type of cancer |
|---|---|---|---|---|
| **Antibodies against intracellular antigens** | | | | |
| Hu (ANNA1)[8]* | Limbic encephalitis | Western blot | >95% | Small-cell lung carcinoma |
| Ma2[9] | Limbic encephalitis† | Western blot | >95% | Testicular seminoma |
| GAD[10] | Limbic encephalitis‡ | Radioimmunoassay | 25%§ | Thymoma, small-cell lung carcinoma |
| **Antibodies against synaptic receptors** | | | | |
| AMPA receptor[12] | Limbic encephalitis | Cell-based assay | 65% | Thymoma, small-cell lung carcinoma |
| $GABA_B$ receptor[13] | Limbic encephalitis | Cell-based assay | 50% | Small-cell lung carcinoma |
| $GABA_A$ receptor[14] | Encephalitis | Cell-based assay | <5% | Thymoma |
| **Antibodies against ion channels and other cell-surface proteins** | | | | |
| LGI1[17] | Limbic encephalitis | Cell-based assay | 5–10% | Thymoma |

# Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series

*Meizan Lai*, Maartje G M Huijbers*, Eric Lancaster, Francesc Graus, Luis Bataller, Rita Balice-Gordon, John K Cowell, Josep Dalmau*

| | Patients (n=57) |
|---|---|
| Men | 37 (65%) |
| Age (years) | 60 (30–80) |
| Tumours present* | 6 (11%)† |
| Clinical diagnosis of limbic encephalitis | 57 (100%) |
| Memory loss | 57 (100%) |
| Myoclonus‡ | 18 (40%) |
| Hyponatraemia§ | 28 (60%) |
| Serum sodium (mM) | 128 (118–132) |
| Seizures¶ | 42 (82%)‖ |
| MRI¶ | |
| Increased T2 signal involving medial temporal lobe(s) | 43 (84%) |
| EEG** | |
| Any abnormality | 26 (76%) |
| Seizures | 11 (32%) |
| Epileptiform discharges | 4 (12%) |
| Diffuse or focal slowing | 11 (32%) |
| CSF analyses†† | |
| Any abnormality | 19 (41%) |
| Elevated protein | 13 (28%) |
| Lymphocytic pleocytosis | 8 (17%) |
| Treatments‡‡ | |
| Any treatment | 48 (96%) |
| Steroids | 42 (84%) |
| Intravenous immunoglobulin | 31 (62%) |
| Plasma exchange | 3 (6%) |
| Other treatments | 6 (12%)§§ |
| Clinical outcomes‡‡ | |
| Full recovery | 12 (24%) |
| Mild disability | 27 (54%) |
| Moderate disability | 8 (16%) |
| Death | 3 (6%) |

