



Published in final edited form as:

Epilepsy Res. 2017 January ; 129: 101–105. doi:10.1016/j.eplepsyres.2016.12.010.

EPILEPSY SURGERY IN DRUG RESISTANT TEMPORAL LOBE EPILEPSY ASSOCIATED WITH NEURONAL ANTIBODIES

Mar Carreño, MD, PhD¹, Christian Bien, MD², Ali A. Asadi-Pooya, MD³, Michael Sperling, MD, PhD³, Petr. Marusic, MD, PhD⁴, Martin Elisak, MD⁴, Jose Pimentel, MD, PhD⁵, Tim Wehner, MD PhD⁶, Rajiv Mohanraj, MB BS, MRCP, PhD⁷, Juan Uranga, MD⁸, Asier Gómez-Ibáñez, MD⁹, Vicente Villanueva, MD, PhD⁹, Francisco Gil, MD¹, Antonio Donaire, MD, PhD¹, Nuria Bargalló, MD, PhD¹⁰, Jordi Rumià, MD¹¹, Pedro Roldán, MD, PhD¹¹, Xavier Setoain, MD, PhD¹², Luis Pintor, MD, PhD¹³, Teresa Boget, PhD¹³, Eva Bailles, PhD¹⁴, Mercè Falip, MD¹⁵, Javier Aparicio, MD¹, Josep Dalmau, MD, PhD¹⁶, and Francesc Graus, MD, PhD¹

¹Epilepsy Unit. Department of Neurology. Hospital Clínic. Barcelona (Spain)

²Epilepsy Center Bethel, Krankenhaus Mara, Bielefeld, Germany

³Jefferson Comprehensive Epilepsy Center, Department of Neurology, Thomas Jefferson University, Philadelphia, PA (USA)

⁴Dpt. of Neurology. Charles University in Prague, 2nd Faculty of Medicine Motol University Hospital. Prague (Czech Republic)

⁵Department of Neurology. Faculty of Medicine of the University of Lisbon- Hospital de Santa Maria. Lisbon (Portugal)

⁶Institute of Neurology, University College London (UK)

⁷Salford Royal NHS Foundation Trust (UK)

⁸Department of Neurology. Clinic of Sagrado Corazón. Sevilla (Spain)

⁹Department of Neurology. Hospital la Fe. Valencia (Spain)

¹⁰Epilepsy Unit. Department of Radiology. Hospital Clínic. Barcelona (Spain)

¹¹Epilepsy Unit. Department of Neurosurgery. Hospital Clínic. Barcelona (Spain)

¹²Epilepsy Unit. Department of Nuclear Medicine. Hospital Clínic. Barcelona (Spain)

¹³Epilepsy Unit. Department of Psychiatry. Hospital Clínic. Barcelona (Spain)

¹⁴Epilepsy Unit. Hospital Clínic. Barcelona (Spain). University Pompeu-Fabra. Barcelona (Spain)

¹⁵Epilepsy Unit. Department of Neurology. Hospital Bellvitge. Barcelona (Spain).

Corresponding author: Mar Carreño. Department of Neurology. Hospital Clínic. c/Villarroel 170. 08036. Barcelona (Spain), mcarreno@clinic.ub.es Phone number: +34932275414 Fax number: +34932275783.

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¹⁶Josep Dalmau. ICREA-IDIBAPS and Department of Neurology. Hospital Clínic. Barcelona (Spain). University of Pennsylvania

Abstract

We assessed the outcome of patients with drug resistant epilepsy and neuronal antibodies who underwent epilepsy surgery. Retrospective study, information collected with a questionnaire sent to epilepsy surgery centers. Thirteen patients identified, with antibodies to GAD (8), Ma2 (2), Hu (1), LGI1 (1) or CASPR2 (1). Mean age at seizure onset: 23 years. Five patients had an encephalitic phase. Three had testicular tumors and five had autoimmune diseases. All had drug resistant temporal lobe epilepsy (median: 20 seizures/month). MRI showed unilateral temporal lobe abnormalities (mainly hippocampal sclerosis) in 9 patients, bilateral abnormalities in 3, and was normal in 1. Surgical procedures included anteromesial temporal lobectomy (10 patients), selective amygdalohippocampectomy (1), temporal pole resection (1) and radiofrequency ablation of mesial structures (1). Perivascular lymphocytic infiltrates were seen in 7/12 patients. One year outcome available in all patients, at 3 years in 9. At last visit 5/13 patients (38.5%) (with Ma2, Hu, LGI1, and 2 GAD antibodies) were in Engel's classes I or II. Epilepsy surgery may be an option for patients with drug resistant seizures associated with neuronal antibodies. Outcome seems to be worse than that expected in other etiologies, even in the presence of unilateral HS. Intracranial EEG may be required in some patients.

