

Epileptic phenotypes in autoimmune encephalitis: from acute symptomatic seizures to autoimmune-associated epilepsy

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ABSTRACT

Objective To describe the clinical and paraclinical findings, treatment options and long-term outcomes in autoimmune encephalitis (AE), with a close look to epilepsy.

Methods In this retrospective observational cohort study, we enrolled patients with new-onset seizures in the context of AE. We compared clinical and paraclinical findings in patients with and without evidence of antibodies.

Results Overall, 263 patients (138 females; median age 55 years, range 4–86) were followed up for a median time of 30 months (range 12–120). Antineuronal antibodies were detected in 63.50%.

Antibody-positive patients had multiple seizure types ($p=0.01$) and prevalent involvement of temporal regions ($p=0.02$). A higher prevalence of episodes of SE was found in the antibody-negative group ($p<0.001$). Immunotherapy was prescribed in 88.60%, and effective in 61.80%. Independent predictors of favourable outcome of the AE were early immunotherapy ($p<0.001$) and the detection of antineuronal surface antibodies ($p=0.01$).

Autoimmune-associated epilepsy was the long-term sequela in 43.73%, associated with cognitive and psychiatric disturbances in 81.73%. Independent predictors of developing epilepsy were difficult to treat seizures at onset ($p=0.04$), a high number of antiseizure medications ($p<0.001$), persisting interictal epileptiform discharges at follow-up ($p<0.001$) and poor response to immunotherapy during the acute phase ($p<0.001$).

Conclusions The recognition of seizures secondary to AE represents a rare chance for aetiology-driven seizures management. Early recognition and treatment at the pathogenic level may reduce the risk of long-term irreversible sequelae. However, the severity of seizures at onset is the major risk factor for the development of chronic epilepsy. This study provides class IV evidence for management recommendations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ There is increasing recognition of a broad spectrum of autoimmune encephalitis (AE) with acute symptomatic epileptic seizures and autoimmune-associated epilepsy, among the most challenging issues in terms of diagnosis and management.
- ⇒ Long-term data are of paramount importance for identifying predisposing factors and biomarkers that may predict the development of chronic epilepsy.

WHAT THIS STUDY ADDS

- ⇒ Autoimmune-associated epilepsy was the long-term sequela in 43.73% of this cohort of AE patients. Independent predictors of developing epilepsy were difficult to treat seizures at the onset with numerous prescribed antiseizure medications, persisting interictal epileptiform discharges at follow-up and poor response to immunotherapy during the acute phase.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

- ⇒ The severity of seizures at onset is the major risk factor for the development of chronic epilepsy in AE. This added information may be a driver for understanding the pathophysiological mechanisms of acute seizure through the identification of specific seizure biomarkers. Clinicians will be supported in their treatment decisions.

INTRODUCTION

The role of neuroinflammation is recognised in triggering or sustaining epileptic activity. A growing number of antineuronal autoantibodies have been identified in various neurological syndromes with seizures.¹ Identifying these antibodies in patients

with seizures of so far unknown aetiology has provided new insights into the relationship between autoimmunity, seizure triggering and epilepsy.^{2,3} On these bases, the latest 2017 International League Against Epilepsy (ILAE) classification of the epilepsies defined ‘epilepsy of immune aetiology’, referring to those epilepsies resulting ‘directly from an immune disorder in which seizures are a core symptom’.⁴ The ILAE Autoimmunity and Inflammation Taskforce challenged this concept and defined two main diagnostic entities: ‘acute symptomatic seizures secondary to autoimmune encephalitis’ (AE) and ‘autoimmune-associated epilepsy’, the latter of which requires the presence of an enduring predisposition to seizures.⁵ Whether ‘immune epilepsy’ is always the ‘poor’ outcome of an acute encephalitic condition and the related brain damage or may represent an enduring predisposition to seizures from its onset is still debated. Collecting more data on different epileptic phenotypes and long-term data is paramount to answering this question.

Despite the increasing evidence in this field, these conditions are still under-recognised without standardised diagnostic and management guidelines.

This study aims to assess clinical features, seizure semiology, paraclinical findings and treatment options of a large retrospective multicentric cohort of patients with seizures secondary to AE. We analysed long-term data to identify predisposing factors and biomarkers that may predict the development of chronic epilepsy.

METHODS

Study design and setting

We performed a retrospective observational cohort study over ten years (from 2010 to 2020). A nationwide study was carried

out in 34 Italian epilepsy centres of the Italian League Against Epilepsy.

The primary endpoint was the characterisation of the epileptic phenotypes. Secondary endpoints addressed treatment options and outcomes to identify potential factors predicting the development of chronic epilepsy.

We selected patients who experienced epileptic seizures at the onset or during the acute phase of AE. The diagnosis of AE was defined according to consensus criteria in adults⁶ and paediatric patients⁷ including: (1) definite antibody-positive AE and (2) probable antibody-negative AE (table 1).

Patients affected by epilepsy with other identified aetiologies (structural, genetic, infectious or metabolic causes) were excluded.

Study setup and data collection

All medical charts were reviewed. Demographic data and clinical information were collected, and for each patient, we recorded: current age, gender, family and personal history for neurological and autoimmune diseases, tumour diagnosis in the last 3 years, and previous prodromal symptoms. We also analysed the age at onset, seizure type and frequency, the occurrence of episodes of status epilepticus (SE), and frequency and quality of other associated symptoms at onset and during the follow-up. Paraclinical findings, including cerebrospinal fluid (CSF) analysis, electroencephalography (EEG) and neuroimaging characteristics at diagnosis and follow-up, were reviewed. Timing of treatment and regimens with antiseizure medications (ASMs) and immunotherapies were evaluated.

We applied the Antibody Prevalence in Epilepsy and Encephalopathy (APE2) predictive model for identifying patients in

Table 1 Inclusion criteria for definite antibody-positive and probable antibody-negative autoimmune encephalitis (AE) according with consensus criteria^{6,7}

	Definite antibody-positive AE	Probable antibody-negative AE
1. Autoantibodies detection		
▶ Detection in serum and/or CSF of well-characterised antineuronal antibodies associated with AE	Yes	No
2. Acute or subacute symptom onset		
▶ Onset and rapid progression of neurologic and/or psychiatric symptoms over less than 3 months in a previously healthy subject	Yes	Yes
3. Clinical evidence of neurologic dysfunction	≥2 features associated with seizures	≥2 features associated with seizures
▶ Altered mental status/level of consciousness		
▶ Focal neurological deficits		
▶ Cognitive impairment		
▶ Memory deficits		
▶ Language impairment		
▶ Movement disorders		
▶ Psychiatric symptoms		
▶ Sleep disorders		
▶ Dysautonomia		
▶ Hyponatraemia		
4. Paraclinical evidence of CNS inflammation	≥1 features	≥1 features
▶ CSF inflammatory changes (elevated CSF protein >50 mg/dL, lymphocytic pleocytosis >5 cell/dL and/or intrathecal synthesis of oligoclonal bands)		
▶ MRI abnormalities suggestive of AE (T2/FLAIR hyperintensities restricted to one or both mesial temporal lobes, or multifocal in grey matter, white matter or both)		
▶ Brain biopsy showing inflammatory infiltrates and excluding other disorders		
5. Reasonable exclusion of alternative causes, including other causes of CNS inflammation	Yes	Yes
CSF: cerebrospinal fluid; CNS: central nervous system; FLAIR: fluid-attenuated inversion recovery.		

whom antineuronal antibody profiles may be negative, estimating the likelihood of an autoimmune aetiology.^{8–10} The APE2 score of the entire cohort was assigned blindly by two authors (SM and TG) to further reduce selection bias. The Response to Immunotherapy in Epilepsy and Encephalopathy [RITE2] scores were assessed among patients who received immunotherapy.

All paired serum and CSF samples were analysed for antineuronal antibodies either with commercial kits (Euroimmun, Germany), or with in-house assays. In detail, commercial fixed cell-based assays (CBAs) were used for the detection of antibodies to leucine-rich glioma-inactivated protein1 (LGI1), N-methyl-D-aspartate receptor (NMDAR), contactin-associated protein 2 (Caspr2), gamma-aminobutyric acid type B receptor (GABA_BR), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA1/2) and commercial fixed tissue-based assays (TBAs) and immunoblots for antibodies to intracellular neuronal antigens (Hu, Yo, Ri, Ma1/2, glutamic acid decarboxylase 65 (GAD65), amphiphysin, etc), whereas, in a few specialised laboratories, live CBAs and TBAs were used for antibodies to neuronal cell-surface antigens, including gamma-aminobutyric acid type A receptor (GABA_AR) and glycine receptor (GlyR).¹¹

Neurological functioning was assessed during the acute phase and at the last available follow-up with the modified Rankin Scale (mRS) for children and adults.¹²

Response to treatment with ASMs and immunotherapy was defined as seizure freedom, significant seizure reduction (>50%), or unchanged seizure frequency. In particular, seizure freedom was defined as no clinical evidence of seizures, neither observed nor reported; at follow-up, seizures have to be absent for at least 6 months. Otherwise, drug-resistant seizures were defined as failure to achieve seizure freedom, despite treatment with two tolerated, adequately dosed ASMs.