Lancet Neurol 2010

# Motor cortex and hippocampus are the two main cortical targets in LGI1-antibody encephalitis

| | Total cohort | | Subdivision in three groups according to suspected cortical origin of the initial symptoms during the first month of encephalitis | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Mesial temporal lobe involvement | | Motor cortex involvement | | Early involvement of both structures | | *P*-value |
| **Demography** | | | | | | | | | |
| Number of patients | 34 | | 15/32 | 46.7% | 7/32 | 21.8% | 10/32 | 31.2% | |
| Gender M/F | 19/15 | 55.8% M | 8/7 | 53.3% M | 3/4 | 42.9% M | 7/3 | 70% M | |
| Age at onset, years, median (range) | 64.1 (21–81.2) | | 65.4 (21–77.9) | | 65.0 (59.3–79.6) | | 55.8 (24.6–81.2) | | |
| | **Number of patients/ number of patients with available data** | **%** | **Number of patients/ number of patients with available data** | **%** | **Number of patients/ number of patients with available data** | **%** | **Number of patients/ number of patients with available data** | **%** | |
| **Initial symptom** | | | | | | | | | |
| Cognitive impairment | 19/34 | 55.8 | 11/15 | 73.3 | 0/7 | 0 | 6/10 | 60 | |
| Seizures | 13/34 | 38.2 | 7/15 | 46.6 | 1/7 | 14.3 | 5/10 | 50 | |
| Motor tonic/dystonic seizures | 11/34 | 32.3 | 0/15 | 0 | 7/7 | 100 | 4/10 | 40 | |
| **Cumulative symptoms** | | | | | | | | | |
| Cognitive impairment | 30/34 | 88.2 | 15/15 | 100 | 5/7 | 71.4 | 8/10 | 80 | 0.081 |
| Seizures | 29/34 | 85.2 | 14/15 | 93.3 | 5/7 | 71.4 | 10/10 | 100 | 0.20 |
| Motor tonic/dystonic seizures | 22/32 | 68.7 | 5/15 | 33.3 | 7/7 | 100 | 10/10 | 100 | 0.0001* |
| Mood disorders | 15/34 | 44.1 | 8/15 | 53.3 | 3/7 | 42.9 | 3/10 | 30 | 0.596 |
| Sleep disorders | 12/32 | 37.5 | 7/15 | 46.6 | 2/7 | 28.6 | 3/10 | 30 | 0.711 |
| Motor disorders[a] | 7/32 | 21.8 | 4/15 | 26.6 | 2/7 | 28.6 | 1/10 | 10 | 0.631 |
| **Sodium level** | | | | | | | | | |
| Hyponatremia during evolution[c] | 20/29 | 68.9 | 8/11 | 72.7 | 5/7 | 71.4 | 6/10 | 60 | 0.879 |
| **MRI** | | | | | | | | | |
| Abnormal MRI at the time of initial symptoms | 8/23 | 34.7 | 5/10 | 50 | 0/4 | 0 | 2/7 | 28.5 | 0.239 |
| Unilateral hippocampal hypersignal | 6/8 | 75 | 4/5 | 80 | 0/4 | 0 | 2/2 | 100 | 0.026** |
| Bilateral hippocampal hypersignal | 2/8 | 25 | 1/5 | 20 | 0/4 | 0 | 0/2 | 0 | 1 |
| Subsequent abnormal MRI | 21/31[b] | 67.7 | 12/15 | 80 | 2/6[b] | 33.3 | 7/10 | 70 | 0.147 |
| Unilateral hippocampal hypersignal | 7/21 | 30.0 | 2/12 | 16.6 | 1/2 | 50 | 3/7 | 42.9 | 0.266 |
| Bilateral hippocampal hypersignal | 13/21 | 61.9 | 10/12 | 83.3 | 0/2 | 0 | 3/7 | 42.9 | 0.031*** |
| Hippocampal sclerosis | 6/21 | 28.5 | 4/12 | 33.3 | 0/2 | 0 | 2/7 | 28.6 | 0.999 |
| **CSF** | | | | | | | | | |
| Abnormal | 3/30 | 10 | 1/15 | 6.6 | 1/7 | 14.3 | 1/8 | 12.5 | 1 |
| Hypercellularity | 3/3 | 100 | 1/15 | 6.6 | 1/7 | 14.3 | 1/8 | 12.5 | |
| **EEG** | | | | | | | | | |
| Abnormal | 24/32 | 75 | 12/13 | 92.3 | 5/7 | 71.4 | 6/10 | 60 | 0.158 |
| Focal or diffuse slowing | 20/24 | 83 | 11/12 | 91.6 | 4/5 | 80 | 4/6 | 66.7 | 0.391 |
| Seizure activity | 17/24 | 70.8 | 9/12 | 75 | 4/5 | 80 | 4/6 | 66.7 | 0.999 |
| **Cancer** | | | | | | | | | |
| Present | 2/32 | 6.2 | 1/15 | 6.6; kidney | 1/6 | 16.7; lung | 0/9 | 0 | 0.448 |