Keywords

hippocampal sclerosis; GAD; Ma2; LGI1; temporal lobectomy

Introduction

Autoimmunity is being increasingly recognized as a cause of drug resistant epilepsy. Some patients develop drug resistant seizures after an episode of well-characterized autoimmune encephalitis (Pillai et al., 2016). There is also evidence that autoimmune (paraneoplastic or non-paraneoplastic) limbic encephalitis may present as temporal lobe epilepsy, sometimes associated with hippocampal sclerosis (HS) (Bien et al., 2007;Gaspard, 2016). As neuronal antibody determination becomes more widely available, they are increasingly identified in a subset of patients with chronic epilepsy during the diagnostic workup.

Patients with autoimmune epilepsy usually have high seizure frequency and often display MRI abnormalities, such as HS. In this setting, when antiepileptic and immunosuppressive drugs fail, surgical treatment may be a therapeutic option. The HS observed in these patients probably represents a “burn out” inflammatory process and it is often considered the underlying “structural” cause of the seizures. Less frequently, surgery is performed when the autoimmune etiology has not been suspected yet and the mesial temporal swelling is mistaken for cortical dysplasia or a low-grade tumor (Almeida et al., 2012). The potential role of epilepsy surgery has been only assessed in isolated case reports and small series of patients with neuronal antibodies (Almeida et al., 2012;Kerling et al., 2008;Malter et al., 2015;Muehlechner et al., 2010). The objective of our study was to determine the outcome of a

series of patients with epilepsy associated with neuronal antibodies who underwent epilepsy surgery.

Methods

This retrospective multicenter study was approved by the Ethics committee of Hospital Clínic, University of Barcelona (Barcelona, Spain). Patients were routinely consented for their clinical information to be included in clinical studies. A questionnaire was sent to 60 tertiary epilepsy surgery centers in Europe, USA, Canada, and Japan to find out if they had any patients who met the inclusion criteria: resective surgery for drug resistant epilepsy and positive neuronal antibodies. We asked about clinical features, acute encephalitic phase if present, immunosuppressive treatment, type and titres of autoantibodies if available, results of presurgical evaluation, pathological findings, and seizure outcome at 1 and 3 years. Surgically treated patients in whom pathological findings were suggestive of chronic encephalitis but no specific antibody was found were excluded from the study. Outcome was assessed by the Engel classification, a widely used tool to categorize the outcome of epilepsy surgery: class I (free of disabling seizures), class II (rare disabling seizures, almost seizure free), class III (worthwhile improvement) and class IV (not worthwhile improvement). Satisfactory outcome included classes I and II.

Results

Most epilepsy centers could not provide any patients who met the inclusion criteria. Finally, a total of 13 patients from 8 centers in Europe and the United States were included in the study. Two patients have been previously reported (Almeida et al., 2012; Haberlandt et al., 2011). Mean age at epilepsy onset was 23 years (range: 2–46 years). The following antibodies were detected in serum: GAD (8 patients), Ma2 (2) patients, Hu (1), LGI1 (1), and CASPR2 (1). Antibodies were also detected in CSF in 5/11 patients (CSF not analyzed in 2). Oligoclonal bands in CSF were found in 3 patients. The antibodies were found after surgery in 5 patients (Table 1), most often because of the pathological findings. Eight patients had drug resistant epilepsy without a previous episode of encephalitis (6 GAD, 1 LGI1, 1 CASPR2), whereas the other five patients developed drug resistant epilepsy after a typical episode of autoimmune encephalitis. Associated comorbidities included 3 testicular tumors (2 anti-Ma2, 1 anti-Hu), and several autoimmune disorders, all in patients with GAD antibodies (Table 1). Six patients (five who had encephalitis and one with chronic epilepsy) were treated with immunosuppressive drugs (intravenous corticosteroids \pm immunoglobulins). Three patients were still taking maintenance corticosteroids at presurgical evaluation.

