Supplementary Table S1: Data extraction sheet

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>STUDY</th>
<th>PATIENTS</th>
<th>INTERVENTION</th>
<th>RESULTS</th>
<th>COMMENTS</th>
<th>LEVEL OF EVIDENCE (SIGN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li Y, 2021</td>
<td>Design: Observational cross-sectional study</td>
<td>Age: 44.84 ± 14.86</td>
<td>Serum IF (ICH OR CBA); confirmed by other techniques</td>
<td>-N⁰ of total patients with positive result=6 (14.28%)</td>
<td>- One positive patient from retrospective cohort. Cannot extract specific results of % GAD65 and LGI1 for patients included in the study.</td>
<td>2+</td>
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<tr>
<td></td>
<td>Objective: To study the prevalence of serum Abs in patients ≥18 years of age with DRE of unknown cause before surgery and to propose and calculate a clinical APES (Antibody Prevalence in Epilepsy before Surgery) score for each subject</td>
<td>Focal DRE with no clear cause before surgery (a) ≥18 years of age; (b) diagnosis of focal DRE, who failed at least two anti-seizure medications; and (c) unknown cause of epilepsy. Exclusion criteria included the following: (a) generalized epilepsy; (b) definitive immune-mediated (autoimmune or paraneoplastic) epilepsy; (c) epilepsy with known cause, including but not limited to stroke, tumor, cortical dysplasia, epileptic syndrome such as tuberous sclerosis, and epilepsy with confirmed genetic etiology; and (d) pregnant. Brain MRI scan showing mesial temporal sclerosis (MTS) was not an exclusion criteria.</td>
<td>- Onconeuronal - NMDAR - AMPA - GABAb - GAD65 - LGI1 - CASPR2</td>
<td>By autoantibody type: - GAD65= 3* - LGI1= 4*</td>
<td>- High titers considered for GAD65-Ab &gt;20nmol/L</td>
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<tr>
<td></td>
<td>Recruitment: Prospective and retrospective (two different groups)</td>
<td>Number of patients included for metanalysis (Inclusion/Exclusion criteria met for our study):</td>
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<tr>
<td></td>
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<td>N= 42.</td>
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<td>Control group:</td>
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</table>
Bruijn MAAM, 2021

Design: Observational cross-sectional study

Objective: to identify neuronal antibodies in a comprehensive cohort of patients with focal epilepsy of unknown etiology, and without, or with unrecognized, signs of encephalitis and to create a score to preselect patients requiring testing

Recruitment: prospective, multicentre study

Age 18-89 adults with focal epilepsy of unknown etiology. (1) to include patients with epilepsy with or without additional symptoms, but with- out suspicion of encephalitis; and (2) to exclude patients strongly suspected of having AIE. Patients with epilepsy with known infectious, genetic, or metabolic etiologies were excluded. Patients with a structural lesion on brain magnetic resonance imaging (MRI) at inclusion were excluded, whereas patients with mesial temporal sclerosis, or with T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities mainly in the mesial temporal lobe, both unilateral and bilateral, were not.

Number of patients included for metanalysis (Inclusion/Exclusion criteria met for our study):
N= 582
66 patients (11%) had an epilepsy duration of <1 year

Control group:
Serum (CSF if available, n=46)
All screened by IF ICH (except GlyR). If positive confirmation with other technics (CBA, GAD-65 also ELISA for titles; onconeuronals with immunoblot)
- Onconeuronals
- NMDAR
- AMPA
- GABAab
- GABAa
- GAD65
- LGI1
- CASPR2
- anti-GlyR

- Nº of total patients with positive result=22 (3,78%)

By autoantibody type:
- GAD65= 13 (2,2%)
- LGI1= 3 (0,5%)
- CASPR2= 3 (0,5%)
- NMDAR=1 (CSF) 0,17%
- anti-GlyR=2 (0,3%)

A subgroup of patients considered for epilepsy surgery were side by side tested by CBA, ELISA, and RIA for antibodies, as a part of a standardized protocol. In addition, patients with an ACES score of 2 or more were tested by commercial CBA and ELISA post hoc

