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EPILEPTIC PHENOTYPES, TREATMENT OPTIONS AND LONG-TERM OUTCOMES OF AUTOIMMUNE EPILEPSIES

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ABSTRACT

Background and aims

Epileptic seizures may be a presenting or prominent symptom of brain dysfunction in autoimmune encephalitis. They are usually resistant to symptomatic therapy with antiseizure medications (ASMs) but may benefit from immunomodulatory treatments. Despite the increasing knowledge in this field and progress in research interest, autoimmune epilepsy is still an under-recognized condition without standardized diagnostic and management guidelines.

This study aims to analyze the epileptic phenotypes of seizures of autoimmune etiology, assessing their clinical presentation, seizure semiology, and associated paraclinical findings. Treatment options, management, and overall outcomes at the long-term were also provided.

Methods

An observational cohort study was retrospectively performed over 10 years period (from 2010 to 2020). This is a nationwide study, carried out in 34 Italian epilepsy centers being part of the network of high expertise centers of the Italian League Against Epilepsy [LICE].

Patients with new-onset seizures of an autoimmune etiology were enrolled. This latter was defined by the detection of antineuronal antibodies or suspected on the basis of clinical presentation and paraclinical findings.

Results

Overall, 263 patients (138 females; median age 55 years, range 4-86) were enrolled and followed-up for a median time of 30 months (range 12-120). The median age at seizure onset was 48 years (range 2-82). Antineuronal antibodies were detected in 63.50% of cases (79.65% of them had antibodies targeting neuronal cell-surface antigens).

No specific seizure semiology was found to be related to antibody-positivity, except for facio-brachial dystonic seizures, which are pathognomonic of LGI1 encephalitis ($p< 0.001$). Most antibody-positive patients had multiple seizure types ($p=0.01$); and a prevalent involvement of the temporal regions ($p=0.02$), but when performing the multivariate analysis, these features were not confirmed to be independent predictors for antibody detection. Of interest, a higher prevalence of episodes of status epilepticus was found in the antibody-negative patients (OR 0.23, 95% CI 0.12-0.45; $p<0.001$**),** which also usually leads to a less favorable prognosis in these cases.

During the acute phase, 87.73% presented seizures drug-resistant to most common ASMs, without any significant prevalence in antibody detection.

Besides seizures, the acute phase was also marked by associated symptoms in 93%; mostly cognitive impairment, psychiatric symptoms, and sleep disorders were prevalent in antibody-positive subgroup (OR 4.70, 95% CI 2.33-9.47; OR 3.43, 95% CI 1.81-6.50; OR 5.41, 95% CI 2.16-13.52, respectively; $p< 0.001$).

Most patients (88.60%) were treated with immunotherapy, and 61.80% of them were considered responders. Independent predictors of a favorable outcome were confirmed to be early immunotherapy (within 3 months from the onset; OR 12.08,

95% CI 5.50-26.50; p<0.001) and the detection of antineuronal surface antibodies (OR 2.38; 95% CI 1.15-4.92; p=0.01)

Long-term outcomes were marked by persisting seizures beyond the acute phase of the encephalitis in 43.73%, with a prevalence in antibody-negative patients (p<0.001), associated with neuropsychological deficits and psychiatric disorders in 81.73% of them.

Conclusions

The increasing recognition of an autoimmune basis of epilepsies and the broad spectrum of autoimmune encephalitis with predominant epileptic seizures has raised interest in scientific and clinical epileptology, opening a new field with challenging issues in diagnosis and treatment.

The comparison between subgroups of antibody findings and outcomes may improve the operative definition and characterization.

An autoimmune etiology represents a rare chance in seizures management, and an early treatment at the pathogenic level may reduce the risk of irreversible sequelae at the long-term.

This study provides Class IV evidence for management recommendations.

RIASSUNTO

Obiettivi

Le crisi epilettiche possono essere sintomo di esordio o prominente di encefaliti autoimmuni. Le crisi sono generalmente farmacoresistenti gli antiepilettici, ma possono beneficiare di trattamenti immunomodulanti. Nonostante le crescenti conoscenze scientifiche in questo ambito, le crisi epilettiche ad eziologia autoimmune sono spesso sotto-diagnosticate e non vi sono linee guida standardizzate per la diagnosi e la gestione terapeutica.

Lo scopo dello studio è di analizzare e descrivere i fenotipi epilettici ad eziologia autoimmune, le opzioni terapeutiche, nonché i possibili esiti a lungo termine.

Metodi

Studio di coorte osservazionale retrospettivo, condotto in un periodo di 10 anni (dal 2010 al 2020). Si tratta di uno studio nazionale multicentrico, che ha coinvolto 34 centri per l'epilessia.

Sono stati arruolati pazienti con crisi di nuova insorgenza ad eziologia autoimmune, definita in base alla rilevazione di anticorpi antineuronali specifici, o sulla base della presentazione clinica e degli esami laboratoristici e strumentali.

Risultati

Sono stati arruolati 263 pazienti (138 di sesso femminile, con età di 55 anni, range 4-86) seguiti per un periodo di tempo di 30 mesi (range 12-20). L'età all'esordio era di 48 anni (range 2-82). Anticorpi antineuronali sono stati identificati nel 63.50% dei casi (79.65% dei quali aveva anticorpi diretti controllo antigeni della superficie neuronale). Nessun tipo di crisi è risultato essere correlato alla positività anticorpale,

ad eccezione delle crisi distoniche facio-brachiali, patognomoniche della encefalite da anticorpi anti-LGI1 (p<0.001). La maggior parte dei pazienti positivi presentava più tipi di crisi (p=0.01); e un coinvolgimento prevalente delle strutture temporali (p=0.02). All'analisi multivariata però queste caratteristiche non sono risultate essere fattori predittivi indipendenti la rilevazione anticorpale. Interessante è risultata essere la maggiore prevalenza di episodi di stato epilettico nei pazienti negativi (p<0.001), correlata anche una prognosi meno favorevole. Durante la fase acuta, l'87.73% dei pazienti presentava crisi farmacoresistenti agli antiepilettici, senza che vi fosse una prevalenza significativa della positività anticorpale. Oltre alle crisi, la fase acuta era caratterizzata da altri sintomi associati nel 93% dei casi; soprattutto disturbi cognitivi, psichiatrici e del sonno, prevalenti nei pazienti con anticorpi negativi (p< 0.001). La maggior parte dei pazienti (88.60%) ha ricevuto un trattamento immunomodulante, e il 61.80% ha presentato una risposta favorevole. Fattori indipendenti predittivi di una risposta favorevole alla terapia sono risultati essere l'inizio precoce della terapia immunomodulante (entro 3 mesi; p<0.001) e la presenza di anticorpi diretti contro antigeni della superficie neuronale (p=0.01).

Gli esiti a lungo termine erano rappresentati dalla persistenza di crisi oltre la fase acuta dell'encefalite nel 43.73% dei casi, con prevalenza nei pazienti negativi (p<0.001), e con associati anche deficit neuropsicologici e sintomi psichiatrici nell'81.73% dei casi.

Conclusioni

Il crescente riconoscimento di forme di epilessia a genesi autoimmune e l'ampio spettro di encefaliti autoimmuni con crisi epilettiche quali sintomo predominante ha

determinato un crescente interesse clinico e scientifico verso un nuovo ambito di difficile diagnosi e gestione terapeutica.

Il confronto tra i vari sottogruppi in base alla determinazione anticorpale e alla risposta terapeutica permette una migliore definizione e caratterizzazione di questi pazienti.

Un'eziologia autoimmune delle crisi epilettiche rappresenta una opportunità terapeutica, e il trattamento precoce a livello patogenetico può ridurre il rischio di sviluppare irreversibili esiti a lungo termine.

Questo studio presenta un livello di evidenza di Classe IV per raccomandazioni nella gestione complessiva di questi pazienti.

1. AUTOIMMUNE EPILEPSY

1.1. Definition and concepts

Many brain disorders may induce epileptic seizures, defined as paroxysmal events due to an excessive, hypersynchronous discharge of neuronal networks in the central nervous system (CNS). This term should be differentiated from epilepsy, a chronic condition affecting fifty million people worldwide, defined as an enduring predisposition to generate epileptic seizures [*Fisher et al., 2005*].