Mean time to presurgical evaluation was 9.4 years (range 1–61 years). All patients underwent prolonged video-EEG monitoring with surface electrodes, MRI and neuropsychological testing. No patients underwent monitoring with invasive electrodes. Seizure frequency was daily or monthly (median number: 20 per month, range 2–720). Mean number of antiepileptic drugs was 2.1 (range 1–3). All patients had seizures with temporal lobe semiology. Ten patients had auras, being abdominal (5 patients), and psychic (5) the most common. Four patients displayed multiple types of auras. The most frequently

recorded seizures were automotor (with oral or distant hand automatisms and alteration of awareness: 11 patients). Two patients had autonomic seizures (objective piloerection). In addition, four patients had complex motor seizures with irregular movements involving trunk and proximal parts of the limbs and 3 had secondarily generalized tonic-clonic seizures. Interictal surface EEG showed unilateral temporal epileptiform discharges in 9/13 patients, and bilateral temporal discharges in the other 4. Surface ictal EEG showed seizure onset zone in one temporal lobe in 9/13 patients and independently in both temporal lobes in 4/13 patients. Neuropsychological evaluation demonstrated bilateral temporal dysfunction in 4 patients (one with severe anterograde amnesia), unilateral temporal dysfunction in 7 and executive deficits only in 2 patients.

MRI was normal in 1 patient, showed unilateral HS in 6/13 patients, bilateral asymmetric HS in 2/13 patients, unilateral increase in size and signal of mesial structures thought to be a malformation or a low grade tumor in 3/13 patients and bilateral increase in size and signal of mesial temporal structures in 1 patient (Table 1).

Surgical procedures included standard anteromesial temporal resection in 10/13 patients, selective amygdalohippocampectomy in 1, resection of the temporal pole sparing the hippocampus in 1, and stereotactic radiofrequency ablation of mesial structures in 1. Complications after surgery included depression (2 patients), semantic memory deficits (1) and quadrantanopsia (1). Neuropathological findings included lymphocytic infiltrates in 7/12 patients (Figure 1), along with variable amounts of neuronophagic nodules, microglia activation, neuronal loss, hippocampal sclerosis, and abnormal cortical lamination (Table 1). Seizure outcome was available at 1 year for all patients and at 3 years for 9. At the last follow-up, 5/13 patients (38.4%) were in Engel classes I or II; 8 patients were in classes III or IV. Two patients became seizure free after surgery. Two patients (CASP2R and GAD) who were initially seizure free moved to a class III outcome during follow-up. We did not find any correlation between outcome of surgery and antibody type, previous history of encephalitis, or presence of uni or bilateral HS in the MRI (only 1 out of 6 patients –16%– with HS had a good outcome).

Discussion

This retrospective multicenter study shows that seizure outcome after temporal lobe surgery in patients with neuronal antibodies seems to be worse than that in other clinical settings. In temporal lobe epilepsy with unilateral HS not associated with neuronal antibodies, up to 70% of patients become seizure free after surgery (Mathon et al., 2015), whereas only 16% of patients with similar MRI findings but with neuronal antibodies became seizure free in the current study. We acknowledge that the number of patients is small and this could have led to an underestimation of the efficacy of the surgical procedure. However, in view of these results it seems reasonable to be cautious when discussing the possibility of seizure freedom with patients and their families.

In such a limited sample it is difficult to extract valuable conclusions regarding the influence of specific types of neuronal antibodies in surgical outcome. A good clinical outcome occurred with different types of onconeural and surface-directed antibodies. Only 2 of 8

patients with GAD antibodies became free or almost seizure free in the long-term. This is in agreement with previously published series reporting improvement in seizure frequency but not seizure freedom in patients with GAD autoimmunity after surgery (Malter et al., 2015).

There are several possible explanations for this type of outcome. First, we have found that active signs of inflammation are present not only in patients undergoing surgery during the “acute” phase of the disease, but also in some patients with HS, reflecting that residual lesions and active inflammation may occur simultaneously in the same patient. Second, the ongoing inflammatory process may well extend beyond the surgically resected area (for example to the insula) and contribute to seizure generation after surgery. The occurrence of prominent autonomic symptoms in some patients suggests involvement of the insular cortex in seizure generation or epileptic network. Consequently, failure to identify a “temporal plus” epilepsy could explain failure of surgery in some cases (Barba et al., 2016). Third, the setting of neuronal antibodies it is not uncommon to observe bilateral involvement of the temporal lobes, both structurally (MRI) and functionally (e.g. memory deficits, bilateral interictal epileptiform discharges, bilateral seizure onset in the ictal EEG). Therefore, the non-resected temporal lobe may become epileptogenic, particularly if there is an ongoing inflammatory process in the brain. (Kerling et al., 2008). Intracranial EEG should be considered in patients with a possible temporal plus or bitemporal epilepsy to delineate better the seizure onset zone and increase the likelihood of successful epilepsy surgery.