The overall clinical improvement was defined as the resolution of associated symptoms or persisting impairment in neurological functioning.

Relapses of AE were defined clinically as recurrence or clear worsening of encephalitis symptoms after 3 months of complete remission or plateauing from prior symptoms, associated to worsening of ancillary testing findings. The clinical and paraclinical findings of relapses were reviewed to assess signs and symptoms at the time of relapse and to evaluate whether these included seizures.

Chronic epilepsy was diagnosed when seizures persisted beyond the timeframe that can be considered the active phase of the AE or the presence of an enduring predisposition to seizures at the long-term follow-up (eg, previous breakthrough seizures when weaning ASMs or interictal epileptiform discharges, IEDs).^{13 14} For each enrolled patient, the diagnosis of chronic epilepsy and the time definition of the acute phase of AE were determined by consensus according to a combination of clinical evidence of active encephalitis and laboratory findings.

Statistics

Descriptive statistics were expressed as proportions and percentages for categorical variables and medians and ranges for continuous variables.

Univariate analyses for categorical variables were performed applying χ^2 and Fisher's exact test, while the assessment of normal distribution of independent variables was performed by independent t-test, and non-normal data were analysed using Mann-Whitney U test.

A multivariate regression model was used to compare variables significant by univariate analyses to identify independent predictors of outcome.

A $p \leq 0.05$ was considered statistically significant.

Data were analysed using STATA/IC V.15.

RESULTS

Demographics

During the 10-year study period, 306 cases were identified based on selection criteria. Forty-three patients were subsequently excluded due to missing data. Overall, we enrolled 263 patients with a current median age of 55 years (IQR 28–70; range 4–86), 138 (52.47%) were female. The median age at onset was 48 years (IQR 20–65; range 2–82). At disease onset, 60 patients (22.81%) were in paediatric age (<18 years old: median age at onset 9 years; IQR 5.5–14; range 1–17).

The median follow-up duration for the entire cohort was 30 months (IQR 20–50; range 12–120).

Antibody evaluation

Antineuronal antibodies were identified in 167 patients (63.50%), of which 133 (79.65%) had antibodies targeting neuronal cell-surface antigens: LGI1 (n=64), NMDAR (n=48), Caspr2 (n=14), GABA_AR (n=3), GABA_BR (n=3), GlyR (n=1). Antibody against intracellular antigens were detected in 34 patients (20.35%) including anti-GAD65 (n=18), and other onconeural antibodies (n=4 anti-Hu, n=6 anti-Ma2, n=2 anti-Yo, n=1 anti-amphiphysin, n=3 anti-cerebellum).

Among the remaining cases, no antineuronal antibodies were identified (n=96, 36.50%), but these patients met the inclusion criteria for probable antibody-negative AE, and other causes of epilepsy were ruled out.

The median APE2 score of the whole cohort was 6 (IQR 5–8; range 3–15), and the percentages of the APE2 score cut-off ≥ 4 did not significantly differ between antibody-positive and antibody-negative patients (95.21% vs 89.58%), while their respective medians differed significantly ($p=0.0002$). Online supplemental table S1 summarises the comparison of clinical and paraclinical data between antibody-positive and antibody-negative patients.

Clinical features

According to the ILAE 2017 operational classification of seizure types,¹³ we recorded during the acute phase: generalised (n=15, 5.70%), focal motor (n=114, 43.35%), focal non-motor (n=107, 40.68%), focal to bilateral (n=72, 27.38%) and faciobrachial dystonic seizures (FBDS) (n=34, 12.93%). No significant differences were detected in the seizure type at onset between antibody-positive and antibody-negative patients (in online supplemental table S1), except for FBDS, which are strictly related to LGI1 encephalitis ($p<0.001$). Overall, multiple seizure types were detected in 43 patients (16.35%), with a significant prevalence in antibody-positive patients ($p=0.01$); but this difference was no longer detectable when applying a multivariate model.

Seizure semiology showed a significant prevalence of bitemporal seizures in antibody-positive patients ($p=0.02$), and extratemporal ones in antibody-negative patients ($p=0.007$). However, these differences did not maintain statistical significance at the multivariate analysis. Figure 1 summarises seizure types (figure 1A) and semiology (figure 1B) of the entire cohort according to antibody findings.

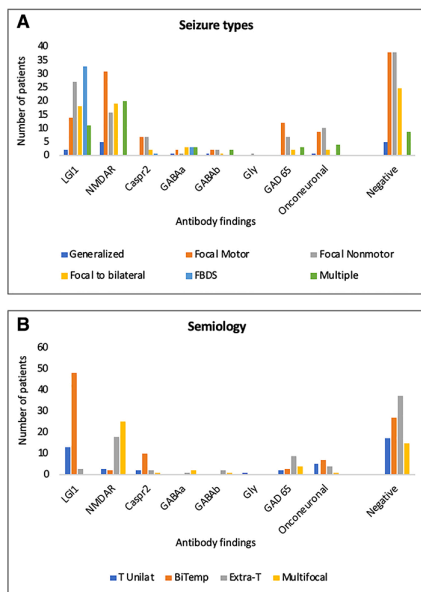


Figure 1 Seizure types (A) and semiology (B) according to the antibody findings. NMDAR, N-methyl-D-aspartate receptor; LGI1, leucine-rich glioma inactivated-1; Caspr2, Contactin-associated protein-2 receptor; GABA_A, gamma-aminobutyric acid type A; GABA_B, gamma-aminobutyric acid type B; Gly, glycine receptor; GAD65, glutamic acid decarboxylase 65; FBDS, facio-brachial dystonic seizures; T Unilat, temporal unilateral; BiTemp, temporal bilateral; Extra-T, extra-temporal.

Most patients presented a stormy seizure onset, with daily ($n=176$, 66.92%) or weekly ($n=39$, 14.83%) frequency.

During the acute phase, 143 patients (87.73%) presented drug-resistant seizures to most common ASMs, without any significant prevalence between antibody-positive and antibody-negative patients.

Overall, 107 patients (40.68%) had at least one episode of SE at disease onset, which was refractory in most ($n=79$, 73.83%). A higher prevalence of SE was found in antibody-negative patients ($p<0.001$), and this significant difference was confirmed by the multivariate regression analysis (OR 0.23, 95% CI 0.12 to 0.45; $p<0.001$).

The acute phase of the disease was also marked by a constellation of symptoms of brain dysfunction ($n=245$, 93%). In most antibody-positive patients, the clinical presentation was correlated with full-blown encephalitis, and multiple symptoms were prominent in this group ($p<0.001$) (online supplemental table S1).

The assessment of the neurological status revealed a significant difference in the mRS scores between antibody-positive and antibody-negative patients ($p<0.02$), not confirmed by the multivariate analysis (online supplemental table S1).

Paraclinical findings

All the enrolled patients underwent CSF analysis, which revealed alteration consistent with inflammation in 144 patients (54.7%), without any significant difference between antibody-positive and antibody-negative patients. At seizure onset and during the acute phase of the disease, the most prominent interictal EEG findings were diffuse ($n=51$, 19.39%) or focal slowing ($n=190$, 72.24%). Focal or multifocal IEDs were observed with a prevalence of bitemporal involvement mainly in antibody-positive patients ($p=0.002$) and extratemporal prevalence in antibody-negative ones ($p=0.02$) (online supplemental table S1). However, these

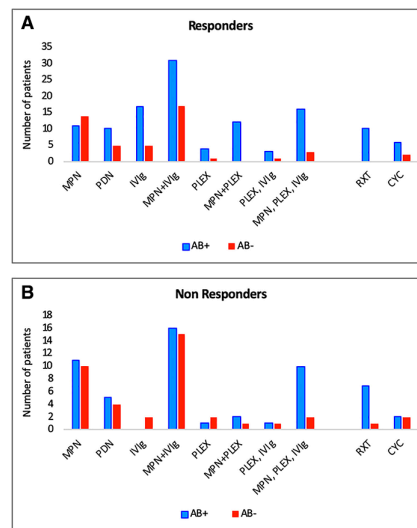


Figure 2 Immunotherapy in responders (A) and non-responders (B) according to the antibody findings. MPN, methylprednisolone; PDN, prednisone; IVIg, intravenous immunoglobulins; PLEX, plasma exchange; RTX, rituximab; CYC, cyclophosphamide; AB+, antibody positive; AB-, antibody negative.

differences did not maintain statistical significance at the multivariate analysis.

Brain MRI findings during the acute phase were unrevealing in a subset of patients ($n=71$, 27%), while T2/FLAIR hyperintensities consistent with inflammation were detected in most ($n=192$, 73%). There were no significant differences in the presence or prevalent localisation of neuroimaging abnormalities in the antibody-positive and antibody-negative groups.