Recently, the guidelines and new epilepsy classifications of the International League Against Epilepsy (ILAE) defined epileptic seizures [*Fisher et al., 2014*], epileptic seizures with an immune etiology [*Scheffer et al., 2017*], status epilepticus [*Trinka et al., 2015*], drug-resistant epilepsy [*Kwan et al., 2010*], and classified seizure types according to their semiology based on the key signs and symptoms [*Fisher et al., 2017*].

In particular, "epilepsy of immune etiology" should refer to patients having at least 2 seizures, not provoked by other factors, occurring more than 24 hours apart, resulting directly from an immune disorder, with evidence of autoimmune-mediated CNS inflammation [*Fisher et al., 2014; Fisher et al., 2017; Scheffer et al., 2017*].

The role of neuroinflammation is increasingly recognized in triggering or sustaining epileptic activity. Over the last 20 years, an increasing number of studies have endorsed the hypothesis that inflammatory brain processes involving innate immunity components play an important role in the pathophysiology of epilepsy [*Marchi et al., 2014; Geis et al., 2019*].

A significant proportion of epilepsies of unknown etiology (15-20%) has been attributed to autoimmunity or a possible autoimmune cause [*Brenner et al., 2013; Dubey et al., 2017a; Dubey et al., 2017b*]. Moreover, patients with autoimmune diseases have a higher risk of epilepsy than the general population [*Ong et al., 2014; Lin et al., 2016*], and immune-related genes may be involved in some types of epilepsy and febrile-seizure susceptibility [*Spatola & Dalmau., 2017*].

An increasing number of antineuronal autoantibodies have been discovered and associated with various neurologic syndromes with epilepsy [*Toledano & Pittock, 2015*]. In particular, the identification of these antibodies in patients with epilepsy of so far unknown cause and the increasing knowledge on these disorders has provided new insights into the relationship between neuroinflammation, autoimmunity, and seizure triggering, giving rise to the concept of "autoimmune epilepsy". Therefore, this term mostly refer to autoimmune encephalitis with predominant epileptic features. Epileptic seizures and episodes of status epilepticus are a frequent manifestation of autoimmune encephalitis and may occur as a presenting or prominent symptom of an acute brain inflammatory process. Despite most autoimmune encephalitis present with seizures during the acute or early stages of the disease, the subsequent risk of developing chronic epilepsy is relatively low, depending on the autoimmune process, and not completely defined. 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. So far the available studies rarely

provide this information and mostly report short-term follow-up considering that some autoimmune encephalitis recover very slowly from the acute phase [*Titulaer et al., 2013; Van Soderen et al., 2016*].

According to all of the above, the frequent definition of seizures occurring in autoimmune encephalitis as autoimmune epilepsy would be inappropriate, thus, despite seizures are quite frequent during the acute, inflammatory-provoked phase, ranging from 33% to 100% depending on the antigen, they mostly resolve after the encephalitis ends [*Geis et al., 2019; de Bruijn et al., 2019*].

Autoimmune epilepsy comes from the predisposition to cause enduring epileptic seizures in autoimmune encephalitis, depending on the mechanism that drives the immune response, ranging from a high predisposition in cytotoxic T cell-mediated encephalitis (intracellular antigens) to a moderate or low predisposition in antibody-mediated encephalitis (surface antigens). In the latter group, the severity of seizures, and the likelihood to develop chronic epilepsy is strictly linked to the antigen. Overall, these disorders may occur with a variable degree of inflammation that could have downstream effects on synaptic function, hyperexcitability, and epileptogenesis [*Spatola & Dalmau., 2017; Geis et al., 2019*].

1.2. Epidemiology

The true incidence of autoimmune epilepsy remains unknown. There are no population-based studies providing an assessment of prevalence and incidence of this condition.

Recently a hospital-based prospective study reported that 20% of adult patients with epilepsy of unknown etiology resulted positive for specific antineuronal antibodies associated with autoimmune epilepsy and encephalopathy [*Dubey et al., 2017a; Dubey et al., 2017b*]. Another UK-retrospective study also estimated the frequency of specific antineuronal antibodies to be 15% among patients with epilepsy of unknown etiology [*Brenner et al., 2013*]. Therefore, the rate of autoimmune epilepsies based on these studies can be estimated to be around 15-20% of all epilepsies, at least in adult patients. The frequency of autoantibodies in pediatric epilepsy is more unclear. Studies from Europe and Australia have reported the presence of autoantibodies in about 10% of pediatric patients with new-onset epilepsy [*Suleiman et al., 2013; Wright et al., 2016*].

2. AUTOIMMUNE ENCEPHALITIS WITH EPILEPTIC SEIZURES

The occurrence of seizures in autoimmune encephalitis resulted in growing interest in epileptology, opening a new field with challenging issues in diagnosis and management [*de Bruijn et al., 2019*].

Several peculiar features raise the suspicion of an autoimmune cause in otherwise unexplained seizures disorders. New onset of drug resistant seizures in an otherwise healthy individual should rise the importance of considering autoimmune encephalitis as the cause of the epileptic seizures.

Cases having a severe disease course with coma and status epilepticus, are usually diagnosed earlier than those who do not have a full-blown encephalitis. In most autoimmune encephalitis, seizures occur in association with other symptoms, including cognitive and neuropsychological deficits, behavioral problems, decreased level of consciousness, movement and sleep disorders, and dysautonomia [*Dalmau & Graus, 2018*]. In a quarter of the cases, seizures may be associated only with subtle signs of the encephalitis, leading in these cases an unrecognition of the underlying process with diagnostic and treatment delay [*Vincent et al., 2010; Irani et al., 2013; Titulaer et al., 2013*]. Treatment delay is associated with poorer outcome. Therefore, it is essential to consider an autoimmune etiology in presence of specific clinical clues [*Graus et al., 2016*].

Although there is a substantial clinical overlap among different autoimmune encephalitis, some clinical features, and electroencephalogram (EEG) or MRI findings may suggest the antigen (*Table A*).

In patients with autoimmune encephalitis, high seizure frequency, generalized seizures, and episodes of status epilepticus contribute to morbidity and mortality of the disease [*Titulaer et al., 2013; Van Soderen et al., 2016; Spatola & Dalmau., 2017*]. Overall, 70-80% of patients respond to immunotherapy. Residual deficits may occur in a subset of patients after recovery from the acute phase, and include cognitive and neuropsychological dysfunctions, behavioral problems, and persisting seizures [*Titulaer et al., 2013; Van Soderen et al., 2016; Spatola & Dalmau., 2017*]. In more than 70% of patients, epileptic seizures are successfully treated with immunotherapy and antiseizure medications (ASMs), and they resolved prior to improvements of cognitive or behavioral functions. In this regard, most patients do not require chronic treatment with ASMs, and usually after 2 years of follow-up, 85% of patients were seizure-free (71% were also drug-free), while 15% continued to have seizures despite ASMs [*Titulaer et al., 2013; Van Soderen et al., 2016; Spatola & Dalmau., 2017*].

Overall, the seizure outcome and the risk of developing chronic epilepsy after autoimmune encephalitis appears low (10-15%), and may varies depending on prompt treatment and the target antigen.

Recently, the recognition of autoimmune encephalitis is improving. In an epidemiological study performed in Olmsted Country highlights a threefold increase in incidence of autoimmune encephalitis from 2006 onward; this increase has been attributed to the improvement in clinical recognition and widespread availability of diagnostic tests [*Dubey et al, 2018*].

Considering the highly favorable response to immunotherapy, clinicians should be increasingly able in the recognition of the clinical features and diagnostic criteria for autoimmune encephalitis to avoid delays in treatment and prompt tailored management [*Graus et al., 2016*]. In many cases, EEG is often nonspecific, and brain MRI and cerebral-spinal fluid (CSF) can be unrevealing, thus leading to diagnostic delay. Nowadays, testing for autoantibodies has been incorporated into epileptology clinical practice, because many tests have been shown to be reliable and specific for distinct phenotypes [*Bien & Holtkamp., 2017*].