Our study has several limitations. The main one is the small number of patients. However these patients are extremely difficult to find. We managed to include 13 after contacting with 60 of the most active epilepsy surgery centers in the world. The reason is that they are very rarely considered for surgery, even after antiepileptic and immunosuppressive drugs have failed. In fact, in 4 patients the resection was performed before the antibodies were discovered, when a possible autoimmune etiology had not been suspected yet. It is possible that epileptologists consider autoimmune epilepsy as an entity less likely to result in seizure freedom after surgery, due to its widespread epileptogenic effects. Our series seems to confirm this belief.

Due to its retrospective design, the study has the inherent bias that only patients with selected “favorable” clinical and MRI features underwent presurgical evaluation (presumably those deemed to have some benefit from surgery). In addition, the titers of GAD antibodies were not available for many patients. However, we believe our findings add valuable information to the decision algorithm in patients with drug resistant seizures and neuronal antibodies that we encounter with increasing frequency in our practice. Taking into account the high seizure frequency and the low rate of surgery complications, the possible benefit of a palliative resection may be considered. Presurgical evaluation may require invasive EEG studies in some patients.

Acknowledgments

Funding sources: This study was supported in part by NIH RO1NS077851 (JD), Fondo de Investigaciones Sanitarias, FEDER, Spain (14/00203, JD), and Fundació CELLEX (JD).

Disclosure of conflicts of interest: Mar Carreño has participated in advisory boards and pharmaceutical industry-sponsored symposia for Eisai, UCB, Bial, Esteve, Medtronic and Cyberonics, and received research grants from

UCB and Eisai. She reports no financial relationships relevant to the manuscript. Christian Bien reports no financial relationships relevant to the manuscript. Aliakbar Asadi-Pooya reports no financial relationships relevant to the manuscript. Michael Sperling reports: Research: Eisai, UCB Pharma, Sunovion, SK Life Sciences, Marinus, Lundbeck, Medtronic, Accordia, Upsher-Smith, Brain Sentinel, Glaxo, Pfizer. Dr. Sperling serves as the Editor-in-Chief of *Epilepsia*. Petr Marusic reports no financial relationships relevant to the manuscript. Martin Elisak reports no financial relationships relevant to the manuscript. José Pimentel reports no financial relationships relevant to the manuscript. Tim Wehner reports no financial relationships relevant to the manuscript. Rajiv Mohanraj reports no financial relationship relevant to the manuscript. Juan Uranga reports no financial relationships relevant to the manuscript. Asier Gómez-Ibáñez reports no financial relationships relevant to the manuscript. Vicente Villanueva has participated in advisory boards and pharmaceutical industry-sponsored symposia for Eisai, UCB, Merck Sharp & Dohme, Bial, Pfizer, GlaxoSmithKline (GSK), Esteve, Medtronic and Cyberonics. He reports no financial relationships relevant to the manuscript. Francisco Gil reports no financial relationships relevant to the manuscript. Antonio Donaire reports no financial relationships relevant to the manuscript. Nuria Bargalló reports no financial relationships relevant to the manuscript. Jordi Rumià reports no financial relationships relevant to the manuscript. Pedro Roldán reports no financial relationships relevant to the manuscript. Xavier Setoain reports no financial relationships relevant to the manuscript. Luis Pintor reports no financial relationships relevant to the manuscript. Teresa Boget reports no financial relationships relevant to the manuscript. Eva Bailles reports no financial relationships relevant to the manuscript. Mercè Falip reports no financial relationships relevant to the manuscript. Javier Aparicio reports no financial relationships relevant to the manuscript. Josep Dalmau has a research grant from Euroimmun, and receives royalties from patents for the use of Ma2, NMDAR, and GABA_B as autoantibody tests. Francesc Graus reports no financial relationships relevant to the manuscript.