Navarro, Brain 2016

# Motor cortex and hippocampus are the two main cortical targets in LGI1-antibody encephalitis

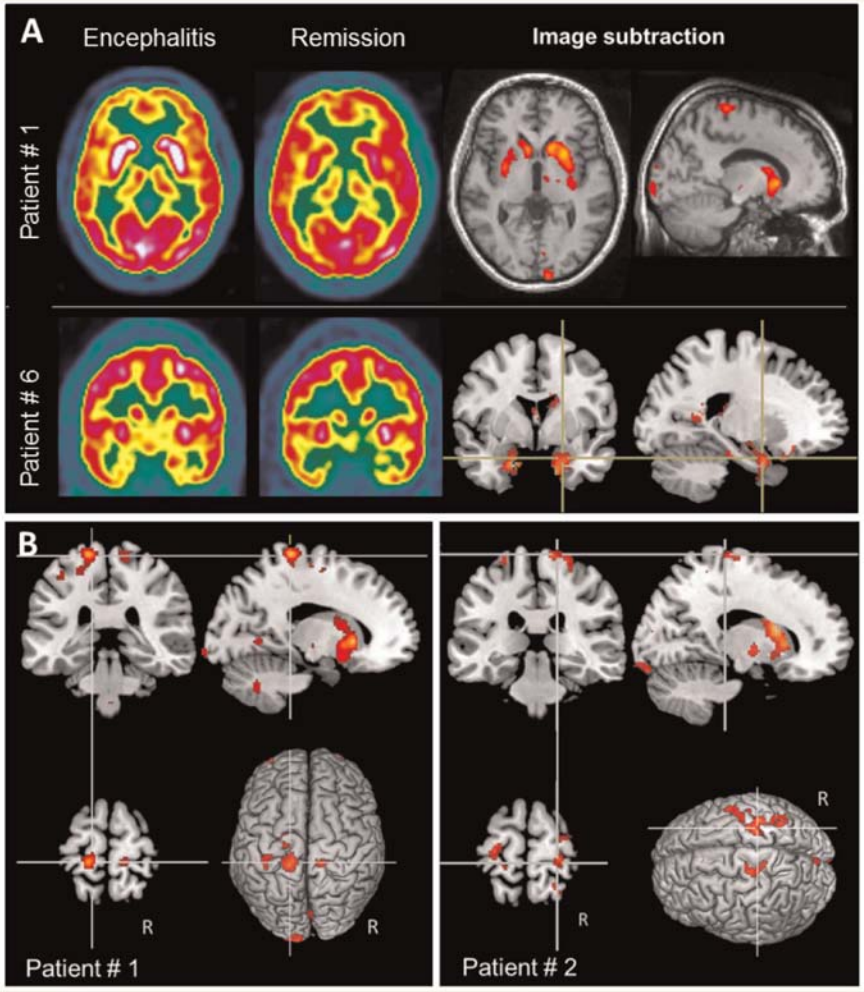



Figure 2 Hypermetabolism in the striatum, mesiotemporal and motor cortex. (A) FDG PET scans reveal striatal and mesiotemporal

Navarro, Brain 2016

# Antibodies to the $GABA_B$ receptor in limbic encephalitis with seizures: case series and characterisation of the antigen

*Eric Lancaster,* Meizan Lai,* Xiaoyu Peng, Ethan Hughes, Radu Constantinescu, Jeffrey Raizer, Daniel Friedman, Mark B Skeen, Wolfgang Grisold, Akio Kimura, Kouichi Ohta, Takahiro Iizuka, Miguel Guzman, Francesc Graus, Stephen J Moss, Rita Balice-Gordon, Josep Dalmau*

**Summary**

**Background** Some encephalitides or seizure disorders once thought idiopathic now seem to be immune mediated. We aimed to describe the clinical features of one such disorder and to identify the autoantigen involved.