Table A summarizes the main clinical features, seizures characteristics and outcomes of autoimmune encephalitis

2.1. Clinical Syndromes

Table A: Main clinical features, seizures characteristics and outcomes of autoimmune encephalitis

Antibody-mediated encephalitis	Clinical features	Seizures	EEG findings	Brain MRI	General Outcome
Anti-NMDAR encephalitis	• Prodromal symptoms • Seizures • Movement disorders • Psychiatric symptoms • Memory deficits • Cognitive decline • Sleep disturbances • Decreased consciousness • Autonomic dysfunction • Associated tumor in ~40% (ovarian teratoma)	• ~75% of patients develop seizures during the acute phase • Generalized or focal • Temporal, extratemporal, or multifocal onset • Low risk of chronic epilepsy (<5%)	• Focal or diffuse slowing • Excessive beta activity range 14-20 Hz • Extreme delta brush • Generalized delta activity • Interictal epileptiform abnormalities and subclinical epileptic discharges	• Normal • Transient non-specific T2/ FLAIR hyperintensities in multiple cortical and subcortical regions	• Favorable in ~80-85% of patients with substantial or full recovery • Relapses in ~15-20%
Anti-LGI1 encephalitis	• Limbic encephalitis • Seizures • Psychiatric symptoms • Memory deficits • Movement disorders • Sleep disturbances • Hyponatremia • Autonomic symptoms • Associated	• Facio-brachial dystonic seizures (FBDS) ~40-50% • Temporal lobe seizures • Ictal piloerection and bradycardia • Subclinical	• FBDS associated findings: electrodecremental pattern or infra-slow activity • Temporal lobe seizures: subclinical epileptic discharges or interictal epileptiform abnormalities	• Normal • Prominent T2/FLAIR hyperintensities in mesial temporal lobes	• Favorable in ~70-80% with partial or complete recovery, • Permanent sequelae in ~65% • Relapses in ~30-35%

	tumor in ~11% (thymoma, SCLC)	seizures • Multiple seizures type in later stages • Risk of chronic epilepsy in ~15% who develop hippocampal atrophy			
Anti-Caspr2 encephalitis	• Limbic encephalitis • Morvan syndrome • Neuromyotonia • Associated tumor in ~5%	• Temporal lobe seizures ~71-89% • Risk of chronic epilepsy is unknown, but probably low (~10%)	• Temporal lobe ictal and interictal discharges • No specific features have been described	• Normal • Prominent T2/FLAIR hyperintensities in mesial temporal lobes	• Favorable in ~48% with response to immunotherapy • Relapses in ~25%
Anti-AMPAR encephalitis	• Limbic encephalitis • Seizures and status epilepticus • Memory deficits • Behavioral changes • Associated tumor in ~50% (Thymoma, SCLC)	• Temporal lobe seizures in ~30-40% • Low risk of chronic epilepsy (~5%)	• Temporal lobe ictal and interictal discharges • Generalized slowing is less common	• Normal • T2/ FLAIR hyperintensities in mesial temporal lobes or other extra-temporal regions	• Depends on the control of the tumor • Favorable in ~70% with partial or full recovery
Anti-$GABA_A$ receptor encephalitis	• Refractory seizures and status epilepticus • Cognitive and memory deficits • Movement	• Refractory focal or generalized seizures (~90%) • Status epileptic	• Unilateral or bilateral epileptiform discharges	• Extensive, multifocal cortical and subcortical T2/FLAIR hyperintensities	• Partially favorable in ~65% with partial recovery • Death in ~15%

	disorders • Behavioral changes • Associated tumor in ~20% (Thymoma)	us (~50%) • EPC • Risk of chronic epilepsy is unknown, but probably moderate (~20-30%)			
Anti-$GABA_B$ receptor encephalitis	• Limbic encephalitis • Seizures • Memory deficits • Psychiatric symptoms • Associated tumor in ~50% (SCLC)	• Temporal lobe seizures • Focal, focal to bilateral, and generalized • Status epilepticus • Low risk of chronic epilepsy (~5%)	• Temporal lobe ictal and interictal discharges	• Normal • T2/ FLAIR hyperintensities in mesial temporal lobes or other regions	• Depends on the control of the tumor • Favorable in ~70% with partial or full recovery • Relapses may occur
Anti-GlyR encephalitis	• SPS • PERM • Limbic encephalitis • Seizures and status epilepticus • Cognitive dysfunction • Movement disorders • Brainstem encephalitis	• Temporal lobe seizures • Risk of chronic epilepsy is unknown	• Diffuse slowing • Temporal lobe epileptiform discharges	• Normal • Non-specific cortical and/or subcortical abnormalities	• Substantial or partial improvement in most patients • Death in ~11% • Relapses in ~14%
Anti-DPPX encephalitis	• Diarrhea • Hyperekplexia • Decreased consciousness	• Epileptic seizures in ~10-20% • Risk of chronic	• Diffuse slowing	• Normal • Non-specific cortical and/or subcortical	• No improvement ~20% • Substantial or moderate

	• Sleep disorders • Brainstem involvement	epilepsy is unknown		abnormalities	improvement in ~60% • Death in ~17% • Relapses in ~23%
Anti-dopamine D2 receptor encephalitis	• Basal Ganglia encephalitis • Lethargy • Psychiatric symptoms • Movement disorders	• Epileptic seizures in ~16% • Low risk of chronic epilepsy (~5%)	• Not available	• Normal • T2/FLAIR hyperintensities in the basal ganglia	• Favorable in ~40% with full recovery • Relapses in ~25%
Anti-MOG associated disease	• ADEM • MDEM • ON • TM • NMOSD • Non-MS course • Relapsing disease	• Cluster of seizures • Focal, focal to bilateral tonic-clonic seizures • Low risk of chronic epilepsy	• No specific findings have been described	• Long optic nerve • >3 spinal segments myelitis • T2-hyperintensities in diencephalon • Multifocal demyelination	• Favorable with immunotherapy • Relapses may occur
Autoimmune GFAP astrocytopathy	• Meningo-encephalomyelitis • Seizures • Aphasia • Ataxia • Autonomic disfunction • Associated tumor in ~14%	• Refractory epileptic seizures • Risk of chronic epilepsy is unknown	• No specific findings have been described	• Periventricular radial/patchy enhancement of diffuse subcortical hyperintensities	• Favorable with immunotherapy • Relapses may occur
Autoimmune encephalitides with intracellular Antibodies	• Seizures • Cognitive deficits • Psychiatric symptoms • Movement disorders • SPS, PERM • Limbic encephalitis	• Temporal lobe seizures • EPC • Status epilepticus • High risk of chronic	• Temporal lobe ictal and interictal discharges • Diffuse or focal slowing	• Normal • Hyperintensity in mesial temporal lobes or other cortical and subcortical regions	• Usually poor outcome in most patients

	• Brainstem encephalitis • Cerebellitis • Encephalo-myelitis • Opsoclonus-myoclonus • Associated tumor in most	epilepsy			

Table legend:

1. NMDAR: N-methyl-D-aspartate receptor; LGI1: Leucine-rich glioma inactivated-1; Caspr2: Contactin-associated protein-2 receptor; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; $GABA_A$: Gamma-aminobutyric acid type A; $GABA_B$: Gamma-aminobutyric acid type B; GlyR: Glycine receptor; DPPX: Dipeptidiyl-peptidase-like protein 6; MOG: Myelin Oligodendrocyte Glycoprotein; GFAP: Glial fibrillary acidic protein; SPS: Stiff-person syndrome; PERM: Progressive encephalomyelitis with rigidity and myoclonus; EPC: Epilepsia partialis continua; SCLC: Small Cell Lung Cancer; ADEM: Acute disseminated encephalomyelitis; MDEM: Multiphasic acute disseminated encephalomyelitis; ON: optic neuritis; TM: Transverse myelitis; NMOSD: Neuromyelitis optica spectrum disorders; MS: Multiple Sclerosis.

3. BACKGROUND AND STUDY AIMS

The role of neuroinflammation is increasingly recognized in triggering or sustaining epileptic activity. Over the last decades, a growing number of antineuronal autoantibodies have been discovered and associated with various neurologic syndromes with epilepsy [*Toledano & Pittock, 2015*]. In particular, the identification of these antibodies in patients with epilepsy of so far unknown etiology and the increasing knowledge on these immune-mediated disorders has provided new insights into the relationship between neuroinflammation, autoimmunity, and seizure triggering, giving rise to the concept of "autoimmune epilepsy" [*Bien & Holtkamp., 2017; Geis et al., 2019*]. On these bases, the latest 2017 International League Against Epilepsy (ILAE) classification of the epilepsies defined "epilepsy of immune etiology" referring to those epilepsies resulting "directly from an immune disorder in which seizures are a core symptom of the disorder… with evidence of autoimmune-mediated central nervous system inflammation" [*Scheffer et al., 2017*].