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HIGHLIGHTS

- Surgery is sometimes performed for temporal lobe epilepsy with neuronal antibodies
- Surgery outcome is poorer than in patients without neuronal antibodies
- No clear relationship between outcome and antibody type or MRI lesion was found
- Presence of unilateral HS does not necessarily associate to good outcome
- Invasive studies may help in some patients to define better the seizure onset zone

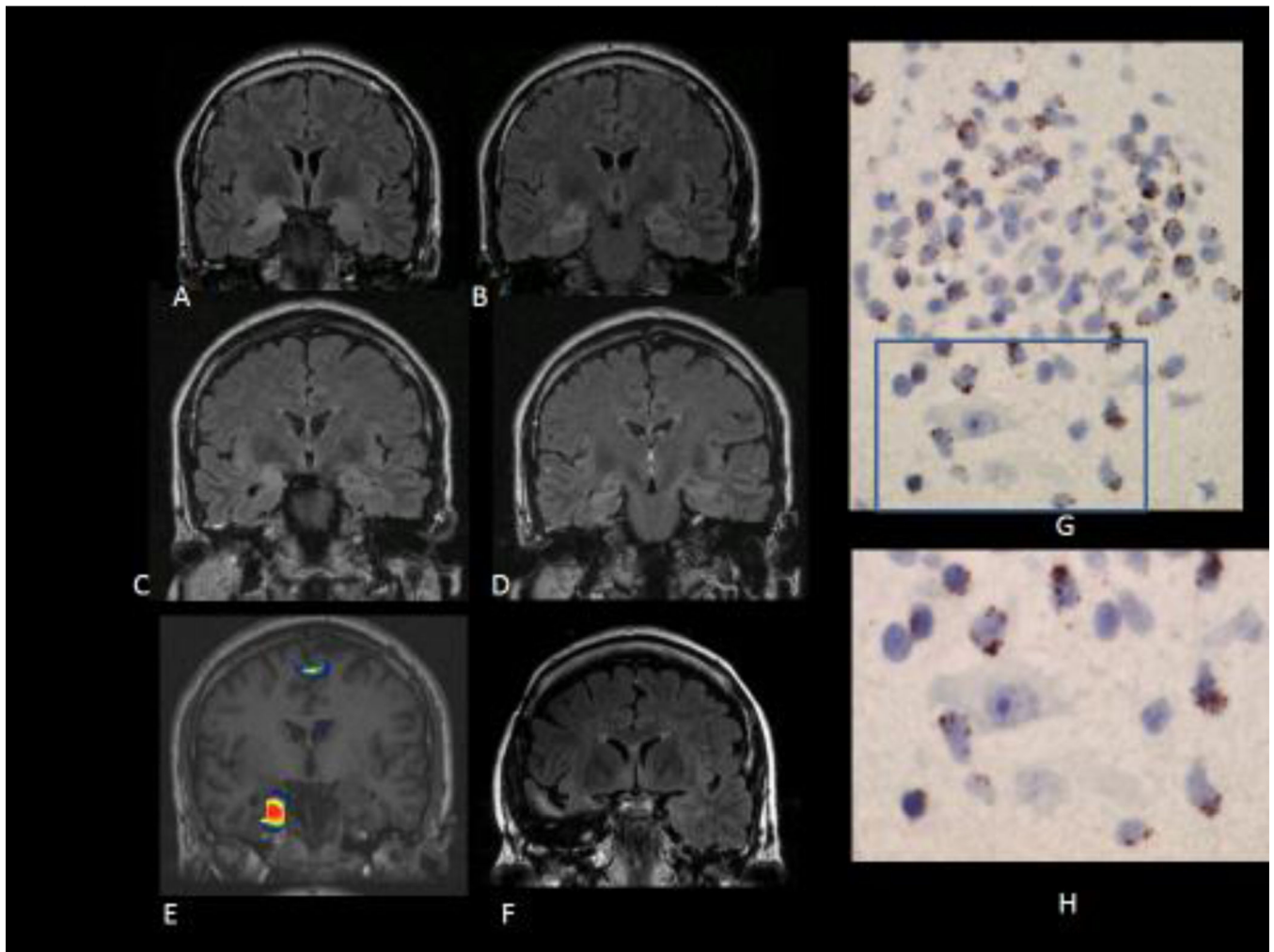


Figure 1.

A, B: Coronal FLAIR MRI images showing increased signal and volumen of right amígdala and hippocampus, suggestive of limbic encephalitis, in a patient with acute onset of seizures. The patient had anti Ma2 antibodies and a past history of seminoma (patient 1, see table).