*Lancet Neurol* 2010; 9: 67–76
Published Online

- 15 (4%) casi osservati (8 maschi) con sospetta EA o paraneoplastica
- Età mediana 62 aa (24-75)
- Clinica: stato confusionale, perdita della memoria di bteve termine e convulsioni
- Presenting symptoms: Convulsioni (13 casi)
  Stato confusionale (2 casi)
- Stato epilettico 3 casi
- Underlying cancer (7 casi)
  Polmonare a piccole cellule (5 casi)
  Polmonare neuroendocrino (1 caso)
  Adenopatia mediastinica (1 caso)
- Trattamento 9/10 migliorano dopo IT+/- chirurgia

# Encephalitis and $GABA_B$ receptor antibodies

## Novel findings in a new case series of 20 patients

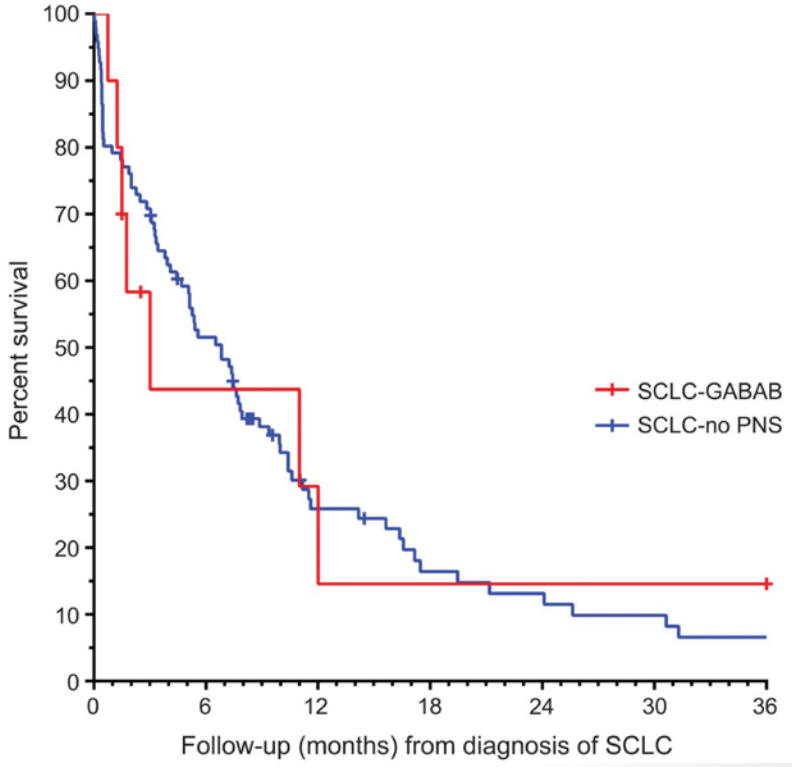
Romana Höftberger, MD

ABSTRACT

**Table 1** Clinical presentation and immunologic findings in patients with $GABA_BR$ autoimmune encephalitis

| | Patients | Idiopathic | Paraneoplastic |
|---|---|---|---|
| No. of patients | 20 | 10 | 10 |
| Male: female | 12:8 | 4:6 | 8:2 |
| Median age, y (range)[a] | 61.5 (16-77) | 39 (16-67) | 67.5 (60-77) |
| Median time until diagnosis, wk (range)[b] | 4 (2-104) | 7 (3-104) | 3.5 (2-18) |
| Clinical symptoms (initial presentation) | | | |
| LE (memory loss, confusion, seizures) | 17 | 7 | 10 |
| Only seizures | 1 | 1 | — |
| OMS | 1 | 1 | — |
| Cerebellar ataxia | 1 | 1 | — |
| Symptoms developed after initial presentation | | | |
| LE | 2[c] | 2 | — |
| Autonomic dysfunction | 1 | — | 1 |
| Mild limb spasticity | 1 | 1 | — |
| Psychiatric symptoms | 1 | 1 | — |
| MRI available | 19 | 10 | 9 |
| Pathologic findings | 12 | 7 | 5 |
| LE | 9 | 4 | 5 |
| Pial/cortical enhancement | 2 | 2 | — |
| Leukoencephalopathy | 1 | 1 | — |