Identifying of an underlying autoimmune etiology for seizures is of paramount importance for management and associated outcomes, as these patients could be refractory to common antiseizure medications [ASMs], but may benefit from immunotherapy [*Toledano et al., 2014; Dubey et al., 2017; Titulaer et al., 2013*]. Recently, predictive models (Antibody Prevalence in Epilepsy and Encephalopathy [APE2] and Response to Immunotherapy in Epilepsy and Encephalopathy [RITE2] scores) based on clinical features and initial neurologic assessment may be utilized

for the selection of cases for autoimmune epilepsy evaluation and management [*Dubey et al., 2017a; Dubey et al., 2017b; Dubey et al., 2019*]

However, despite the increasing evidence in this field and progress in research interest, autoimmune epilepsy is still an under-recognized condition without standardized diagnostic and management guidelines.

This study aims to analyze the epileptic phenotypes of seizures of autoimmune etiology, assessing their clinical presentation, seizure semiology, and associated paraclinical findings. Treatment options, management, and overall outcomes were also provided.

4. METHODS

4.1. Study design and setting

We performed a retrospective observational cohort study over 10 years period (from 2010 to 2020). This is a nationwide study, which was carried out in 34 Italian epilepsy centers being part of the network of high expertise centers of the Italian League Against Epilepsy [LICE].

The primary endpoint was the characterization of the epileptic phenotype, and secondary endpoints addressed treatment options and outcomes.

We selected patients who fulfilled the following inclusion criteria: (1) new-onset epilepsy, with seizures as a presenting or prominent symptom, and (2) an autoimmune etiology suspected on the basis of clinical presentation, cerebrospinal fluid [CSF] findings consistent with inflammation (elevated CSF protein > 50 mg/dl,

and/or lymphocytic pleocytosis > 5 cell/dl, IEF oligoclonal bands intrathecal synthesis), brain MRI abnormalities fitting with inflammation (T2/FLAIR hyperintensities restricted to one or both mesial temporal lobes, or multifocal in grey matter, white matter, or both), and/or (3) detection of antineuronal antibody in serum and/or CSF.

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

4.2. Study setup and data collection

All medical charts and reports of selected patients were carefully reviewed. Demographic data and clinical information were collected in a dataset, and for each patient, we recorded: current age, gender, family and personal history for neurological and autoimmune diseases, tumor diagnosis in the last 5 years, and previous prodromal symptoms. We also analyzed the age at onset, seizure type and frequency, the occurrence of episodes of status epilepticus, and frequency and quality of other associated symptoms at onset and during follow-up. Paraclinical findings comprising CSF analysis, EEG, and neuroimaging characteristics at diagnosis and follow-up were reviewed. Timing of treatment and regimens with ASMs and/or immunomodulatory agents were also evaluated.

We applied the APE2 score [*Dubey et al., 2017a; Dubey et al., 2017b; Dubey et al., 2019*] as a useful tool for identifying patients in whom antineuronal antibody profiles may be negative, estimating the likelihood of an autoimmune etiology in these cases.

The APE2 score of the entire cohort was assigned in a blind and prospective manner by two Authors (SM, TG) to further reduce selection bias. Among patients who received immunotherapy, the RITE2 score was also assessed.

All paired serum and CSF samples were analyzed for an antibodies panel performed with fixed and live cell-based assays (CBAs), tissue-based assays, and immunoblot with standardized procedures and according to experts guidelines [*Ricken et al., 2018*], in order to investigate the presence of antineuronal antibodies.

High levels of thyroid peroxidase [TPO] antibodies (> 200 IU/ml) were not considered as part of the antibody search in the inclusion criteria due to the lack of specificity of this antibody for antibody-mediated encephalitis [*Olmez et al., 2013; Mattozzi et al., 2020*].

Testing for subtypes of anti-voltage-gated potassium channels [VGKCc] antibodies (such as anti-leucine-rich glioma-inactivated protein1 [LGI1] anti-contactin-associated protein 2[Caspr2]) was not available at the time of first observation for a subgroup of patients. Patients who resulted positive for VGKCc antibodies, but in whom LGI1 and Caspr2 antibody testing was negative, were not considered in the antibody-positive group for further analysis due to their low specificity [*van Soderen et a., 2016; Graus & Gorman, 2016*].

Furthermore, only patients with high serum titer (> 20 nmol/L) of anti-glutamic acid decarboxylase 65 antibody [GAD65] or CSF detection were considered of neurologic specificity [*Dubey et al., 2017*].

Response to treatment with ASMs and/or immunotherapy was defined in terms of seizure freedom, a significant reduction (> 50%), or no changes in seizure frequency. Moreover, the overall clinical improvement was defined as complete or nearly complete resolution of associated symptoms, or persisting impairment in neurological functioning.

4.3. Statistics

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

Univariate analyses for categorical variables were performed applying Chi Square and Fisher exact test, while the assessment of normative distribution of independent variables was performed by independent T test and non-normative data were analyzed using Mann-Whitney U test.

A multivariate regression model was utilized to compare variables significant by univariate analyses. A p-value ≤ 0.05 was considered statistically significant.

Data were analyzed using STATA/IC version 15.

5. RESULTS

5.1. Demographics

During the 10 years study period, a total of 306 cases were identified based on selection criteria.

Forty-three patients were subsequently excluded due to missing clinical and paraclinical details.

Overall, we enrolled 263 patients, with a current median age of 55 years (interquartile range [IQR] 28-70; range 4-86), 138 (52.47%) were female. The median age at seizure onset was 48 years (IQR 20-65; range 2-82). At disease onset, 60 patients (22.81%) were in pediatric age (< 18 years old: median age at onset 9 years; IQR 5.5-14; range 1-17).

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

5.2. Antibody evaluation

Antineuronal antibodies were identified in 167 patients (63,50%), of which 133 (79.65%) had antibody targeting neuronal cell-surface antigens: anti-N-methyl-D-aspartate receptor [NMDAR] (n=48), anti-LGI1 (n=64), anti- Caspr2 (n=15), anti-Gamma-aminobutyric acid type A [$GABA_A$] (n=3), anti-Gamma-aminobutyric acid type B [$GABA_B$] (n=3), anti- Glycine receptor [Gly] (n=1); among those, one patient resulted positive for both LGI1 and Caspr2 antibodies. Antibody against intracellular antigens were detected in 34 patients (20.35%): anti-GAD65 (n=18), and other onconeural antibodies (5 anti-Hu, 6 anti-Ma2, 2 anti-Yo, 1 anti-amphiphysin, 3 anti-cerebellum); one patient had both LGI1 and anti-Hu antibodies.

Among the remaining cases, no antineuronal antibody was identified (n=96, 36.50%), but these patients met the inclusion criteria, 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).

In *table 1* was reported the comparison of clinical and paraclinical data between antibody-positive and antibody-negative patients.

5.3. Clinical features

According to the ILAE 2017 operational classification of seizure types, we recorded during the acute phase: generalized onset (n=15, 5.70%), focal motor onset (n=114, 43.35%), focal non-motor onset (n=107, 40.68%), focal to bilateral (n=72, 27.38%), and facio-brachial 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 (see *Table 1*), except for FBDS, which are pathognomonic of 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 not still detectable when applying a multivariate model. *Figure 1a* summarizes seizure types of the entire cohort according to the antibody findings.

Seizure semiology was multifocal (n=49, 18.63%), temporal unilateral (n=43, 16.35%), temporal bilateral (n=95, 36.12%), and extra-temporal (n=76, 28.90%), with a significant prevalence of bitemporal seizures in antibody-positive patients

(p=0.02), and extra-temporal ones in antibody-negative patients (p=0.007). However, these differences did not maintain statistical significance at the multivariate analysis. *Figure 1b* summarizes seizure semiology of the entire cohort according to the antibody findings.

The majority of patients presented a stormy seizure onset, with daily (n=176, 66.92%) or weekly (n=39, 14.83%) frequency, while in a few it was monthly (n= 22, 8.37%) or sporadic (n= 26, 9.89%). There was not a significant difference in seizure frequency between antibody-positive and antibody-negative patients. Seizures lasted seconds (n=49, 18.63%) mainly in antibody-positive patients (p=0.002), minutes (n=161, 61.22%), or were prolonged (n=53, 20.15%).