Treatment response

Overall, 233 patients (88.60%) received immunotherapy combined with ASMs. Patients were treated after a median delay from onset of 3 months (IQR 1–7; range 0.5–84), and most ($n=143$, 61.37%) received an early treatment (within 3 months). All patients received first-line treatment, while second-line treatment was administered in 28 patients (12%), most often with antibody-positive findings ($p=0.02$) (online supplemental table S1). Only five antibody-negative patients received second-line treatments. Figure 2 summarises first-line and second-line treatments according to antibody findings and responses.

In patients receiving immunotherapy, the median RITE2 score was 10 (IQR 8–12; range 3–16), with significant differences between antibody-positive and antibody-negative patients in their respective medians ($p=0.005$) and the percentages of the RITE2 score cut-off ≥ 7 ($p=0.03$).

Among the 233 patients who received immunotherapy, 144 (61.80%) were considered responders. Online supplemental table S2 summarises the comparison between responder and non-responder patients of all disease-related factors.

Neither seizure type, semiology, frequency, paraclinical findings at disease onset, nor first-line or second-line treatment regimens predicted the likelihood of response. More severely compromised patients at the onset, with difficult to treat seizures resulted to have a less favourable outcome ($p<0.001$), and the prevalence of drug-resistant seizures at onset in non-responders was confirmed at multivariate analysis (OR 0.39, 95% CI 0.20 to 0.76; $p=0.006$). Otherwise, independent predictors of a favourable response to immunotherapy were the detection of

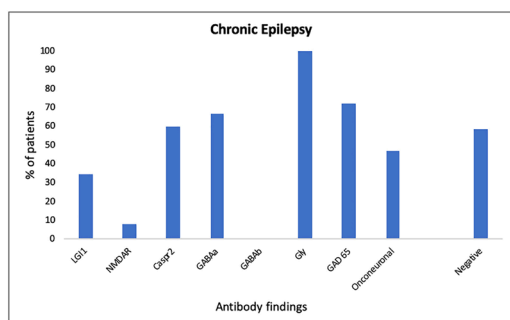


Figure 3 Proportion of patients developing chronic epilepsy at the end of the follow-up according to antibody findings. NMDAR, N-methyl-D-aspartate receptor; LGI1, leucine-rich glioma inactivated-1; Caspr2, contactin-associated protein-2 receptor; GABA_A, gamma-aminobutyric acid type A; GABA_B, gamma-aminobutyric acid type B; Gly, glycine receptor; GAD65, glutamic acid decarboxylase 65.

antineuronal surface antibodies (OR 2.38; 95% CI 1.15 to 4.92; $p=0.01$) and early initiation of immunotherapy (OR 12.08, 95% CI 5.50 to 26.50; $p<0.001$).

All patients but 7 (97.33%) were treated with one or more ASMs, with a median number of 2 (IQR 2–3; range 1–12). At the onset, the overall prevalence of drug-resistant seizures was 54.37% ($n=143$), and the most commonly ASMs prescribed are reported in online supplemental figure S1.

Thirty patients (11.40%) received ASMs only. The clinical presentation was less severe in these patients, and 12 patients were initially responders. Seven of them resulted positive for specific autoantibodies: 1 NMDAR, 1 GABA_B, 2 LGI1 and three onconeural antibodies, but four had disease relapse after the initial favourable response, hence immunotherapy has been prescribed. These patients initially presented with ‘forms frustes’ of AE, and the disease course was more protracted with transitory improvement and seizure control with ASMs only. In the four patients with disease relapse, the diagnosis of AE was delayed and made afterward at that time, while in the remaining, the antibody search was performed during an oncological work-up.

Outcomes

Encephalitis relapses with seizures were reported in 22 patients (8.37%) during the observational period, without a significant difference in antibody-positive and antibody-negative patients. Thirteen patients (59%) regained seizure freedom after a second trial of immunotherapy.

At the end of follow-up, enduring seizures after the acute phase of the disease were detected in 115 patients (43.73%), with a higher prevalence in antibody-negative patients (35.33% vs 58.33%; $p<0.001$). Figure 3 summarises the proportion of patients developing chronic epilepsy at the end of the follow-up according to antibody findings.

Analysing the subgroup of antibody-negative patients only, an enduring predisposition to seizures was present in those with more difficult to treat seizures (67.86% vs 30%; $p<0.001$), a higher number of ASMs prescribed during the acute phase ($p<0.001$), longer delay to immunotherapy initiation ($p=0.008$), and delayed immunotherapy after 3 months from disease onset (50% vs 85.71%; $p=0.001$).

Ninety-four patients (81.73%) also had associated symptoms, including cognitive deficits and psychiatric disorders.

No differences in mRS scores were found between antibody-positive and antibody-negative patients, while higher scores

were detected in patients with poor response to immunotherapy ($p=0.006$) (online supplemental table S2).

One hundred and two patients (38.78%) had persisting IEDs at follow-up, without a significant prevalence in antibody-positive and antibody-negative patients, while they were prevalent in patients with poor response to immunotherapy during the acute phase (20.83% vs 69.66%; $p<0.0001$) (online supplemental materials).

Fifty-five patients (20.91%) developed brain atrophy with a prevalent temporal involvement (unilateral: 5.32%, and bilateral: 9.13%). These neuroimaging findings were not significantly associated with an enduring predisposition to seizures (table 2), as well as to antibody detection, and response to immunotherapy during the acute phase (details in online supplemental materials).

Disease-related factors associated with persisting seizures were: younger age at disease onset ($p=0.03$), the detection of antibodies to intracellular antigens (18.26% vs 8.78%; $p=0.01$), at least one episode of SE during the acute phase of the disease (49.57% vs 33.78%; $p=0.007$), drug-resistant seizures at onset (67.83% vs 43.92%; $p<0.001$), the median number of ASMs prescribed during the acute phase ($p<0.001$), longer delay to immunotherapy initiation ($p<0.001$), initiation of immunotherapy after 3 months from disease onset (41.00% vs 76.69%; $p<0.001$), poor response to immunotherapy during the acute phase (74% vs 11.28%; $p=0.001$), and persisting IEDs at follow-up (65.22% vs 18.24%; $p<0.0001$). Table 2 summarises the comparison between patients developing epilepsy and those who became seizure-free (see also online supplemental table S3). When performing the multivariate regression analysis, independent predictors for the development of chronic epilepsy were drug-resistant seizures at onset (OR 0.32, 95% CI 0.11 to 0.95; $p=0.04$), with a higher number of ASMs prescribed (OR 2.30, 95% CI 1.55 to 3.43; $p<0.001$), persisting IEDs at follow-up (OR 4.23, 95% CI 1.78 to 10.06; $p<0.001$) and poor response to immunotherapy during the acute phase (OR 0.04, 95% CI 0.02 to 0.11; $p<0.001$).

Other sequelae such as cognitive deficits and psychiatric symptoms were detected in further 87 patients (33.07%) who did not have enduring seizures after the recovery from the acute phase. No independent predictors were detected to be significantly associated with this poor outcome.

DISCUSSION

The increasing recognition of a broad spectrum of AE with epileptic seizures has raised interest among researchers, opening a new field with challenging issues in diagnosis and management of acute symptomatic seizures secondary to AE and in the recognition of a more chronic condition characterised by an enduring predisposition to seizures, as autoimmune-associated epilepsy. In this regard, chronic epilepsy was diagnosed when seizures continue beyond a timeframe that can be considered the active phase of the disease. The time definition of the acute phase of AE is still lacking in literature due to the wide spectrum in clinical presentation, which may vary depending on the associated antibody and timing of immunotherapy. In this regard, for each patient, the determination of the active disease may stem from a combination of clinical evidence and paraclinical findings.⁵ Although antineuronal antibodies may be responsible for a small proportion of acute seizures, identifying such cases is paramount because many patients may benefit from disease-modifying immunotherapy.