**Figure 2** Survival of patients with SCLC with $GABA_BR$ antibodies does not differ from that of patients with SCLC without PNS




Neurology 2013

# ENCEFALITE DA GABA-R-Ab: caratteristiche RMN e Liquorali

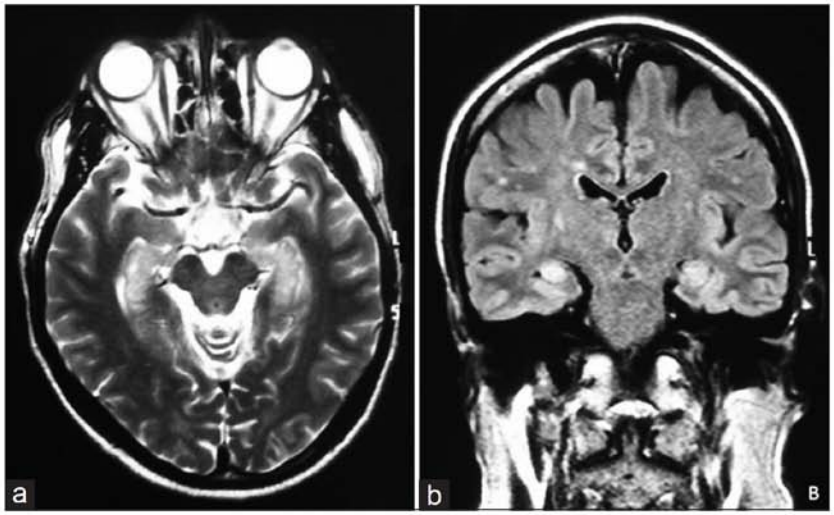



**Figure 1:** Magnetic resonance imaging of limbic encephalitis associated with anti-GABAB receptor antibodies. (a) T2-weighted magnetic resonance imaging of a patient with γ-aminobutyric acid B receptor abs and limbic encephalitis show increased signal in the mesial temporal lobes; (b) Fluid-attenuated inversion recovery magnetic resonance imaging show increased signal in the mesial temporal lobes.

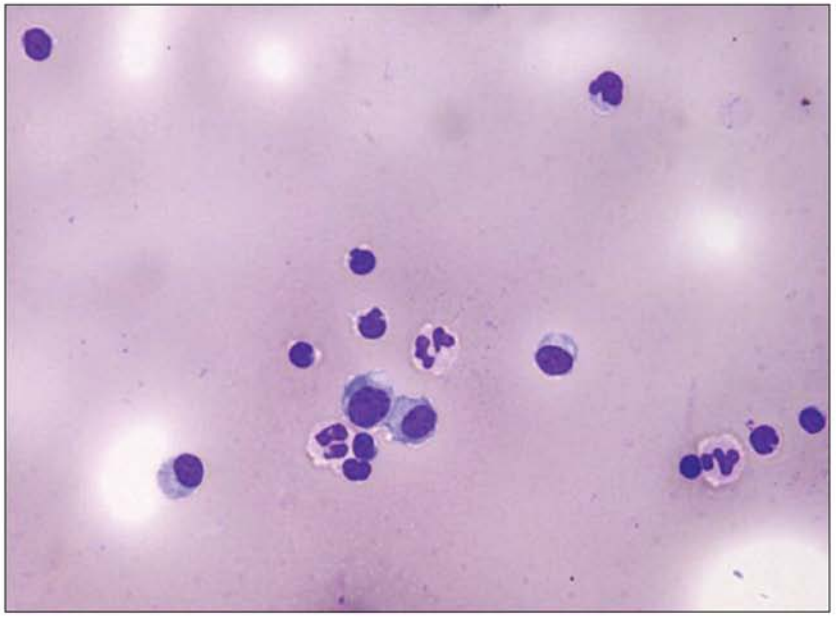


**Figure 2:** Cerebrospinal fluid cytology of a patient with γ-aminobutyric acid B receptor antibodies show mild lymphocytic-neutrophilic pleocytosis (May-Granwald-Giemsa stain, original magnification ×200).