During the acute phase, 143 patients (87.73%) presented seizures which were drug-resistant 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 status epilepticus (SE) at disease onset, which was refractory in most of them (n=79, 73.83%). A higher prevalence of SE, particularly with prominent motor symptoms, was found in antibody-negative patients (p<0.001), and this significant difference was also confirmed in the multivariate regression analysis (OR 0.23, 95% CI 0.12-0.45; p<0.001). *Figure 1c* summarizes seizure frequency of the entire cohort according to the antibody findings.

Besides seizures, the acute phase of the disease was also marked by a constellation of signs and symptoms due to the autoimmune brain dysfunction and related encephalopathy in most patients (n=245, 93%). In the whole cohort, the prominent

associated symptoms were: regression (n=56, 21.29%), cognitive impairment (n=92, 34.98%), memory deficits (n=110, 41.83%), language disintegration (n=53, 20.15%), movement disorders (n=72; 27.38%), psychiatric symptoms (n=153, 58.17%), mood disorders (n=40, 15.21%), sleep disorders (n=59, 22.43%), loss of consciousness (n=19, 7.22%), dysautonomia (n=29, 11.03%), and hyponatremia (n=20, 7.60%). In the majority of antibody-positive patients, the clinical presentation mostly correlated with the full-blown encephalitis, and multiple associated symptoms were prominent in this group ($p< 0.001$). In particular, cognitive impairment, psychiatric symptoms, and sleep disorders were confirmed to be prevalent in antibody-positive patients even to the multivariate regression analysis (OR 4.70, 95% CI 2.33-9.47; OR 3.43, 95% CI 1.81-6.50; OR 5.41, 95% CI 2.16-13.52, respectively; $p<0.001$).

Figures 2 summarizes associated symptoms of the entire cohort according to the antibody findings.

5.4. 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, most prominent interictal EEG finding were diffuse slowing (n=51, 19.39%) or focal slowing (n=190, 72.24%) of the background activity, and interictal epileptiform discharges (IEDs), which could be multifocal (n=34, 12.93%), diffuse (n=10, 3.80%), temporal unilateral (n=53, 20.15%), temporal bilateral (n=85, 32.32%), or extra-temporal (n=72, 27.38%). In

particular, the bitemporal involvement was most frequent in antibody-positive patients (p=0.002), while an extra-temporal prevalence of IEDs was detected in antibody-negative patients (p=0.02). However, these 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 compatible with inflammation were detected in most (n=192, 73%). The neuroimaging alterations were: temporal unilateral (n=46, 17.49%), temporal bilateral (n=72, 27.38%), extra-temporal (n=15, 5.70%), and multifocal in grey and white matter (n=38, 14.45%). There were not significant differences in the presence or the prevalent localization of neuroimaging signal abnormalities in the two groups, antibody-positive and antibody negative.

5.5. Treatment and response

Overall, 233 patients (88.60%) received at least one form of immunotherapy combined with ASMs. They were treated after a median delay from symptom onset of 3 months (IQR 1-7; range 0.5-84), and the majority of them (n=143, 61.37%) obtained an early treatment (within 3 months). All patients received first-line treatment: one agent was administered in 102 (43.78%), two agents in 100 (42.92%), while three agents in 31 patients (13.30%). Three immunomodulatory agents were most often prescribed to antibody-positive patients (p=0.01). First-line agents used were: methylprednisolone [MPN] (n=46, 19.74%), prednisone [PDN] (n=24, 10.30%), immunoglobulins [IVIg] (n=24, 10.30%), MPN and IVIg combined (n=79,

33.90%), plasma exchange [PLEX] (n=8, 3.43%), MPN and PLEX (n=15, 6.43%), PLEX followed by IVIg (n=6, 2.5%), and MPN, PLEX and IVIg (n=31, 13.30%). Second-line treatment was administered in 28 patients (12%), most often with antibody-positive findings (p=0.02). Second-line agents administered were: rituximab [RTX] (n=16, 6.86%), cyclophosphamide [CYC] (n=10, 4.29%), RTX and CYC (n=2, 0.85%).

The interval between disease onset and immunotherapy initiation, and treatment protocols with first- or second-line agents did not differ significantly between antibody-positive and antibody-negative patients when performing a multivariate model.

Maintenance immunotherapy was administered to 171 patients (73.40%), and it lasted a median time of 6 months (IQR 6-10; range 3-27), without detectable differences in regimes between antibody-positive and antibody-negative patients. Most common agents prescribed as maintenance treatment were: PDN (n=104, 60.81%), azathioprine [AZA] (n=12, 7.02%), mycophenolate mofetil [MFM] (n= 5, 2.92%), IVIg (n=11, 6.43), PDN and AZA combined (n=12,7.02%), PDN and IVIg (n=21, 12.28%), and other treatments as methotrexate, infliximab, or adalimumab in selected patients (n=6, 3.50%) already affected by other autoimmune diseases. *Figures 3 (a, b) and 4 (a, b)* summarize the use of immunotherapy agents in the whole study cohort.

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.

Table 2 summarizes the comparison between responders and non-responders patients of all disease-related factors.

Neither seizure type, semiology, frequency, paraclinical findings at disease onset, nor first- 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 favorable outcome (p<0.001), and the prevalence of drug-resistant epilepsy at onset in non-responder patients was also confirmed at multivariate analysis (OR 0.39, 95% CI 0.20-0.76; p=0.006). Otherwise, independent predictors of a favorable response to immunotherapy were the detection of antineuronal surface antibodies (OR 2.38; 95% CI 1.15-4.92; p=0.01) and early initiation of immunotherapy (OR 12.08, 95% CI 5.50-26.50; p<0.001).

In the whole cohort, 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 onset an overall prevalence of drug-resistant seizures was 54.37% (n=143), and the most commonly ASMs prescribed were: levetiracetam [LEV] (n=171, 65.01%), benzodiazepine [BZP] (n=88, 33.46%), lacosamide [LCM] (n=73, 27.75%), carbamazepine [CBZ] (n= 72, 27.37%), sodium valproate [VPA] (n= 26.23%), phenytoin [PHT] (n=47, 17.87%), phenobarbital [PB] (n=39, 14.82%), oxcarbazepine [OXC] (n=26, 9.88%),

lamotrigine [LTG] (n=19, 7.22%), perampanel [PER] (n=11, 4.18%), zonisamide [ZNS] (n=8, 3.04%), pregabalin [PGB] (n=3, 1.14%), gabapentin [GBP] (n=2, 0.76%), vigabatrin [VGB] (n=2, 0.76%), primidone [PRM] (n=2, 0.76%), rufinamide [RUF] (n=1, 0.38%), ethosuximide [ETS] (n=1, 0.38%); 2 patients (0.76%) underwent implantation of vagus nerve stimulation [VNS], and 1 (0.38%) was on ketogenic diet [KD]. *Figure 5* summarizes ASMs prescription in the whole cohort. A better response in association with immunotherapy was reported for CBZ (6 patients), LEV (3 patients), LTG (2 patients), VPA (2 patients), and LCM (1 patient). Thirty patients (11.40%) received ASMs alone. These patients had a less severe clinical presentation, and 12 initially responded to symptomatic therapy. Among patients who had an initial favorable response to ASMs, the most commonly prescribed drugs were: LEV (8/12), CBZ (2/12), and VPA (2/12). Seven of them resulted positive for antibody search: 1 NMDAR, 1 $GABA_B$, 2 LGI1, and 3 onconeuronal antibodies, but 4 of them underwent disease relapse after the initial favorable response.

5.6. Outcomes

Relapses were reported in 22 patients (8.37%) during the observational period, without a significant difference in antibody-positive and antibody-negative patients, and 59% of them (n=13) regained seizure freedom after a trial of immunotherapy. At the end of follow-up, chronic epilepsy was reported in 115 patients (43.73%), with a prevalence in antibody-negative patients (p<0.001). Ninety-four patients (81.73%)

also had associated symptoms, including neuropsychological deficits and psychiatric disorders.