Epileptic seizures in AE may present in patients at any age. These patients most often present with new-onset seizures

Table 2 Comparison between patients developing chronic epilepsy and those who were seizure free at last follow-up

Variables	Chronic epilepsy (n=115, 43.73%)	Seizure free (n=148, 56.27%)	P value
Median age at onset	44 years (IQR: 18–61; range: 2–84)	54.5 years (IQR: 20.5–68; range: 2–82)	0.03*
Antibody findings			
▶ Antibody positive, N (%)	59 (51.30%)	108 (72.97%)	<0.001†
▶ Antibodies to surface antigens, N (%)	38 (33.04%)	95 (64.19%)	<0.001†
▶ Antibodies to intracellular antigens, N (%)	21 (18.26%)	13 (8.78%)	0.01†
Status epilepticus, N (%)	57 (49.57%)	50 (33.78%)	0.007†
Associated symptoms at onset, N (%)	102 (88.70%)	143 (96.62%)	0.01†
Median number of associated symptoms	2 (IQR: 1–3; range: 0–6)	3 (IQR: 1.5–4; range: 0–8)	0.01*
Difficult to treat seizures at onset, N (%)	78 (67.83%)	65 (43.92%)	<0.001†‡
Median of ASMs during the acute phase	3 (IQR: 2–4; range 1–12)	2 (IQR: 1–3; range 0–5)	<0.001†‡
Immunotherapy			
▶ Early immunotherapy (<3 months), N (%)	41 (41.00%)	102 (76.69%)	<0.001†‡
▶ Median time from disease onset to immunotherapy	4 months (IQR 2–9; range 0.5–90)	2 months (IQR: 1–3; range 0.5–84)	<0.001†
Follow-up of the entire cohort: 30 months (IQR 20–50; 12–120)			
Median follow-up	36 months (IQR: 23–72; range 12–120)	24 months (IQR: 18–36.5; range 12–96)	<0.001*
mRS at the last available FU	2 (IQR: 2–3; range 1–3)	2 (IQR: 0–2; range 0–3)	<0.001*
Persisting IEDs at FU	75 (65.22%)	27 (18.24%)	<0.0001†‡
Brain MRI Atrophy at FU, N (%)	29 (25.22%)	26 (17.57%)	0.08†
Relapses, N (%)	9 (7.83%)	13 (8.78%)	0.48†
Non Responder to Immunotherapy, N (%)	74 (74%)	15 (11.28%)	<0.001†‡

*Mann-Whitney U-test.

† χ^2 of Fisher's exact test.

‡Independent predictors at the multivariate regression analysis.

.IEDs, interictal epileptiform discharges.

drug-resistant to common ASMs, along with subacute progressive cognitive decline and psychiatric dysfunctions.^{3 15–17}

Although there is substantial overlap among different AE in terms of clinical presentation and paraclinical findings, some clinical features and different biomarkers may suggest a specific antigen, response to treatment and long-term prognosis for seizures and cognitive/psychiatric disturbances.^{2 18}

Our multicentre study, based on a large series with long-term data, allows a significant comparison of clinical features, response to ASMs and immunotherapy, and evolution to chronic epilepsy in different groups of patients.

We found a predominant involvement of the limbic regions in patients harbouring antineuronal antibodies and an extra-temporal prevalence in antibody-negative patients, probably due to a high proportion of limbic encephalitis, mostly LGI1 antibody-related, in our cohort. In this regard, the temporal lobe involvement in seizure activity does not represent an independent predictor of antibody detection. Epileptic seizures occur as one of the key symptoms in a broad clinical spectrum of brain dysfunction. No specific seizure semiology was related to antibody positivity, except for FBDS.

Our study underscores the importance of clinical features that increase suspicion for an autoimmune aetiology, such as stormy onset, SE in a previous healthy subject, multiple seizure types and a high prevalence of drug-resistance. The higher prevalence of episodes of SE in antibody-negative patients, which also usually leads to a less favourable prognosis, could reflect the underlying pathogenetic mechanisms related to inflammation per se.^{19 20} However, antibody-negative findings should prompt further investigations since the prevalent rate of SE in the antibody-negative subgroup could reflect an antibody-related mechanism so far undiscovered.

Our study emphasises the importance of early diagnosis and prompt immunotherapy, with disease-modifying treatments, the only way to limit the extent of the brain damage and neurological disability.^{8 15 21}

Although increasing expert opinions and recommendations are available, there are no current guidelines for choosing a specific medication, length of treatment or timing for switching to second-line treatment.^{22 23} The initiation of immunotherapy remains a challenging concern for clinicians in cases of drug-resistant seizures due to AE, particularly for those cases in which the antibody search is negative.^{8 15 21} In this subgroup, the prescription of second-line treatments is still scanty due to limited evidence-based medicine data in these cases and legislative limitations.

Early immunotherapy has been proven to be a pivotal independent predictor of response and outcome in our cohort. Another independent predictor of response to immunotherapy and a favourable outcome is the detection of antineuronal surface antibodies, as already pointed out in the literature.^{15 24}

Previous reports have demonstrated that the response to immunotherapy may vary depending on the type of antibody that reflects the different forms of central nervous system inflammation.^{3 15 25}

Epileptic seizures occurring in AE are typically refractory to conventional ASMs in most patients. However, ASMs could effectively control seizures in selected cases.²⁶ Some studies have suggested the potential effects on humoral immune responses of some ASMs.^{27 28}

A long-lasting prescription of ASMs does not appear to be necessary for most patients, and discontinuation should be considered after a period of clinical stability.²⁹

Some authors have argued against the definition of 'autoimmune epilepsy',^{3 5 18 30} referring to epilepsy with an autoimmune origin during the acute phase of the encephalitis,^{4 13} reserving it to those patients who develop an enduring predisposition to seizures after the encephalitis has been resolved.

In our series, 43.73% of patients had chronic epilepsy at long-term follow-up, varying according to antibody type (figure 3), associated with other neuropsychological and psychiatric sequelae in 81.73% of them. Younger age at disease onset, the detection of intracellular antibodies, and delay in immunotherapy may be risk factors for persisting seizures after the acute phase. Moreover, a more severely compromised neurological status at the onset, with drug-resistant seizures, episodes of refractory SE and multiple comorbidities, may predict this worst outcome. In this regard, difficult to treat seizures at onset, with a high number of ASMs prescribed, persisting IEDs at follow-up, and a poor response to immunotherapy during the acute phase, are independent predictive factors of seizure outcome.

Geis *et al* suggested that persisting seizures for more than 1 year in patients with AE should lead to the diagnosis of chronic epilepsy.³ On the other hand, Rada *et al* showed that it can take up to 7 years before continuously recurrent seizures secondary to an AE subside.³¹ Recent studies have evaluated seizure outcomes in patients with AE associated with antibodies to the neuronal cell surface and intracellular antigens,^{14 30–34} in which the definition of seizure outcome was variable. We adopted the definition of 'autoimmune-associated epilepsy'⁵ to refer to those patients with seizures that persist after the resolution of the acute phase of the AE, according to a combination of clinical and paraclinical findings. In previous studies, the reported risk factors for epilepsy included younger age at disease onset and female gender,¹⁴ immunotherapy delay, and the presence of IEDs on EEG.³³ According to Smith *et al*,¹⁴ in our series, the delay in the initiation of immunotherapy was not an independent predictor for the development of epilepsy. In this regard, patients with autoimmune-associated epilepsy tend to have a poor response to immunotherapy, while early immunotherapy has been shown to be effective for acute symptomatic seizures secondary to AE, particularly in cases with antibodies to cell-surface antigens.

Chronic epilepsy may result from an ongoing inflammatory process that persists after the acute phase, or as sequelae due to irreversible changes altering the neuronal networks and persisting after the inflammatory process resolves, or a combination of both.⁵ The exact mechanism has not been elucidated, but the intrinsic severity of the disease may be a possible explanation.

Unexpectedly, the presence of brain atrophy at follow-up was not an independent predictor for epilepsy, according to some previous observations.^{14 33} Indeed, not all patients developing chronic epilepsy have MRI or histopathological evidence of brain atrophy, and structural changes may be microscopic and not always detectable on neuroimaging.⁵

The detection of predictive factors of seizure outcome may be beneficial to develop alternative interventions to prevent the development of autoimmune-associated epilepsy and determine the best comprehensive management of seizures during the acute phase and at the long-term.

The limitations of our study are related to its retrospective design. Some patients with seizures due to AE could have been missed, and the number of cases is likely to be underestimated, mostly of those who do not have full-blown encephalitis. Furthermore, the heterogeneity of clinical syndrome and assessment makes comparison and correlation difficult. Patients were not treated per protocol and received different immunotherapy

regimens and a variety of ASMs schedules, thus making the comparison more challenging.

Early diagnosis and timely treatment of seizures of autoimmune aetiology are paramount and significantly associated with a better overall clinical outcome.^{9 15–17 21}

Future prospective studies are warranted to determine the ideal immunomodulatory treatment regimen for patients based on clinical presentation and antibody-specificity.

Clinicians should maintain a high level of suspicion in the evaluation of patients with new-onset seizures since AE could be associated with other symptoms of brain dysfunction and, in such cases, could remain under-recognised. Antibody-negative patients and cases in whom seizures may be associated with only subtle signs of encephalitis represent important but challenging clinical groups.

This study provides class IV evidence for management recommendations.

Although AE is still considered a rare cause of epilepsy, the real impact of this aetiology is still to be clarified, considering the high prevalence of autoantibodies in epileptic populations.⁸ The appropriate management and early treatment with disease-modifying treatments may reduce the risk of irreversible long-term sequelae, including epilepsy.