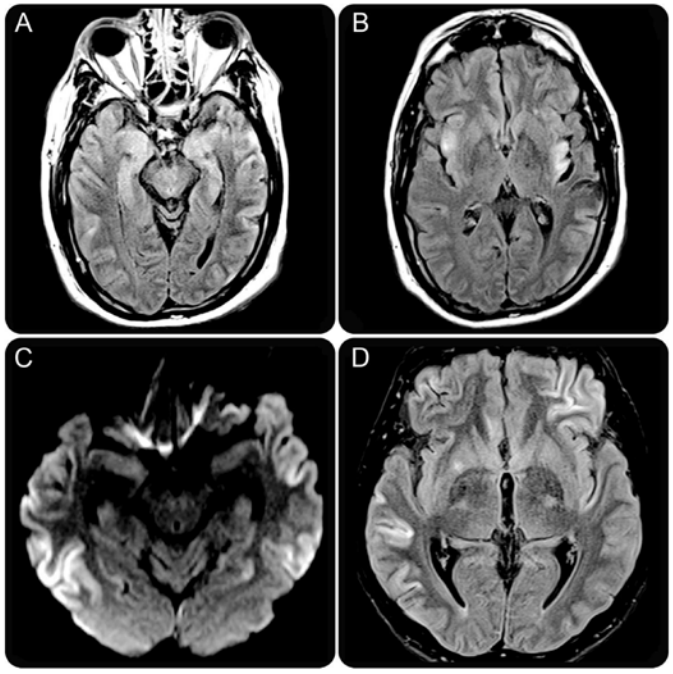
# ENCEFALITE DA AB ANTI-AMPA-R: CASE-SERIES

- 22 Pazienti (14 F)
- Età mediana — 62 aa (range 23-81)
- Tumore concomitante — 14
  - K polmonare a small cell — 5
  - Timoma — 4
  - K mammario — 2
  - OTE — 2
  - K polmonare — 1
- Tempo sintomi/diagnosi — 6.5 settimane (range3.8-8.8)
  - LE-Like esordio — 12/22
  - Convulsioni — 4/22
  - Psicosi — 5/22
- CSF pleocitosi — 11/22
- CSF Proteine↑ — 10/22

HOFTBERGER, NEUROLOGY2015

# ENCEFALITE DA AB ANTI-AMPA-R: CASE-SERIES

- Presentazione neuroradiologica
  - Interessamento del lobo temporale 8/22
  - Interessamento gangli della base 2/22
  - Altro 8/22
  - No segni 4/22




HOFTBERGER, NEUROLOGY2015

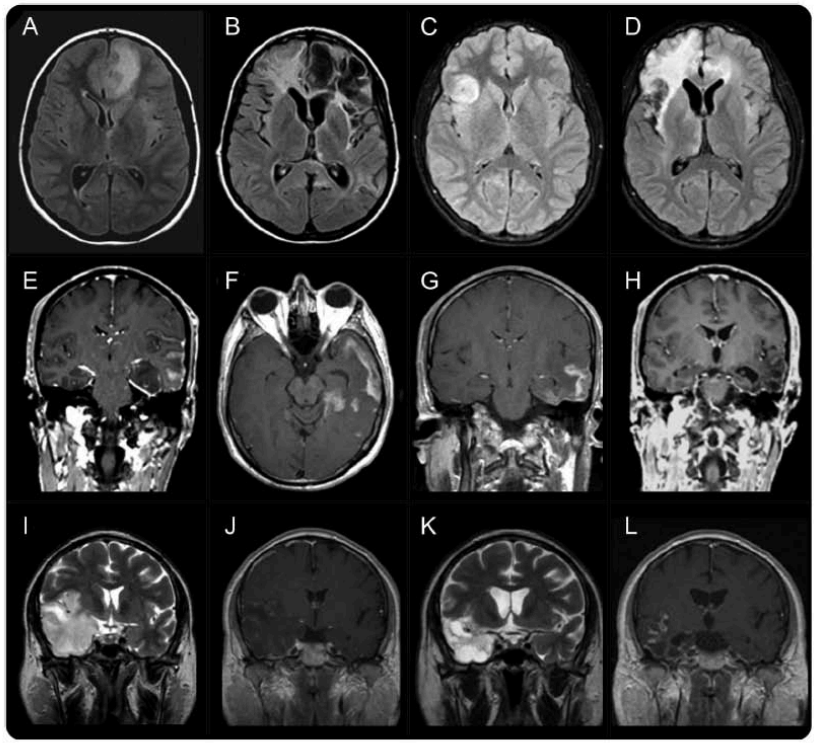
# ENCEFALITE AUTOIMMUNE POST HSV-E: CASE SERIES