Disease-related factors associated with a poor outcome and persisting seizures as sequelae of the autoimmune encephalitis were: at least one episode of status epilepticus at disease onset (57/115 vs 50/115; p=0.007), drug-resistant epilepsy at onset (78/115 vs 65/115; p<0.001), the median number of ASMs prescribed during the acute phase (p<0.001), multiple associated symptoms at onset (p=0.01), longer time in immunotherapy initiation (p<0.001), initiation of immunotherapy after 3 months from disease onset (59/115 vs 31/115; p<0.001), and detection of intracellular antibodies (77/115 vs 53/115; p<0.001). When performing the multivariate regression analysis, independent predictors for the development of chronic epilepsy were: higher number of ASMs prescribed during the acute phase (OR 1.75, 95% CI 1.26-2.44; p=0.001), immunotherapy initiation after 3 months (OR 0.13, 95% CI 0.05-0.28; p<0.001), and the presence of intracellular antibodies (OR 0.29, 95% CI 0.13-0.63; p=0.002).

Other sequelae in terms of cognitive deficits and psychiatric symptoms were detected in further 87 patients (33.07%) who did not develop chronic epilepsy after the recovery from the autoimmune process. No independent predictors were detected to be significantly associated with this poor outcome.

6. CONCLUSIONS

The increasing recognition of an autoimmune basis of epilepsies and the broad spectrum of autoimmune encephalitis with predominant epileptic seizures has raised

interest in scientific and clinical epileptology, opening a new field with challenging issues in diagnosis and management. Despite the detection of antineuronal antibodies may be responsible for a small proportion of epilepsies, the identification of such cases is of paramount importance because many patients may benefit of immunotherapy and have a favorable prognosis.

Epileptic seizures in autoimmune encephalitis may present in patients at any age. These patients most often present with new-onset seizures drug-resistant to common ASMs, along with subacute progressive cognitive decline and behavioral and psychiatric dysfunction [*Geis et al., 2019; Titulaer et al., 2013; Thompson et al., 2018; Dubey et al., 2018*].

Although there is a substantial overlap among different autoimmune encephalitis in terms of clinical presentation and paraclinical findings, some clinical features and EEG or MRI characteristics may suggest the antigen [*Spatola & Dalmau 2017; Bien & Holtkamp 2017*]. For instance, FBDS are very specific of LGI1-encephalitis, and although detected in a subset of patients only, their prompt recognition may provide a window of treatment before the development of the full-blown limbic encephalitis [*van Soderen et al., 2016; Thompson et al., 2018*]. The extreme delta brush EEG pattern can be present in a subset of patients with anti-NMDAR-encephalitis and be associated with a more protracted disease course [*Schmitt et al., 2012*]. Extensive multifocal cortical and subcortical brain MRI abnormalities occur in the majority of patients with anti-$GABA_A$-encephalitis but seldom occur in other autoimmune encephalitis [*Petit-Pedrol et al., 2014; Spatola et al., 2017*].

Our study adds better characterization of the epilepsy-related findings, confirming the known clinical features of definite autoimmune encephalitis, and describing the phenotypic spectrum of possible and probable forms. We found a predominant involvement of the temporal regions in patients harboring antineuronal antibodies compared to 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 involvement in seizure activity does not represent an independent predictor of antibody detection. No specific seizure semiology was found to be related to antibody-positivity, with the exception of FBDS, and epileptic seizures mostly occur as one of the key symptoms in a broad clinical spectrum of associated signs and symptoms.

In this cohort, epileptic seizures were the main presenting and prominent feature and an inclusion criteria, we did not assess the overall prevalence of seizures in autoimmune encephalitis in general or in antibody-related subgroups.

Our study aims to point out some clinical diagnostic characteristics that increase clinical suspicion for an autoimmune etiology, including high seizure frequency sometimes with storming onset and episodes of SE in a previous healthy subject, multiple seizure types, and a high prevalence of drug-resistance to most common prescribed ASMs. Of interest, the higher prevalence of episodes of SE in antibody-negative patients**,** which also usually leads to a less favorable prognosis in these cases, could reflect the underlying pathogenetic mechanisms more connected to inflammation per se than to a specific antibody-related pathway [*Gaspard et al.,*

2018]. However, antibody-negative findings should prompt further investigations and improvement in experimental techniques since the prevalent rate of SE in the antibody-negative subgroup could simply reflect an antibody-related mechanism so far undiscovered.

This study also highlights the importance to assess deeper not only clinical and electrographic aspects but also the association with peculiar symptoms of brain dysfunction, which should lead to early clinical suspicion and diagnostic work-up. About one-third of the patients, although having clinical, electrographic, radiological, and CSF findings consistent with autoimmune etiology, even without detection of antibody positivity, could reflect a yet undetermined array of neuronal antibodies that could result in autoimmune epilepsy.

We emphasize to consider an underlying autoimmune cause of new-onset seizures based on the overall clinical presentation including EEG, MRI, CSF, and laboratory findings; moreover, the careful assessment by mean of all paraclinical tools can also help to differentiate autoimmune etiology from other causes.

Our study confirms the significance of early diagnosis and prompt immunotherapy, which may potentially limit the extent of neurological disability [*Toledano et al., 2014; Dubey et al., 2017; Titulaer et al., 2013*].

Nowadays, there are no current guidelines for choice of agent, length of treatment, or indications for switching to a second agent, although increasing expert opinions are rising up. Practice varies widely between individual physicians, and it is usually based on personal expertise and clinical context. The initiation of immunotherapy

remains a challenge concern for clinicians in cases of drug-resistant seizures with suspected autoimmune etiology, mainly in those cases in which the antibody search is negative or non-specific [*Dubey et al., 2017; Toledano et al., 2014; Titulaer et al., 2013*].

Even in our cohort, early immunotherapy has been proven to be a pivotal independent predictor of response and outcome. In this regard, negative results to the antibody panel should not preclude consideration of immunotherapy in an appropriate context. Furthermore, in some cases, the decision to treat may be guided by disease severity, and immunotherapy should be eventually started even to support the diagnosis of an autoimmune cause of seizures in "grey cases".

A favorable response to an immunotherapy drug trial not only supports an autoimmune etiology but may also justify considerations of long-term maintenance immunotherapy [*Toledano et al., 2014*].

Another independent predictor of response to immunotherapy and a favorable outcome is the detection of antineuronal surface antibodies, as already pointed out in literature [*Dubey et al., 2017; Bozzetti et al., 2020*].

Previous reports [*Dubey et al., 2017; Dalmau & Graus, 2018*] have also demonstrated the response to immunotherapy may vary depending on the type of antibody that reflect different form of CNS inflammation. Indeed, patients harboring intracellular antibodies most often fail to respond to immunotherapy due to the intrinsic pathogenetic mechanism of these antibodies.

Epileptic seizures occurring in autoimmune encephalitis are typically refractory to conventional ASMs therapy in most patients. However, in selected cases, ASMs could be effective alone in controlling seizures. According to literature data [*Feyissa et al., 2017*], in our cohort, sodium channel blockers ASMs resulted in seizure response in a few cases.

Some studies have demonstrated potential effects on humoral immune responses of some ASMs [*Beghi & Shorvon, 2011; Gomez et al., 2014*]. In this regard, CBZ and VPA have been shown to increase the serum levels of IL-1β, IL-2, IL-4, IL-6, IL-17, and tumor necrosis factor-alpha (TNFα). Nevertheless, so far, no single ASM stands out for a major immune-modulating role than others, and further tailored studies are warranted to elucidate deeper possible immunomodulatory properties of some ASMs.

Symptomatic treatment with ASMs remains of a pivotal role in the management of these patients during the acute and the recovery phase, cause in some, seizure relapse may occur even after the encephalitis is solved. On the other hand, 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 [*Britton & Dalmau, 2019*]. Indeed, the ongoing symptomatic treatment at long-term should be debatable and reserved to those cases with clear evidence of the development of chronic epilepsy.

Some authors [*Spatola & Dalmau, 2017; Geis et al., 2019; de Bruijn 2019, Steriade et al 2020*]. have recently argued against the definition of "autoimmune epilepsy" referring to epilepsy with an autoimmune origin [Fisher et al., 2017; *Scheffer et al.,*

2017] during the acute phase of the encephalitis, reserving it to those patients who develop chronic epilepsy after the encephalitis has been resolved.

In our series, 43.73% of patients develop epilepsy at long-term follow-up, associated with other neuropsychological and psychiatric sequelae in 81.73% of them. No clinical and paraclinical findings detected during the acute phase may predict the outcome, with the exception of a more severely compromised neurological status at the onset, with drug-resistant seizures, refractory SE, and multiple comorbidities also due to the overall complex management of those cases. In this regard, a more difficult to treat epilepsy at onset could predict a poorer outcome.