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REFERENCES

- Toledano M, Pittock SJ. Autoimmune epilepsy. *Semin Neurol* 2015;35:245–58.
- Bien CG, Holtkamp M. "Autoimmune Epilepsy": Encephalitis with autoantibodies for Epileptologists. *Epilepsy Curr* 2017;17:134–41.
- Geis C, Planagumà J, Carreño M, et al. Autoimmune seizures and epilepsy. *J Clin Invest* 2019;129:926–40.
- Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for classification and terminology. *Epilepsia* 2017;58:512–21.
- Steriade C, Britton J, Dale RC, et al. Acute symptomatic seizures secondary to autoimmune encephalitis and autoimmune-associated epilepsy: conceptual definitions. *Epilepsia* 2020;61:1341–51.
- Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391–404.
- Cellucci T, Van Mater H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurol Neuroimmunol Neuroinflamm* 2020;7:e663.
- Dubey D, Alqallaf A, Hays R, et al. Neurological autoantibody prevalence in epilepsy of unknown etiology. *JAMA Neurol* 2017;74:397–402.
- Dubey D, Singh J, Britton JW, et al. Predictive models in the diagnosis and treatment of autoimmune epilepsy. *Epilepsia* 2017;58:1181–9.
- Dubey D, Pittock SJ, McKeon A. Antibody prevalence in epilepsy and encephalopathy score: increased specificity and applicability. *Epilepsia* 2019;60:367–9.
- Graus F, Vogrig A, Muñoz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. *Neurol Neuroimmunol Neuroinflamm* 2021;8:e1014.
- Bigi S, Fischer U, Wehrli E, et al. Acute ischemic stroke in children versus young adults. *Ann Neurol* 2011;70:245–54.
- Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League against epilepsy: position paper of the ILAE Commission for classification and terminology. *Epilepsia* 2017;58:522–30.
- Smith KM, Dubey D, Liebo GB, et al. Clinical course and features of seizures associated with LGI1-antibody encephalitis. *Neurology* 2021;97:e1141–9.
- Titulaer MJ, McCracken L, Gabilondo I, et al. 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.
- Thompson J, Bi M, Murchison AG, et al. The importance of early immunotherapy in patients with Faciobrachial dystonic seizures. *Brain* 2018;141:348–56.
- Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann Neurol* 2018;83:166–77.
- Spatola M, Dalmau J. Seizures and risk of epilepsy in autoimmune and other inflammatory encephalitis. *Curr Opin Neurol* 2017;30:345–53.
- Gaspard N, Hirsch LJ, Sculier C, et al. New-Onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (fires): state of the art and perspectives. *Epilepsia* 2018;59:745–52.
- Lattanzi S, Leiting M, Rocchi C, et al. Unraveling the enigma of new-onset refractory status epilepticus: a systematic review of aetiologies. *Eur J Neurol* 2022;29:626–47.
- Toledano M, Britton JW, McKeon A, et al. Utility of an immunotherapy trial in evaluating patients with presumed autoimmune epilepsy. *Neurology* 2014;82:1578–86.
- Abboud H, Probasco JC, Irani S, et al. Autoimmune encephalitis: proposed best practice recommendations for diagnosis and acute management. *J Neurol Neurosurg Psychiatry* 2021;92:757–68.
- Abboud H, Probasco J, Irani SR, et al. Autoimmune encephalitis: proposed recommendations for symptomatic and long-term management. *J Neurol Neurosurg Psychiatry* 2021;92:897–907.
- Bozzetti S, Rossini F, Ferrari S, et al. Epileptic seizures of suspected autoimmune origin: a multicentre retrospective study. *J Neurol Neurosurg Psychiatry* 2020;91:1145–53.
- Dalmau J, Graus F. Antibody-Mediated encephalitis. *N Engl J Med* 2018;378:840–51.
- Feyissa AM, López Chiriboga AS, Britton JW. Antiepileptic drug therapy in patients with autoimmune epilepsy. *Neurol Neuroimmunol Neuroinflamm* 2017;4:e353.
- Beghi E, Shorvon S. Antiepileptic drugs and the immune system. *Epilepsia* 2011;52 Suppl 3:40–4.
- Gómez CD, Buijs RM, Sitges M. The anti-seizure drugs vinpocetine and carbamazepine, but not valproic acid, reduce inflammatory IL-1 β and TNF- α expression in rat hippocampus. *J Neurochem* 2014;130:770–9.
- Britton JW, Dalmau J. Recognizing autoimmune encephalitis as a cause of seizures: treating cause and not effect. *Neurology* 2019;92:877–8.
- de Bruijn MAAM, van Sonderen A, van Coevorden-Hameete MH, et al. Evaluation of seizure treatment in anti-LGI1, anti-NMDAR, and anti-GABA $_B$ R encephalitis. *Neurology* 2019;92:e2185–96.
- Rada A, Birnbacher R, Gobbi C, et al. Seizures associated with antibodies against cell surface antigens are acute symptomatic and not indicative of epilepsy: insights from long-term data. *J Neurol* 2021;268:1059–69.
- Zhang W, Wang X, Shao N, et al. Seizure characteristics, treatment, and outcome in autoimmune synaptic encephalitis: a long-term study. *Epilepsy Behav* 2019;94:198–203.
- Shen C-H, Fang G-L, Yang F, et al. Seizures and risk of epilepsy in anti-NMDAR, anti-LGI1, and anti-GABA $_B$ R encephalitis. *Ann Clin Transl Neurol* 2020;7:1392–9.
- Yao L, Yue W, Xunyi W, et al. Clinical features and long-term outcomes of seizures associated with autoimmune encephalitis: a follow-up study in East China. *J Clin Neurosci* 2019;68:73–9.

Table S1: Comparison between antibody-positive and antibody-negative patients

VARIABLES	Antibody-positive (n=167, 63.50%)	Antibody-negative (n=96, 36.50%)	p-value
Median age at onset	53 years (IQR: 26-67; range: 4-84)	41 years (IQR: 15.5-62; range: 2-82)	0.05 ^a
Female, N (%)	93 (55.69%)	45 (46.88%)	0.10 ^b
Pediatric patients (age < 18years), N (%)	32 (19.16%)	28 (29.17%)	0.04 ^b
mRS during acute phase	4 (IQR 3-4, range 1-5)	4 (IQR 3-4, range 1-5)	0.02^a
APE2 score	7 (IQR 5-9, range 2-13)	6 (IQR 4-7, range 3-12)	0.0002^a
APE2 score $\geq$ 4, N (%)	159 (95.21%)	86 (89.58%)	0.07
RITE2 score	10 (IQR 8-13, range 4-17)	8 (IQR 5-9, range 3-14)	<0.001^a
RITE2 score $\geq$ 7, N(%)	149 (89.22%)	58 (60.42%)	<0.001^a
Seizure type			
•Generalized Onset, N (%)	10 (5.99%)	5 (5.21%)	0.51 ^b
•Focal motor onset, N (%)	76 (45.51%)	38 (39.58%)	0.21 ^b
•Focal non-motor onset, N (%)	69 (41.32%)	38 (39.58%)	0.44 ^b
•Focal to bilateral, N (%)	47 (28.14%)	25 (26.04%)	0.41 ^b
•FBDS, N (%)	34 (20.36%)	0 (0%)	< 0.001^b
•Multiple seizure type, N (%)	34 (20.36%)	9 (9.38%)	0.01^b
Seizure semiology			
•Multifocal, N (%)	34 (20.36%)	15 (5.62%)	0.21 ^b
•Temporal Unilateral, N (%)	26 (15.57%)	17 (17.71%)	0.38 ^b
•Bitemporal, N (%)	68 (40.72%)	27 (28.12%)	0.02^b
•Extra-Temporal, N (%)	39 (23.35%)	37 (38.54%)	0.007^b
Status epilepticus, N (%)	49 (9.34%)	58 (60.42%)	< 0.001^b
•CSE, N (%)	35 (20.96%)	41 (42.71%)	< 0.001^b
•NCSE, N (%)	13 (7.78%)	14 (14.58%)	0.06 ^b
•EPC, N (%)	2 (1.20%)	8 (8.33%)	0.006^b
Associated symptoms at onset, N (%)	162 (97.1%)	83 (86.46%)	0.002^b
Median number of associated symptoms	3 (IQR: 2-4; range: 0-8)	2 (IQR: 1-3; range: 0-6)	< 0.001^a
•Severe disability, N (%)	36 (21.56%)	20 (20.83%)	0.51 ^b