GAD65 ELISA > 10000 IU/mL 2++
| Ansari B, 2019 | Design: Observational cross-sectional study  
Objective: To investigate the difference in the prevalence of neural autoantibodies in patients with temporal lobe epilepsy of unknown etiology with hippocampal sclerosis vs without hippocampal sclerosis  
Recruitment: Prospective | Age 15-50 adult patients aged 15-50 years, diagnosed with International League Against Epilepsy (ILAE) and with TLE seizures. The patients with an obvious remote origin such as brain tumor, trauma, central nervous system (CNS) infection, vascular malformation, and generalized epilepsy were excluded.  
Number of patients included for metanalysis (Inclusion/Exclusion criteria met for our study): N=33 (17 with HS and 12 without HS)  
Control group: No | Serum IF CBA -GAD-Ab  
-Onconeuronal -NMDAR-Ab  
-AMPA1/2-Ab  
-LGI1-Ab  
-CASPR2-Ab  
-GABA B  
-GLYR | -Nº of total patients with positive result=14 (42,4%). With HS n=6 (35,2%)  
By Autoantibody type:  
-GABA B= 11 (33,3%)  
-NMDAR-Ab= 2 (6,0%)  
-Onconeuronal= 1 (3,0%) [Tr+CV2 1] | - All positive results were weak positive.  
- No difference HS vs non-HS  
No included for metanalysis due to extreme value (also high frequency of GABAb no reproducible in other studies) | 2- |
| Tecellioğlu M, 2018 | Design: Observational cross-sectional study  
Objective: To determine the autoimmune and oncological antibodies in Adult drug-resistant epilepsy of unknown cause and identify the clinical, radiological, and EEG findings associated | patients with drug- resistant epilepsy of unknown cause. None of the patients included in the study had any neurological signs or neurological diseases other than epilepsy. Patients with focal and diffuse atrophy, nonspecific white matter lesions and idiopathic mesial temporal sclerosis (MTS) were not excluded. The seizures and syndromes were diagnosed according to the International League Against Epilepsy (ILAE) Commission on Classification  
Plasma: -Anti-GAD (IRMA) - Onconeuronal (Immunoblot, Euroinmun) | -Nº of patients with positive result= 1 (1,2%)  
Bi autoantibody type:  
-Onconeuronal= 1 anti-MA2/TA 1 patient) | 2+ |
with these antibodies according to data in the literature.

Recruitment: Prospective 12 months

and Terminology 2017 [14]. The exclusion criteria were as follows:
1. Structural brain lesions (ischaemia, tumour, head trauma, vascular malformation, abscess, congenital malformation, heterotypic conditions).
2. Metabolic abnormalities (severe hypoglycaemia or hyperglycaemia, severe renal or hepatic deficiency, malignant hypertension, alcoholism).
3. Proven or suspected chromosomal anomalies and genetic syndromes.
4. Any malignancy

Number of patients included for metanalysis (Inclusion/Exclusion criteria met for our study): N= 77 (HS not excluded) > 18 years.

Control group: No

Dubey D, 2017

Design: Observational cross-sectional study

Objective: To determine the prevalence of neurological autoantibodies (Abs) among Adult patients

Age: 17-80 years

Patients with new- onset epilepsy or a history of epilepsy of unknown etiology. Patients were excluded they had underlying metabolic abnormalities that would explain their seizures (ie, severe renal or

Serum: Method not specified
-NMDAR-Ab
-LGI1-Ab
-GABAb-Ab
-AMPAR-Ab
-Onconeuronal
-GAD65-Ab (RIA)

- Nº of patients with positive result=15 (13.39%)
Bi autoantibody type:
- NMDAR-Ab= 4 (3.57%)
-LGI1-Ab=4

2+ -High titers considered for GAD65-Ab >20nmol/L
Design: Observational cross-sectional study
Objective: To investigate the presence of neuronal autoantibodies in focal epilepsy with unknown cause and hepatic failure, alcoholism, malignant hypertension, and severe hypoglycemia or hyperglycemia or presence of structural brain lesions (e.g., stroke, tumor, trauma, heterotopias, vascular malformation, abscess or infectious lesion, congenital malformations). Patients with idiopathic mesial temporal sclerosis were not excluded. suspected chromosomal anomaly, genetic syndromes, or in-born errors of metabolism leading to a syndrome of developmental delay with associated seizures were also excluded from the study.

Number of patients included for metaanalysis (Inclusion/Exclusion criteria met for our study):
N=112 (HS not excluded)
Control group: No

Gozubatik-Celik G, 2017

- GAD65-Ab=6 (5.35%)
- Onconeural=1 (0.89%) (anti-HU).

Age: ≥ 18 years.