Besides epilepsy, encephalopathy or other associated symptoms contributes to significant morbidity and may impact long-term outcomes. In our cohort, the detection of multiple associated symptoms at the onset negatively influences the outcome, even though this factor does not represent an independent predictor.

There are some limitations associated with the retrospective design of this study concerning data collection and analysis. Some autoimmune epilepsy patients could have been missed, and the number of autoimmune cases is likely to be underestimated, mostly of those who do not have a 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 etiology are of paramount importance and significantly associated with better overall clinical outcome [*Dubey et al., 2017; Dubey et al., 2018; Toledano et al., 2014; Titulaer et al., 2013; Thompson et al., 2018*].

Future prospective studies will be necessary 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 an autoimmune etiology could be associated with other symptoms of brain dysfunction and, in such case, could remain under-assessed and under-recognized. Antibody-negative patients and cases in whom seizures may be associated only with subtle signs of encephalitis represent important, but challenging clinical groups.

This study provides Class IV evidence for management recommendations.

An autoimmune etiology represents a rare chance in seizures management, and an early treatment at the pathogenic level may reduce the risk of irreversible sequelae at the long-term.

Figure 1a.: Seizure types according to the antibody findings.

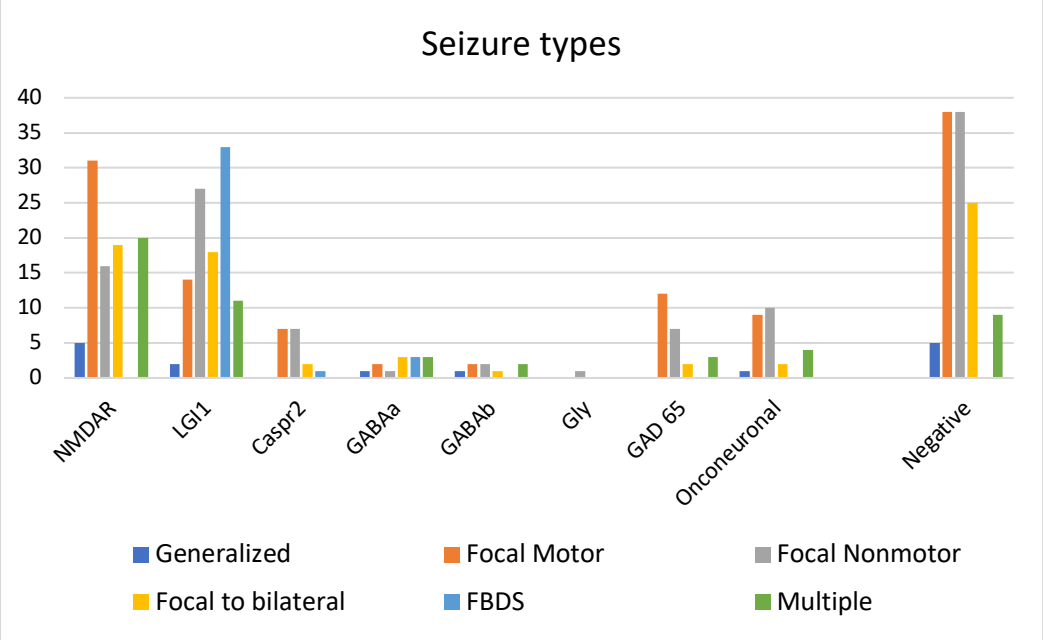


Figure 1b.: Seizure semiology according to the antibody findings.

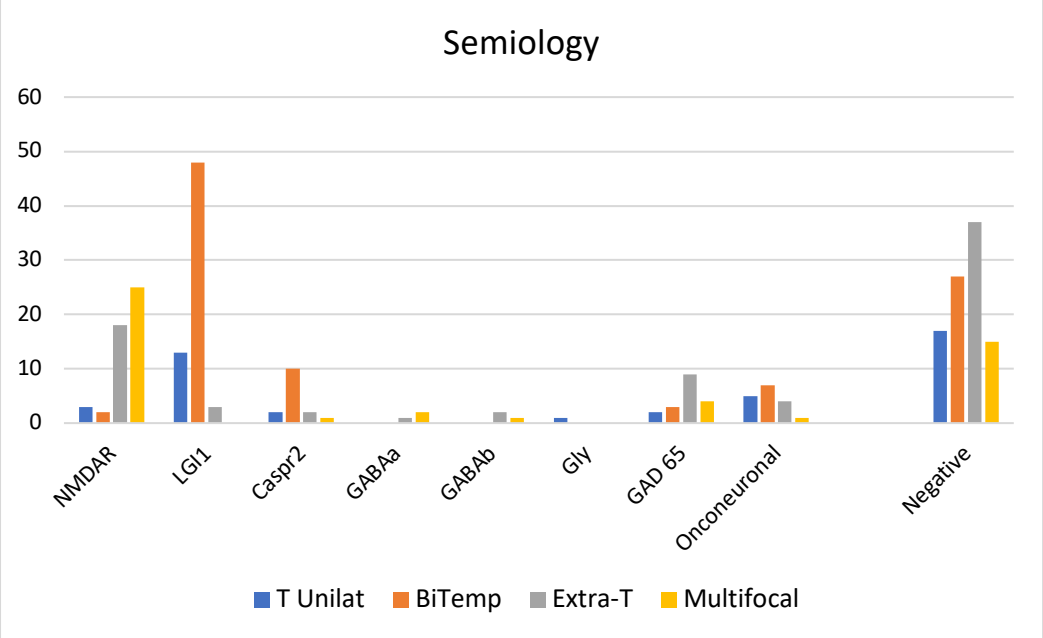
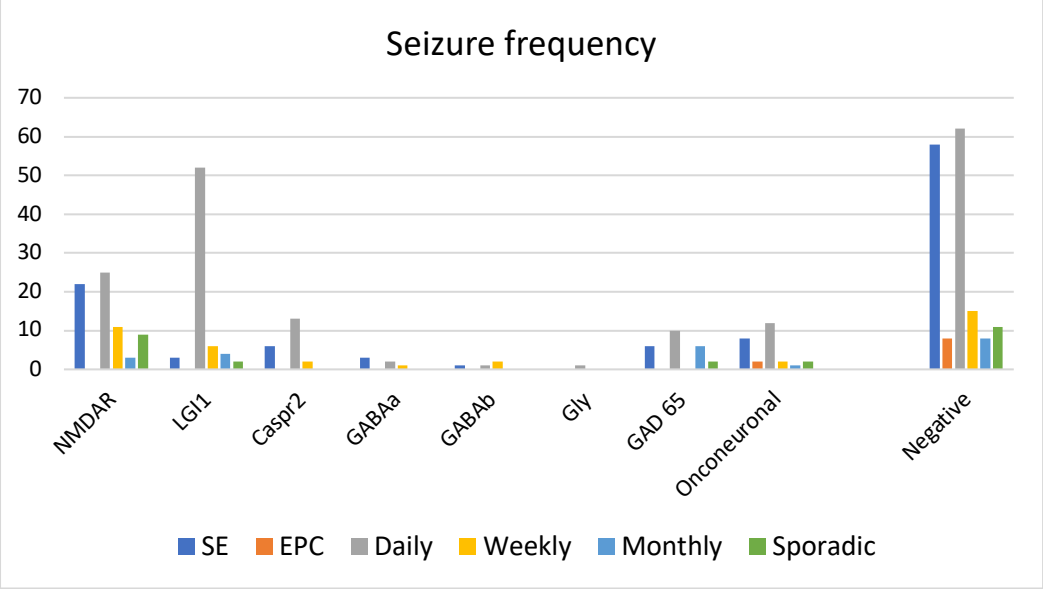
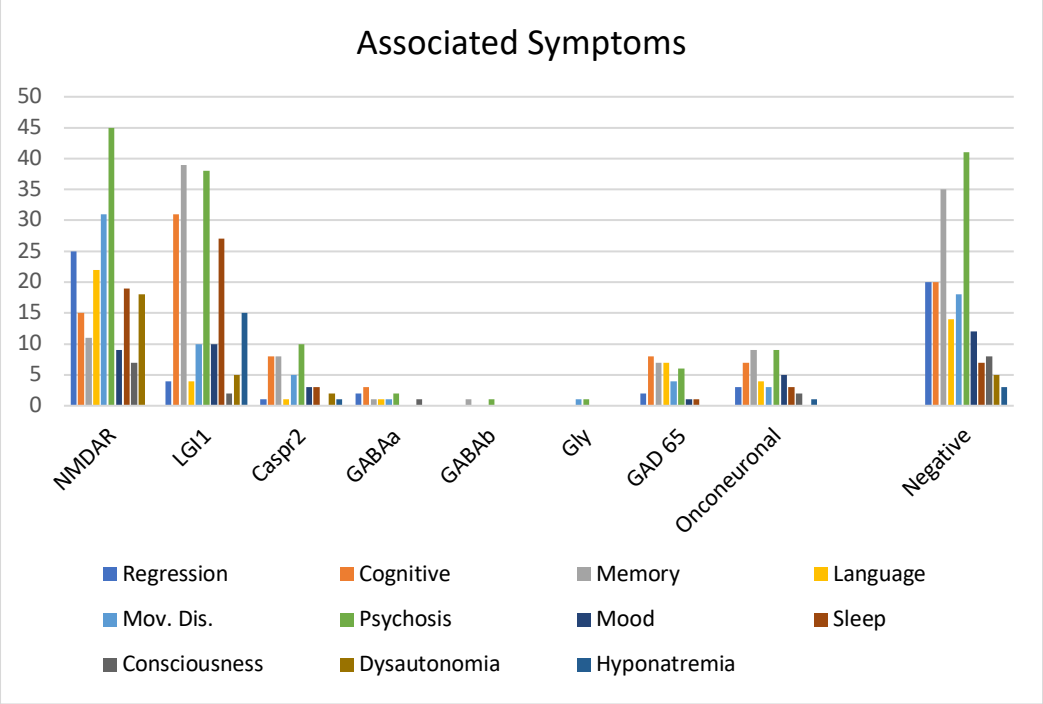