•Cognitive impairment, N (%)	72 (43.11%)	20 (20.83%)	< 0.001 ^b
•Memory deficits, N (%)	75 (44.91%)	35 (36.46%)	0.11
•Language impairment, N (%)	39 (23.35%)	14 (14.58%)	0.06
•Movement disorders, N (%)	54 (32.34%)	18 (18.75%)	0.01 ^b
•Behavioral symptoms, N (%)	112 (67.07%)	41 (42.71%)	<0.001 ^b
•Mood disorders, N (%)	28 (16.77%)	12 (12.50%)	0.22
•Sleep disorders, N (%)	52 (31.14%)	7 (7.29%)	<0.001 ^b
•Loss of consciousness, N (%)	11 (6.59%)	8 (8.33%)	0.38
•Dysautonomia, N (%)	24 (14.37%)	5 (5.21%)	0.02 ^b
•Hyponatremia, N (%)	17 (10.18%)	3 (3.12%)	0.03 ^b
Interictal EEG findings			
•Multifocal IEDs, N (%)	21 (12.57%)	13 (13.54%)	0.48 ^b
•Diffuse IEDs, N (%)	6 (3.59%)	4 (4.17%)	0.52 ^b
•Temporal unilateral IEDs, N (%)	28 (16.77%)	25 (26.04%)	0.05 ^b
•Bitemporal IEDs, N (%)	65 (38.92%)	20 (20.83%)	0.002 ^b
•Extra-temporal IEDs, N (%)	38 (22.75%)	34 (35.42%)	0.02 ^b
Brain MRI findings[^]			
•Normal, N (%)	44 (26.35%)	27 (28.12%)	0.43 ^b
•Temporal unilateral, N (%)	29 (17.37%)	17 (17.71%)	0.53 ^b
•Temporal bilateral, N (%)	47 (28.14%)	25 (26.04%)	0.41 ^b
•Extratemporal, N (%)	10 (5.99%)	5 (5.21%)	0.51 ^b
•Multifocal in GW and WM, N (%)	20 (11.98%)	18 (18.75%)	0.09 ^b
Drug-resistance to ASMs, N (%)	93 (55.69%)	50 (52.08%)	0.33 ^b
Median of ASMs	2 (IQR: 2-3; range 0-8)	2 (IQR: 2-4; range 0-13)	0.14 ^a
Immunotherapy, N (%)	150 (89.82%)	83 (86.46%)	0.26 ^b
•Early immunotherapy (< 3 months), N (%)	89 (59.33%)	54 (65.06%)	0.23 ^b
•Median time from disease onset to immunotherapy	3 months (IQR 1-7; range 0.5-96)	3 months (IQR: 1-6; range 0.5-84)	0.40 ^a
First-line immunotherapy, N (%)	150 (89.82%)	83 (86.46%)	0.26 ^b
•1 agent, N (%)	59 (39.33%)	43 (51.81%)	0.05 ^b
•2 agents, N (%)	65 (43.33%)	35 (42.17%)	0.48 ^b

• 3 agents, N (%)	26 (17.33%)	5 (6.02%)	0.01^b
Second-line immunotherapy, N (%)	23 (13.77%)	5 (5.21%)	0.02^b
• 1 agent, N (%)	21 (14.00%)	5 (6.02%)	0.04 ^b
• 2 agents, N (%)	2 (1.33%)	0 (0%)	0.41 ^b
Maintenance, N (%)	111 (66.47%)	60 (62.50%)	0.30 ^b
• Median time of maintenance	6 months (IQR: 6-12; range 3-24)	6 months (IQR: 6-6; range 2-39)	0.21 ^a
Tumor removal, N (%)	3 (1.80%)	1 (1.04%)	0.53 ^b
Response to immunotherapy, N (%)	98 (65.33%)	46 (55.42%)	0.08 ^b
Median time from starting Immunotherapy to improvement	2 months (IQR 1-3, range 0.5-14)	2 months (IQR 0.5-4, range 0.5-24)	0.92 ^a
Follow-up or the entire cohort: 30 months (IQR 20-50; 12-120)			
Median time of follow-up	34 months (IQR: 21-48; range 12-120)	24 months (IQR: 18-60; range 12-120)	0.80 ^a
mRS at the last available FU	2 (IQR: 0-3; range 0-3)	2 (IQR: 1-2.5; range 0-3)	0.08 ^a
Interictal EEG findings at FU	59 (35.33%)	43 (44.79%)	0.14 ^b
• Multifocal IEDs, N (%)	6 (3.59%)	4 (4.17%)	1.00 ^b
• Diffuse IEDs, N (%)	6 (3.59%)	4 (4.17%)	1.00 ^b
• Temporal unilateral IEDs, N (%)	9 (5.39%)	10 (10.42%)	0.14 ^b
• Bitemporal IEDs, N (%)	26 (15.57%)	9 (9.38%)	0.18 ^b
• Extra-temporal IEDs, N (%)	12 (7.19%)	16 (16.67%)	0.02^b
Brain MRI Atrophy at FU, N (%)	31 (18.56%)	24 (25%)	0.27 ^b
• Temporal unilateral, N (%)	7 (4.19%)	7 (7.29%)	0.39 ^b
• Temporal bilateral, N (%)	15 (8.98%)	9 (9.38%)	1.00 ^b
• Extratemporal, N (%)	9 (5.39%)	8 (8.33%)	0.43 ^b
Relapses, N (%)	17 (10.18%)	5 (5.21%)	0.11 ^b
Enduring seizures, N (%)	59 (35.33%)	56 (58.33%)	<0.001^b
Other Sequelae, N (%)	108 (64.67%)	73 (76.04%)	0.03^b
• Cognitive deficits, N (%)	95 (56.89%)	69 (71.88%)	0.01^b
• Psychiatric disorders, N (%)	54 (32.34%)	28 (29.17%)	0.34 ^b

^aMann-Whitney *U*-test, ^bchi-square of Fisher's exact test,

^cT2/FLAIR hyperintensity consistent with inflammation

Table S2: Comparison between responders and non-responders among patients receiving immunotherapy

VARIABLES	Responders (n= 144, 61.80 %)	Non- responders (n=89, 38.20 %)	p-value
Median age at onset	51 years (IQR: 16-68; range: 2-84)	43 years (IQR: 20-63; range: 2-82)	0.33 ^a
Female, N (%)	78 (54.17%)	45 (50.56%)	0.34 ^b
Pediatric patients (age < 18years), N (%)	38 (26.39%)	19 (21.35%)	0.23 ^b
Antibody findings			
• Antibody positive, N (%)	98 (68.06%)	52 (58.43%)	0.09
• Antibodies to surface antigens, N (%)	87 (60.42%)	35 (39.33%)	0.001^b
• GAD65, N (%)	5 (3.47%)	11 (2.36%)	0.01^b
• Onconeural antibody, N (%)	6 (4.17%)	7 (7.87%)	0.18 ^b
mRS during acute phase	4 (IQR 3-4, range 1-5)	4 (IQR 3-4, range 1-5)	0.31 ^a
APE2 score	7 (IQR 5-9, range 2-13)	6 (IQR 5-8, range 2-11)	0.11 ^a
APE2 score $\geq$ 4, N (%)	138 (95.83%)	83 (93.26%)	0.28 ^b
RITE2 score	10 (IQR 8-13, range 3-17)	9 (IQR 7-11, range 3-15)	0.005^a
RITE2 score $\geq$ 7, N (%)	125 (86.81%)	68 (76.40%)	0.03^b
Seizure type			
• Generalized Onset, N (%)	9 (6.25%)	4 (4.49%)	0.40 ^b
• Focal motor onset, N (%)	56 (38.89%)	45 (50.56%)	0.05 ^b
• Focal non-motor onset, N (%)	64 (44.44%)	35 (39.33%)	0.26 ^b
• Focal to bilateral, N (%)	44 (30.56%)	20 (22.47%)	0.11 ^b
• FBDS, N (%)	25 (17.36%)	8 (8.99%)	0.05 ^b
• Multiple seizure type, N (%)	31 (21.53%)	11 (12.36%)	0.05 ^b
Seizure semiology			
• Multifocal, N (%)	30 (20.83%)	13 (14.61%)	0.15 ^b
• Temporal Unilateral, N (%)	25 (17.36%)	13 (14.61)	0.35 ^b