Patients with structural lesions in brain magnetic resonance imaging (MRI) such as tumor or dysplasia were excluded from the study. However, patients with focal or diffuse atrophy or nonspecific white matter

plasma:
- NMDAR-Ab (IF CBA)
- LGI1-Ab (IF CBA)
- CASPR2-Ab (IF CBA)
- GABAb-Ab (IF CBA)
- AMPAR-Ab (IF CBA)

- Nº of patients with positive result=2 (2.12%)
- Nº of controls with positive result=0 (0.0%)

Bi autoantibody type:
- Six patients GAD positive but without saying titers
- Semiquantitive Scale for IF from 0-4. Positive when >1.
their clinical correlates in both drug-responsive and resistant patients. 

Recruitment: Prospective 12 months 

hyperintensities were not excluded. In addition, none of the included patients had current findings or past medical history of any neurological conditions. Patients with systemic autoimmune disorders, febrile seizures or systemic infections were included if there was no direct temporal association between these medical conditions and the onset of seizures. Likewise, patients with mesial temporal lobe epilepsy with hippocampal sclerosis were not excluded since their seizure features and locations could not be explained by hippocampal sclerosis alone. Seizures and syndromes were diagnosed according to the International League Against Epilepsy (ILAE) Commission on Classification and Terminology 2014. All MRI studies were performed with 1.5 T scanners with thin coronal, sagittal and axial planes including T1, T2, and fluid-attenuated inversion recovery (FLAIR) images.

Number of patients included for metanalysis (Inclusion/Exclusion criteria met for our study):
- N=94 (HS not excluded

- Control group: n=50 healthy age and gender paired

CBA)
- GAD-Ab (RIA)
- NMDAR-Ab= 1 (1,06%)
- AMPAR-Ab=1 (1,06%)
Design: Observational prospective

Objective: the frequency of neural autoantibodies in patients with epilepsy due to unknown cause and the response to immunotherapy in patients with AED-resistant seizures were evaluated.

Materials

Recruitment: Prospective

Group 1 included patients with epilepsy due to unknown etiology responding to ≤2 different AEDs associated with at least one of the following conditions: psychiatric disturbances (psychosis, delirium); movement disorders (dystonia, chorea, tremor); cognitive impairment (with subacute onset); associated autoimmune diseases (e.g., lupus, Sjogren, myasthenia gravis). Group 2 included patients with AED-resistant epilepsy defined according to the definition of the International League Against Epilepsy Commission on Therapeutic Strategies. Patients with structural/metabolic epilepsy were excluded from the study. Electroencephalography and brain magnetic resonance imaging (MRI) were performed in all patients enrolled in the study.

Number of patients included for metanalysis (Inclusion/Exclusion criteria met for our study):
N=42 with drug resistant epilepsy
Mean Age 36 +/-16.1

Control group:
Yes
N=75; healthy sex-age matched

Serum (CSF if available)
IF ICH (onconeuronals confirmed by immunoblot and surface by CBA);
GAD65 by RIA
- Onconeuronals
- NMDAR
- AMPA
- GABAb
- LGI1
- CASPR2
- GAD65

-N° of total patients with positive result=6 (14,28%)

By autoantibody type:
- GAD65=2
- LGI1=3
- NMDAR=1

Study with to different cohorts. Only second cohort included (first cohort exclusion criteria)

In methods the say about control group but any information is lacking in the rest of the article.

2+
Ekizoglu E, 2014

**Design:** Observational cross-sectional study

**Objective:** To investigate the prevalence of these autoantibodies in patients with focal epilepsy of unknown cause and in the group having mesial temporal lobe epilepsy with hippocampal sclerosis.

**Recruitment:** Prospective.

<table>
<thead>
<tr>
<th>Number of patients included for metaanalysis (Inclusion/Exclusion criteria met for our study):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum:</td>
</tr>
<tr>
<td>NMDAR-Ab (IF CBA)</td>
</tr>
<tr>
<td>LGI1-Ab (IF CBA)</td>
</tr>
<tr>
<td>CASPR2-Ab (IF CBA)</td>
</tr>
<tr>
<td>AMPAR-Ab (IF CBA)</td>
</tr>
<tr>
<td>GLY-R (IF CBA)</td>
</tr>
<tr>
<td>GAD-Ab (IPA)</td>
</tr>
</tbody>
</table>

| Nº of patients with positive result=11 (13,58%). With HS n=5 (19,23%) |
| Nº of controls with positive result=0 (0,0%) |

By autoantibody type:
- NMDAR-Ab=2 (2,46%)
- CASPR2-Ab=4 (4,93%)
- GLY-R=5 (6,17%)
**Brenner T, 2013**

**Design:** Observational cross-sectional study  
**Objective:** To determine the prevalence of autoantibodies in patients with established epilepsy and new onset epilepsy.