- 8 Casi riportati in adulti
- Inizio sintomi — 12 -21 gg dopo l'esordio di HSE
  - Sintomi psichiatrici — 7 casi
  - Stato di male — 1 caso
- Esame del CSF
  - Pleocitosi — 5/8
  - Aumento proteine — 4/8
- Pattern anticorpale
  - Anti-NMDA-R — 5 CSF (2+ siero)
  - Anti-neurali unknown — 3 CSF (1 siero)

Armangue, Neurology 2015

# ENCEFALITE AUTOIMMUNE POST HSV-E: CASE SERIES

Figure 3 MRI findings in patients with relapsing symptoms post-herpes simplex encephalitis




Axial fluid-attenuated inversion recovery sequences of patients 1 (A, B) and 2 (C, D) during herpes simplex virus encephalitis (HSE) (A, C) and during relapsing symptoms due to autoimmune encephalitis (B, D). In both cases, there is an interval change due to areas of encephalomalacia, brain atrophy, and white matter changes. Panels E–H correspond to T1 sequences with contrast from patient 3 obtained during HSE (E), a few weeks later during relapsing symptoms due to autoimmune encephalitis (F, G), and after symptom improvement (H). Note that the areas of contrast enhancement during autoimmune encephalitis resolved after symptom improvement. Panels I–L correspond to patient 4 during HSE (I, T2; J, T1 with contrast) and 1 year later (K, T2; L, T1 with contrast). In this patient, the relapsing symptoms post-HSE were not recognized as autoimmune encephalitis for 1 year; during this year, he did not receive immunotherapy and had persistent symptoms and contrast enhancement in MRI.

Armangue, Neurology 2015

## Key points

1. A rapidly expanding subset of autoimmune encephalitis occurs in association with antibodies to neuronal cell surface or synaptic proteins
2. Symptoms of autoimmune encephalitis are diverse and include psychiatric manifestations (psychosis, catatonia, abnormal behavior), seizures, abnormal movements, decrease of level of consciousness, or autonomic dysfunction.
3. Detection of antibodies to cell surface or synaptic proteins often associates with response to immunotherapy.
4. Autoimmune encephalitis can mimic infectious encephalitis. Comprehensive testing for autoantibodies should include CSF and serum.

*Lancet Neurol*. 2008 December ; 7(12): 1091–1098. doi:10.1016/S1474-4422(08)70224-2.

# Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies

**Josep Dalmau**, **Amy J Gleichman**[*], **Ethan G Hughes**[*], **Jeffrey E Rossi**, **Xiaoyu Peng**, **Meizan Lai**, **Scott K Dessain**, **Myrna R Rosenfeld**, **Rita Balice-Gordon**, and **David R Lynch**