• Bitemporal, N (%)	54 (37.50%)	34 (38.20%)	0.51 ^b
• Extra-Temporal, N (%)	35 (24.31%)	29 (32.58%)	0.11 ^b
Status epilepticus, N (%)	55 (38.19%)	39 (43.82%)	0.23 ^b
• CSE, N (%)	37 (25.69%)	29 (32.58%)	0.16 ^b
• NCSE, N (%)	18 (12.50%)	6 (6.74%)	0.11 ^b
• EPC, N (%)	1 (0.69%)	9 (10.11%)	0.001^b
Associated symptoms at onset, N (%)	140 (97.22%)	82 (92.13%)	0.07 ^b
Median number of associated symptoms	3 (IQR: 2-4; range: 0-8)	2 (IQR: 2-3; range: 0-7)	0.01^a
• Severe disability, N (%)	37 (25.69%)	14 (15.73%)	0.05 ^b
• Cognitive impairment, N (%)	55 (38.19%)	30 (33.71%)	0.29 ^b
• Memory deficits, N (%)	61 (42.36%)	41 (46.07%)	0.33
• Language impairment, N (%)	33 (22.92%)	18 (20.22%)	0.37
• Movement disorders, N (%)	47 (32.64%)	20 (22.47%)	0.06 ^b
• Behavioral symptoms, N (%)	89 (61.81%)	52 (58.43%)	0.35 ^b
• Mood disorders, N (%)	23 (15.97%)	14 (15.73%)	0.55 ^b
• Sleep disorders, N (%)	42 (29.17%)	15 (16.85%)	<0.02^b
• Loss of consciousness, N (%)	14 (9.72%)	5 (5.62%)	0.19
• Dysautonomia, N (%)	23 (15.97%)	6 (6.74%)	0.03^b
• Hyponatremia, N (%)	17 (11.81%)	2 (2.25%)	0.006^b
Interictal EEG findings			
• Multifocal IEDs, N (%)	18 (12.50%)	12 (13.48%)	0.48 ^b
• Diffuse IEDs, N (%)	7 (4.86%)	2 (2.25%)	0.26 ^b
• Temporal unilateral IEDs, N (%)	30 (20.83%)	16 (17.98%)	0.36 ^b
• Bitemporal IEDs, N (%)	49 (34.03%)	30 (33.71%)	0.05 ^b
• Extra-temporal IEDs, N (%)	33 (22.92%)	27 (30.34%)	0.13 ^b
Brain MRI findings[^]			
• Normal, N (%)	42 (29.17%)	21 (23.60%)	0.21 ^b
• Temporal unilateral, N (%)	24 (16.67%)	18 (20.22%)	0.30 ^b
• Temporal bilateral, N (%)	38 (26.39%)	28 (31.46%)	0.24 ^b
• Extratemporal, N (%)	6 (4.17%)	7 (7.87%)	0.18 ^b
• Multifocal in GW and WM, N (%)	20 (13.89%)	12 (13.48%)	0.54 ^b
Difficult to treat seizures at onset, N (%)	67 (46.53%)	60 (67.42%)	0.001^b

Median of ASMs during the acute phase	2 (IQR: 1-3; range 0-8)	3 (IQR: 2-4; range 0-12)	<0.001^b
Immunotherapy			
• Early immunotherapy (< 3 months), N (%)	114 (79.17%)	114 (79.17%)	<0.001^b
• Median time from disease onset to immunotherapy	2 months (IQR: 1-3; range 0.5-84)	6 months (IQR: 3-9; range 0.5-96)	<0.001^b
First-line immunotherapy			
• 1 agent, N (%)	61 (42.36%)	41 (46.07%)	0.33
• 2 agents, N (%)	64 (44.44%)	36 (40.45%)	0.32
• 3 agents, N(%)	19 (13.19%)	12 (13.48%)	0.54
Second-line immunotherapy, N (%)	16 (11.11%)	12 (13.48%)	0.36 ^b
• 1 agent, N (%)	14 (9.72%)	12 (13.48%)	0.24
• 2 agents, N (%)	2 (1.39%)	0 (0%)	0.38
Maintenance, N (%)	109 (75.69%)	62 (69.66%)	0.19 ^b
• Median time of maintenance	6 months (IQR: 6-8; range 3-24)	6 months (IQR: 6-12; range 2-39)	0.19 ^a
Tumor removal, N (%)	2 (1.39%)	2 (2.25%)	0.49 ^b
Follow-up or the entire cohort: 30 months (IQR 20-50; 12-120)			
Median time of follow-up	28.5 months (IQR: 18-44.5; range 12-120)	36 months (IQR: 24-72; range 12-120)	0.02^a
mRS at the last available FU	2 (IQR: 0-2; range 0-3)	2 (IQR: 2-3; range 0-3)	0.006^a
Relapses, N (%)	11 (7.64%)	10 (11.24%)	0.24 ^b
Interictal EEG findings at FU	30 (20.83%)	62 (69.66%)	<0.0001^b
• Multifocal IEDs, N (%)	3 (2.08%)	7 (7.87%)	0.04^b
• Diffuse IEDs, N (%)	5 (3.47%)	4 (4.49%)	0.73 ^b
• Temporal unilateral IEDs, N (%)	7 (4.86%)	10 (11.24%)	0.07 ^b
• Bitemporal IEDs, N (%)	7 (4.86%)	22 (24.72%)	<0.0001^b
• Extra-temporal IEDs, N (%)	8 (5.56%)	19 (21.35%)	0.02^b
Brain MRI Atrophy at FU, N (%)	28 (19.44%)	22 (24.72%)	0.41 ^b
• Temporal unilateral, N (%)	6 (4.17%)	7 (7.87%)	0.25 ^b
• Temporal bilateral, N (%)	13 (9.03%)	8 (8.99%)	1.00 ^b
• Extratemporal, N (%)	9 (6.25%)	7 (7.87%)	0.79 ^b
Seizure freedom at last available follow-up, N (%)	118 (81.94%)	15 (16.85%)	<0.001^b
Other Symptoms freedom	50 (34.72%)	21 (23.60%)	0.05 ^b

at last follow-up, N (%)			
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^aMann-Whitney *U*-test, ^bchi-square of Fisher’s exact test,

[^]T2/FLAIR hyperintensity compatible with inflammation

Table S3: Comparison between patients developing chronic epilepsy and those who were seizure free at last follow-up (all assessed data)

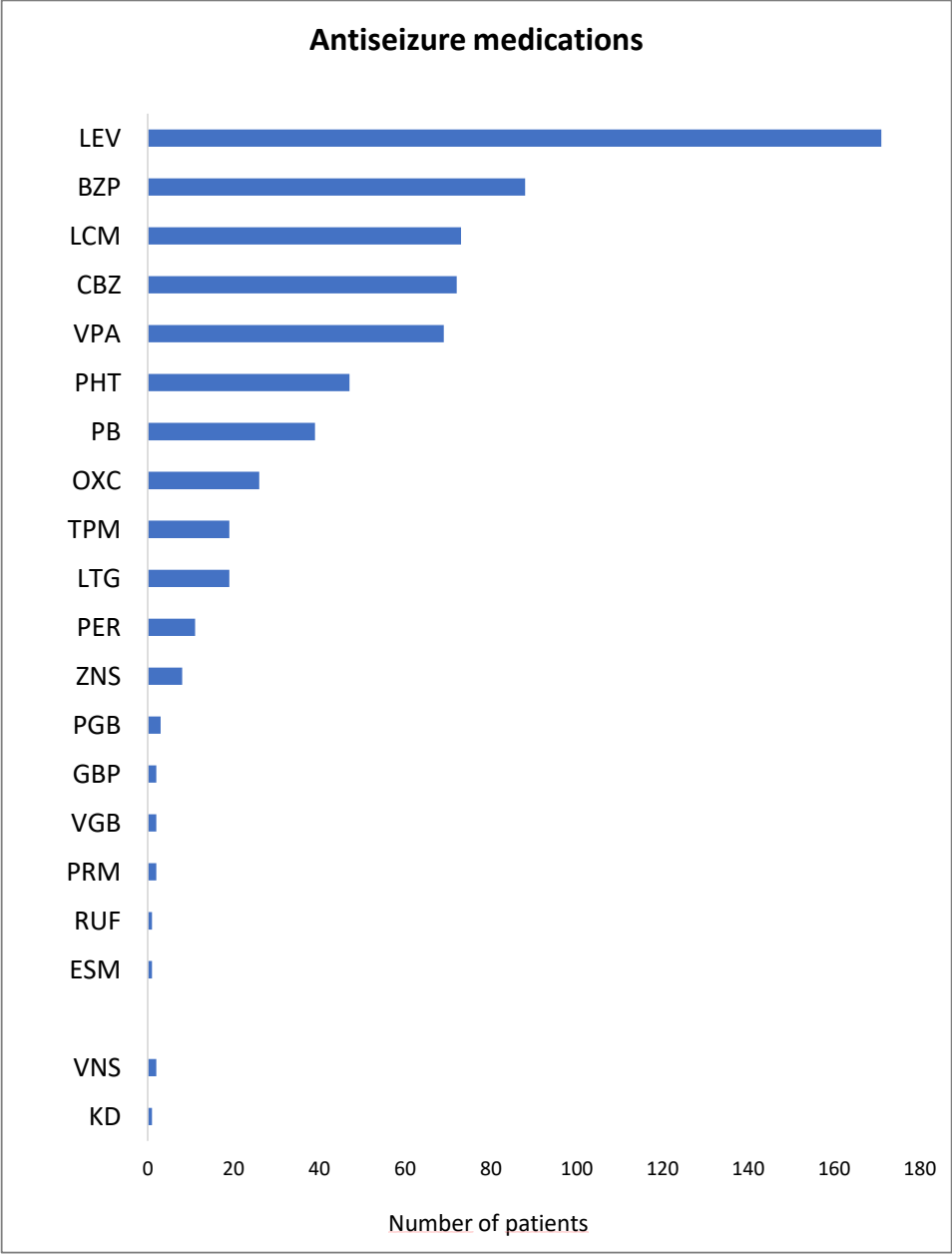
VARIABLES	Chronic epilepsy (n= 115, 43.73 %)	Seizure Free (n=148, 56.27 %)	p-value
Median age at onset	44 years (IQR: 18-61; range: 2-84)	54.5 years (IQR: 20.5-68; range: 2-82)	0.03^a
Female, N (%)	55 (47.83%)	83 (56.08%)	0.11 ^b
Pediatric patients (age < 18years), N (%)	27 (23.48%)	33 (22.30%)	0.46 ^b
Antibody findings			
• Antibody positive, N (%)	59 (51.30%)	108 (72.97%)	<0.001^b
• Antibodies to surface antigens, N (%)	38 (33.04%)	95 (64.19%)	<0.001^b
• Antibodies to intracellular antigens, N (%)	21 (18.26%)	13 (8.78%)	0.01^b
mRS during acute phase	4 (IQR 3-4, range 1-5)	4 (IQR 3-5, range 1-5)	0.06 ^a
APE2 score	6 (IQR 5-8, range 3-12)	6 (IQR 5-8, range 2-13)	0.99 ^a
APE2 score $\geq$ 4, N (%)	108 (93.91%)	137 (92.57%)	0.43 ^b
RITE2 score	9 (IQR 6-11, range 3-15)	10 (IQR 8-12, range 3-17)	0.02^a
RITE2 score $\geq$ 7, N (%)	85 (73.91%)	122 (82.43%)	0.06 ^b
Seizure type			
• Generalized Onset, N (%)	4 (3.48%)	11 (7.43%)	0.13 ^b
• Focal motor onset, N (%)	54 (46.96%)	60 (40.54%)	0.18 ^b
• Focal non-motor onset, N (%)	47 (40.87%)	60 (40.54%)	0.52 ^b
• Focal to bilateral, N (%)	31 (26.96%)	41 (27.70%)	0.50 ^b
• FBDS, N (%)	11 (9.57%)	23 (15.54%)	0.10 ^b
• Multiple seizure type, N (%)	16 (13.91%)	27 (18.24%)	0.22 ^b
Seizure semiology			
• Multifocal, N (%)	22 (19.13%)	27 (18.24%)	0.48 ^b
• Temporal Unilateral, N (%)	12 (10.43%)	31 (20.95%)	0.01^b
• Bitemporal, N (%)	42 (36.52%)	53 (35.81%)	0.50 ^b
• Extra-Temporal, N (%)	39 (33.91%)	37 (25.00%)	0.07 ^b