- Established epilepsy or new-onset epilepsy. Subjects with a history of alcohol or recreational drug abuse, suspected nonepileptic seizures, or a progressive neurologic disorder were specifically excluded.
- Appropriate Number of patients included for metanalysis (Inclusion/Exclusion criteria met for our study):
  - N=176 patients with focal epilepsy of unknown etiology. ≥ 16 years.

**Serum:**
- NMDAR-Ab (IF CBA)
- LGI1-Ab (IF CBA)
- CASPR2-Ab (IF CBA)
- GLY-R (IF CBA)
- GAD-Ab (RIA)

- N° of patients with positive result= 14 (7.95%)
- N° of controls with positive result= 0 (0.0%)

By autoantibody type:
- NMDAR-Ab= 5 (2.84%)
- GLY-R= 9 (5.02%)

-A positive LGI1 result is not included in the analysis because it does not specify whether it corresponds to the group of epilepsy of unknown etiology.

- 4 patients with positive GAD-Ab are not included because they did not specify a titre> 1000 U / ml.

- It is unknown whether they consider hippocampal sclerosis a structural etiology.

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**Falip M, 2012**

**Design:** Observational cross-sectional study  
**Objective:** To describe the prevalence of GAD-Ab in patients with temporal lobe epilepsy with/without HS and to patients with epilepsy onset beyond the age of 30 and with clinical (using seizure semiology) MRI and EEG features of TLE, whether associated or not with hippocampal sclerosis (HS). Known aetiology: 19 patients with a confirmed initial precipitating injury: nine patients had viral encephalitis or meningitis, five had personal history of febrile seizures and

- Serum (CSF if available):
  - GAD-65Ab (IF ICH and RIA)

- Number of patients with a positive result= 2 (8.7%)

By autoantibody type
- GAD-65Ab= 2 (8.7%)

- High GAD-65Ab titers considered> 1000 U / ml.

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| Study | Design: | Observational cross-sectional study  
| Liimatainen S, 2010 | Objective: | To Study the prevalence of anti-GAD in a cohort of patients with focal and generalized idiopathic epilepsy  
| | Recruitment: | Prospective 24 months.  
| | Description: | patients with epilepsy and recurrent seizures treated including patients with refractory focal epilepsy. Patients with dementia or high-grade brain tumor and epilepsy were excluded from the study. Focal epilepsy types were categorized into temporal lobe (TLE), frontal lobe (FLE), parietal lobe (PLE), occipital lobe (OLE), multifocal, or unknown focal epilepsies according to the International League Against Epilepsy (ILAE) guidelines (Commission, 1989), based on the seizure semiology, electroencephalography (EEG)/video-EEG, and etiology. IGEs were categorized into unclassified IGE, juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE), or juvenile absence epilepsy  
| | Serum: | -GAD-Ab (RIA). If positive, then confirmed by IHC/immunoblot and also determination in CSF  
| | - Nº of patients with positive result= 3 (4,1%)  
| | By autoantibody type | -GAD-Ab= 3 (4,1%)  
| | -The 3 positive patients had temporal lobe epilepsy (1 with intrathecal synthesis).  
| |  
| | characterize the clinical-immunological profile of TLE patients with high levels of GAD-ab  
| | Recruitment: | Prospective 18 months.  
| | Number of patients included for metanalysis (Inclusion/Exclusion criteria met for our study):  
| | - N=23 patients with temporal lobe epilepsy of unknown etiology >30 years. (HS not excluded)  
| | - Control group: No  
| | five had severe head trauma. Unknown aetiology: patients with no initial precipitating injury and no  
| |  
| | Liimatainen S, 2010 | Design: | Observational cross-sectional study  
| | Objective: | To Study the prevalence of anti-GAD in a cohort of patients with focal and generalized idiopathic epilepsy  
| | Recruitment: | Prospective 24 months.  
| | Description: | patients with epilepsy and recurrent seizures treated including patients with refractory focal epilepsy. Patients with dementia or high-grade brain tumor and epilepsy were excluded from the study. Focal epilepsy types were categorized into temporal lobe (TLE), frontal lobe (FLE), parietal lobe (PLE), occipital lobe (OLE), multifocal, or unknown focal epilepsies according to the International League Against Epilepsy (ILAE) guidelines (Commission, 1989), based on the seizure semiology, electroencephalography (EEG)/video-EEG, and etiology. IGEs were categorized into unclassified IGE, juvenile myoclonic epilepsy (JME), childhood absence epilepsy (CAE), or juvenile absence epilepsy  
| | Serum: | -GAD-Ab (RIA). If positive, then confirmed by IHC/immunoblot and also determination in CSF  
| | - Nº of patients with positive result= 3 (4,1%)  
| | By autoantibody type | -GAD-Ab= 3 (4,1%)  
| | -The 3 positive patients had temporal lobe epilepsy (1 with intrathecal synthesis).  
| |  