Characteristics and clinical features

| | Patients |
|---|---|
| Women and girls | 91 |
| Median age, range (years) | 23, 5–76 |
| Prodromal symptoms (information available for 84 patients) | 72 |
| Symptom presentation | |
| Psychiatric (first seen by psychiatrist) | 77 |
| Neuropsychiatric (first seen by neurologists) | 23 |
| Seizures | |
| Any type | 76 |
| Generalised tonic-clonic | 45 |
| Partial complex | 10 |
| Other[*] | 30 |
| Dyskinesias and movement disorders | |
| Any type | 86 |
| Orofacial | 55 |
| Choreoathetoid and complex movements with extremities, abdomen or pelvis | 47 |
| Abnormal postures (dystonic, extension), muscle rigidity, or increased tone | 47 |
| Other[†] | 25 |
| Autonomic instability[‡] | 69 |
| Central hypoventilation | 66 |

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| | Patients |
|---|---|
| **EEG (information for 92 patients)** | |
| Total with abnormal findings | 92 |
| Slow activity* | 71 |
| Epileptic activity | 21 |
| **Brain MRI** | |
| Total with abnormal findings | 55 |
| Medial temporal lobes | 22 |
| Cerebral cortex | 17 |
| Cerebellum | 6 |
| Brainstem | 6 |
| Basal ganglia | 5 |
| Contrast enhancement in cortex, meninges, basal ganglia | 14 |
| Other† | 8 |
| **CSF** | |
| Total with abnormal findings | 95 |
| Lymphocytic pleocytosis‡ | 91 |
| Increased protein concentration§ | 32 |
| Oligoclonal bands positive (information for 39 patients) | 26 |
| **Tumour (information for 98 patients)** | |
| All | 58 |
| Women | |
| Mature teratoma of the ovary | 35 |
| Inmature teratoma of the ovary | 14 |
| Radiologically demonstrated teratoma | 4 |
| Other¶ | 3 |
| Men | |
| Immature teratoma of the testis | 1 |
| Small-cell lung cancer | 1 |
| **Treatment** | |
| Tumour resection | 51 |
| Immunotherapy | 92 |
| Corticosteroids | 76 |
| Intravenous immunoglobulin | 62 |
| Plasma exchange | 34 |
| Rituximab | 10 |
| Cyclophosphamide | 9 |
| Azathioprine | 1 |
| Other‖ | 10 |
| Only supportive care | 2 |

# ENCEFALITI AUTOIMMUNI E TARGET

Autoimmune encephalitis with antibodies against cell surface and synaptic proteins

| Antigen | Clinical syndrome | Tumor |
|---|---|---|
| NMDAR (GluN1) | Anti-NMDAR encephalitis: prodromal symptoms, psychiatric, seizures, amnesia, movement disorders, catatonia, autonomic instability, coma | Age-dependent 10–45% ovarian teratomas, infrequently carcinomas |
| AMPAR | Limbic encephalitis, psychiatric symptoms | 70% (lung, breast, thymoma) |
| GABAbR | Limbic encephalitis, prominent seizures | 50% lung, neuroendocrine |
| LGI1 | Limbic encephalitis, 60% hyponatremia, occasional focal faciobrachial seizures prior to encephalitis | <10% (lung, thymoma) |
| CASPR2 | Encephalitis, Morvan syndrome, neuromyotonia | 0–40% thymoma |
| mGluR5 | Limbic encephalitis (reported in less than 10 patients) | Frequently, Hodgkin lymphoma |
| D2R | Basal ganglia encephalitis, Sydenham chorea. | Infrequent |
| DPPX | Diarrhea, encephalitis with CNS hyperexcitability: confusion, psychiatric symptoms, tremor, myoclonus, nystagmus, hyperekplexia, PERM-like symptoms, ataxia. | No tumor association |
| GABAaR | Refractory seizures, status epilepticus, or epilepsia partialis continua, stiff-person, opsoclonus | Infrequent |
| GlyR | Stiff-person, PERM, limbic encephalitis, cerebellar degeneration, optic neuritis | Infrequent |
| IgLON5 | Abnormal sleep movements and behaviors,obstructive sleep apnea, stridor, dysarthria, dysphagia, ataxia, chorea (reported in less than 10 patients) | No tumor association |