Status epilepticus, N (%)	57 (49.57%)	50 (33.78%)	0.007^b
• CSE, N (%)	39 (33.91%)	37 (25.00%)	0.07 ^b
• NCSE, N (%)	14 (12.17%)	13 (8.78%)	0.24 ^b
• EPC, N (%)	10 (8.70%)	0 (0%)	<0.001^b
Associated symptoms at onset, N (%)	102 (88.70%)	143 (96.62%)	0.01^b
Median number of associated symptoms	2 (IQR: 1-3; range: 0-6)	3 (IQR: 1.5-4; range: 0-8)	0.01^a
• Severe disability, N (%)	22 (19.13%)	34 (22.97%)	0.27 ^b
• Cognitive impairment, N (%)	43 (37.39%)	49 (33.11%)	0.27 ^b
• Memory deficits, N (%)	49 (42.61%)	61 (41.22%)	0.45 ^b
• Language impairment, N (%)	19 (16.52%)	34 (22.97%)	0.12 ^b
• Movement disorders, N (%)	26 (22.61%)	46 (31.08%)	0.08 ^b
• Behavioral symptoms, N (%)	59 (51.30%)	94 (63.51%)	0.03^b
• Mood disorders, N (%)	17 (14.78%)	23 (15.54%)	0.50 ^b
• Sleep disorders, N (%)	20 (17.39%)	39 (26.35%)	0.05^b
• Loss of consciousness, N (%)	8 (6.96%)	11 (7.43%)	0.54 ^b
• Dysautonomia, N (%)	5 (4.35%)	24 (16.22%)	0.002^b
• Hyponatremia, N (%)	8 (6.96%)	12 (8.11%)	0.45 ^b
Interictal EEG findings			
• Multifocal IEDs, N (%)	15 (13.04%)	19 (12.84%)	0.55 ^b
• Diffuse IEDs, N (%)	3 (2.61%)	7 (4.73%)	0.29 ^b
• Temporal unilateral IEDs, N (%)	20 (17.39%)	33 (22.30%)	0.20 ^b
• Bitemporal IEDs, N (%)	36 (31.30%)	49 (33.11%)	0.43 ^b
• Extra-temporal IEDs, N (%)	40 (34.78%)	32 (21.62%)	0.01^b
Brain MRI findings[^]			
• Normal, N (%)	24 (20.87%)	47 (31.76%)	0.03^b *
• Temporal unilateral, N (%)	22 (19.12%)	24 (16.22%)	0.32 ^b
• Temporal bilateral, N (%)	37 (32.17%)	35 (23.65%)	0.08 ^b
• Extratemporal, N (%)	7 (6.09%)	8 (5.41%)	0.50 ^b
• Multifocal in GW and WM, N (%)	20 (17.39%)	18 (12.16%)	0.15 ^b
Difficult to treat seizures at onset, N (%)	78 (67.83%)	65 (43.92%)	<0.001^b *
Median of ASMs during the acute phase	3 (IQR: 2-4; range 1-12)	2 (IQR: 1-3; range 0-5)	<0.001^b *

Immunotherapy			
• Early immunotherapy (< 3 months), N (%)	41 (41.00%)	102 (76.69%)	<0.001^{b*}
• Median time from disease onset to immunotherapy	4 months (IQR 2-9; range 0.5-90)	2 months (IQR: 1-3; range 0.5-84)	<0.001^b
First-line immunotherapy			
• 1 agent, N (%)	44 (44%)	58 (43.61%)	0.52 ^b
• 2 agents, N (%)	41 (41%)	59 (44.36%)	0.35 ^b
• 3 agents, N(%)	15 (15%)	16 (12.03%)	0.31 ^b
Second-line immunotherapy, N (%)	12 (10.43%)	16 (10.81%)	0.54 ^b
• 1 agent, N (%)	11 (11%)	15 (11.28%)	0.56 ^b
• 2 agents, N (%)	1 (1%)	1 (0.75%)	0.67 ^b
Maintenance, N (%)	74 (64.35%)	97 (65.54%)	0.47 ^b
• Median time of maintenance	6 months (IQR: 6-10; range 3-39)	6 months (IQR: 6-10; range 2-27)	0.54 ^a
Tumor removal, N (%)	2 (1.74%)	1 (1.35%)	0.58 ^b
Follow-up of the entire cohort: 30 months (IQR 20-50; 12-120)			
Median follow-up	36 months (IQR: 23-72; range 12-120)	24 months (IQR: 18-36.5; range 12-96)	<0.001^a
mRS at the last available FU	2 (IQR: 2-3; range 1-3)	2 (IQR: 0-2; range 0-3)	<0.001^a
Persisting IEDs at FU	75 (65.22%)	27 (18.24%)	<0.0001^{b*}
• Multifocal IEDs, N (%)	9 (7.83%)	1 (0.86%)	0.006^b
• Diffuse IEDs, N (%)	6 (5.22%)	4 (2.70%)	0.34 ^b
• Temporal unilateral IEDs, N (%)	15 (13.04%)	4 (2.70%)	0.002^b
• Bitemporal IEDs, N (%)	25 (21.74%)	10 (6.76%)	<0.0001^b
• Extra-temporal IEDs, N (%)	20 (17.39%)	8 (5.41%)	0.002^b
Brain MRI Atrophy at FU, N (%)	29 (25.22%)	26 (17.57%)	0.08 ^b
• Temporal unilateral, N (%)	10 (8.70%)	4 (2.70%)	0.05 ^b
• Temporal bilateral, N (%)	10 (8.70%)	14 (9.46%)	1.00 ^b
• Extratemporal, N (%)	9 (7.83%)	8 (5.41%)	0.45 ^b
Relapses, N (%)	9 (7.83%)	13 (8.78%)	0.48 ^b
Non Responder to Immunotherapy, N (%)	74 (74%)	15 (11.28%)	<0.001^{b*}
Other Symptoms freedom at last follow-up, N (%)	94 (81.74%)	87 (58.78%)	0.05 ^b

IEDs: Interictal epileptiform discharges, ^aMann-Whitney *U*-test, ^bchi-square of Fisher's exact test, *Independent predictors at the multivariate regression analysis.

Figure S1: Antiseizure medications prescribed in the whole cohort.



LEV: Levetiracetam; BZP: Benzodiazepine; LCM: Lacosamide; CBZ: Carbamazepine; VPA: Valproate; PHT: Phenytoin; PB: Phenobarbital; OXC: oxcarbazepine; LTG: lamotrigine; PER: Perampanel; ZNS: Zonisamide; PGB: Pregabalin; GBP: Gabapentin; VGB: Vigabatrin; PRM: Primidone; RUF

Rufinamide; ETS: ethosuximide; VNS: vagus nerve stimulation; KD: ketogenic diet.