epilepsy (JAE). Etiology was defined based on the brain magnetic resonance imaging (MRI), histologic analysis in some tumors, and medical history into the following categories: hippocampal sclerosis (HS) + dual pathology (HS associated with another brain lesion), cortical dysplasia (CD) (cortical dysgenesis, heterotopia, tuberous sclerosis), other (tumor, vascular malformation, vascular lesion, trauma, other hippocampal abnormality, CNS infection, local or diffuse atrophy, specific signal change, demyelination, or non-specific gliosis) and cryptogenic. Ninety-three percent of the patients had undergone a high resolution 1.5 Tesla brain MRI with a specific epilepsy protocol. The evaluation of brain atrophy was based on an MRI examination performed on a 1.5 or 3 Tesla machine or computer tomography (CT).

Number of patients included for metanalysis (Inclusion/Exclusion criteria met for our study):
- n= 73 patients with focal epilepsy of unknown etiology ≥ 16 years. (HS patients excluded from unknown etiology group)
- Control group: N=200 non-Diabetic non epilepsy organ donors
**Supplementary Table S2:** Excluded studies and their reason.

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
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<tbody>
<tr>
<td>McGinty 2020(1)</td>
<td>Etiology of new-onset epilepsy no specified (even in supplementary material)</td>
</tr>
<tr>
<td>Zhang 2020(2)</td>
<td>Retrospective recruitment</td>
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<tr>
<td>Kuehn 2020(3)</td>
<td>Cohort of patients with suspected autoimmune epilepsy exclusively</td>
</tr>
<tr>
<td>Liu 2020(4)</td>
<td>Retrospective. Cohort of patients with suspected autoimmune encephalitis exclusively. Some patients with seizures but not epilepsy.</td>
</tr>
<tr>
<td>Bozzetti 2020(5)</td>
<td>Retrospective recruitment. Patients &lt;16 years.</td>
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<tr>
<td>Tizazu 2020 (6)</td>
<td>Retrospective. Patients with etiology different from unknown etiology included (example, 2 patients with positive results etiology were viral encephalitis and TBI)</td>
</tr>
<tr>
<td>Zelano 2019 (7)</td>
<td>ILAE criteria for epilepsy not met. Epilepsy of various etiologies included.</td>
</tr>
<tr>
<td>Nóbrega-Jr 2018 (8)</td>
<td>Hippocampal sclerosis of different etiologies included (even MS). Not possible to extract data from patients with unknown etiology</td>
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<tr>
<td>Elisak 2018 (9)</td>
<td>Patients with temporal lobe epilepsy “Irrespective of MRI findings”. Patients with all TLE aetiologies, except primary neurogliial tumours and brain metastasis were included.</td>
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<tr>
<td>Lv 2018 (10)</td>
<td>Retrospective.</td>
</tr>
<tr>
<td>Vanli-Yavuz 2016 (11)</td>
<td>Included patients with hippocampal sclerosis with classical risk factors included as febrile seizure, meningitis, birth trauma and head trauma as well as patients with cognitive disfunction.</td>
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<tr>
<td>Ceyhan-Dirican 2016 (12)</td>
<td>Included patients with drug-resistant epilepsy with hippocampal sclerosis with classical risk factors included as febrile seizure, CNS infection and birth trauma.</td>
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<tr>
<td>Lilleker 2013 (13) and 2014 (14)</td>
<td>Retrospective recruitment</td>
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<tr>
<td>Errichielo 2009 (15)</td>
<td>Patients &lt; 16 years</td>
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<tr>
<td>McKnight 2005 (16)</td>
<td>Patients with drug resistant epilepsy of various etiologies (example cortical dysplasia, neoplasia, abscess etc..)</td>
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<tr>
<td>Sokol 2004 (17)</td>
<td>GAD titles absent</td>
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<tr>
<td>Verrotti 2003 (18)</td>
<td>Patients with different etiologies included</td>
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<tr>
<td>Peltola 2000(20)</td>
<td>Different etiologies included</td>
</tr>
<tr>
<td>Dambinova 1997 (21)</td>
<td>Epilepsy and etiologies not defined</td>
</tr>
</tbody>
</table>