C, D: Coronal FLAIR images one year later, showing atrophy of right mesial temporal structures with persistence of the increased signal (right MTS) (patient 1)

E: SISCOM showing increased ictal perfusion over the right hippocampus and parahippocampal gyrus during a right temporal lobe seizure with epigastric aura, piloerection and loss of awareness (patient 1).

F: Coronal FLAIR image showing resection of the temporal pole and the right mesial temporal structures. The patient continued to have seizures after surgery although with some seizure reduction (Engel's class III) (patient 1)

G: Inflammatory infiltrate in the surgical specimen. The tissue section was immunostained with TIA-1 antibody, a marker of cytotoxic T cells. There are positive cells clearly showing the characteristic TIA-1 granular pattern in the inflammatory infiltrate. Some TIA-1 positive cells are in close apposition with neurons (H). (patient 1)

Table 1 Clinical characteristics and seizure outcome after epilepsy surgery of patients with drug resistant epilepsy with neuronal antibodies

Patient	Age* / sex	Encephalitic phase	Antibodies titres (if GAD)	CSF features	Comorbidity	MRI	Immunotherapy	Ictal EEG	Surgery (delay)	Outcome** (Engel)	Inflammation infiltrates (additional findings)
1	34/M	yes	Ma2 (serum, CSF)	Oligoclonal bands *	Testicular tumor	Unilateral MTS	CS, Ig	Unilateral	AMTL (1y)	III	Yes (neuronal loss, gliosis)
2	27/M	yes	Ma2 (serum, CSF)	N.A.	Testicular tumor	Bilateral MTS	CS, Ig	Bilateral	AMTL (7m)	II	Yes (neuronal loss)
3	37/M	yes	Hu (serum)	Normal	Testicular tumor	Unilateral MTS	CS	Unilateral	AMTL (11y)	I	No (neuronal loss)
4***	15/F	yes	GAD (serum, CSF)	N.A.	Type I DM, Stiff person	Bilateral LE	CS	Bilateral	AMTL (6y)	IV	Yes (hippocampal sclerosis)
5	9/F	yes	GAD (serum)	N.A.	Stiff person	Normal	CS	Bilateral	AMTL (8y)	III	Yes
6	24/F	No	GAD (serum, CSF)	Oligoclonal bands ++	RA, cutaneous vasculitis	Unilateral MTS	CS	Unilateral	AMTL (8y)	III	No (hippocampal sclerosis)
7	26/F	No	GAD (serum)	Not done	None	Unilateral MTS	No	Bilateral	AMTL (3y)	IV	No (gliosis, satellitosis)
8	19/F	No	GAD (serum)	Oligoclonal bands ++	No	Unilateral MTS	No	Unilateral	AMTL (10y)	III	No (abnormal cortical lamination)
9	2/F	No	GAD (serum, CSF) *****	N.A.	Type I DM	Unilateral MTS	No	Unilateral	AMTL (61 y)	IV	No (hippocampal sclerosis)
10	16/F	No	GAD (serum) *****	N.A.	None	Unilateral LE	No	Unilateral	T pole resection (4y)	II	Yes (gliosis)
11	20/M	No	CASPR2 (serum) *****	Normal	None	Bilateral MTS	No	Unilateral	STRA (18y)	III	Not available

Patient	Age / sex	Encephalitic phase	Antibodies (if GAD)	CSF features	Comorbidity	MRI	Immunotherapy	Ictal EEG	Surgery (delay)	Outcome ^{**} (Engel)	Inflammatory infiltrates (additional findings)
12 ^{***}	19/M	No	LGI1 (serum) ^{****}	Not done	None	Unilateral LE	No	Unilateral	SAH (1y)	I	Yes (gliosis, microglial activation)
13	46/F	No	GAD (serum) ^{****}	Not done	Type I DM, celiac, thyroid	Unilateral LE	No	Unilateral	AMTL (9m)	II	Yes (gliosis, neuronal loss and cytomegaly)

M: male, F: female, CS: corticosteroids, RT: right temporal AMTL: anteromedial temporal lobectomy, RA: rheumatoid arthritis, STRA: stereotactic radiofrequency ablation, SAH: selective amygdalohippocampectomy, LE: limbic encephalitis, HS: hippocampal sclerosis,

* at seizure onset.

N.A.: not available

** at last follow up.

*** patient previously reported

**** antibodies found after surgery