Figure 1c. Seizure frequency according to the antibody findings.



Figures 2: Associated symptoms 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.

Figure 3a.: Immunotherapy in responders according to the antibody findings

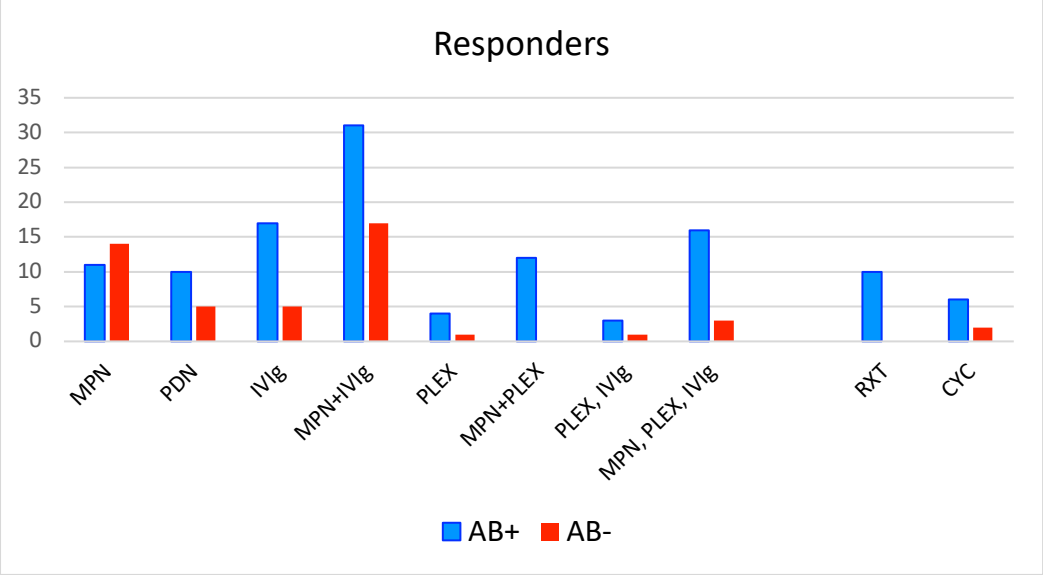
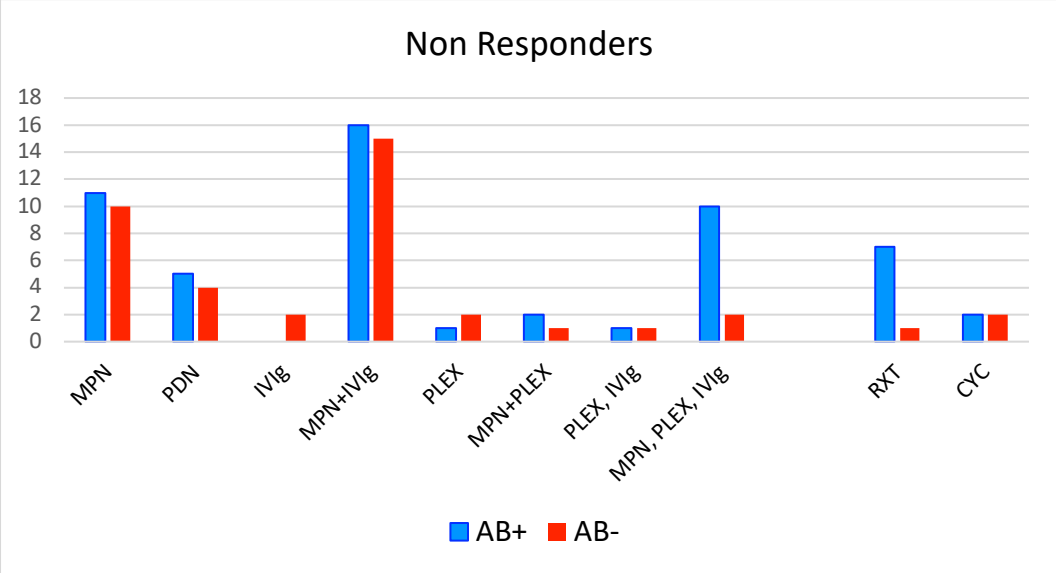


Figure 3b.: Immunotherapy in non-responders according to the antibody findings



MPN: methylprednisolone; PDN: prednisone; IVIg: immunoglobulins; PLEX: palsma exchange; RTX: rituximab;CYC: cyclophosphamide.

Figure 4a: Maintenance therapy in responders according to the antibody findings

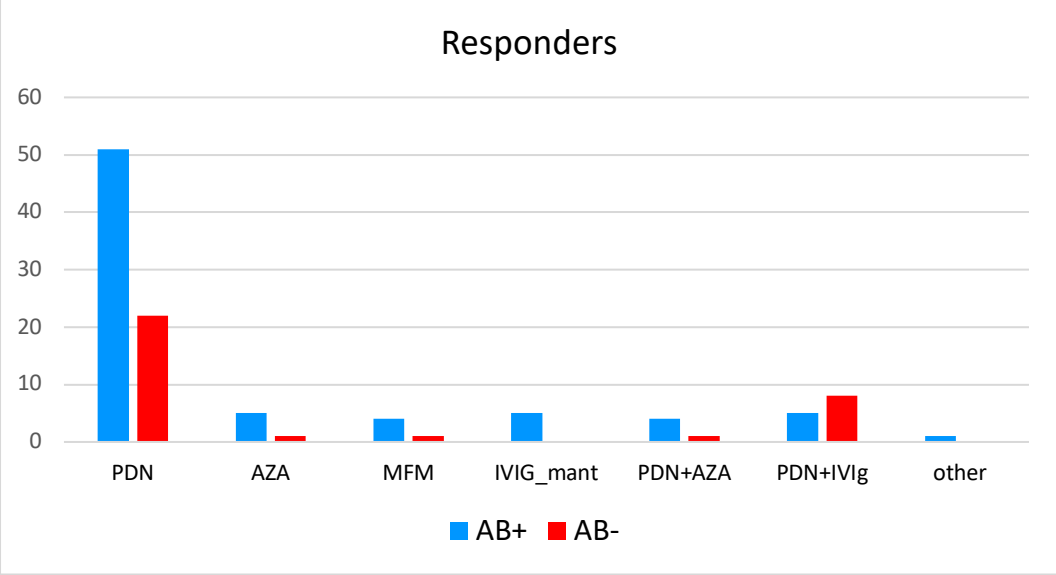
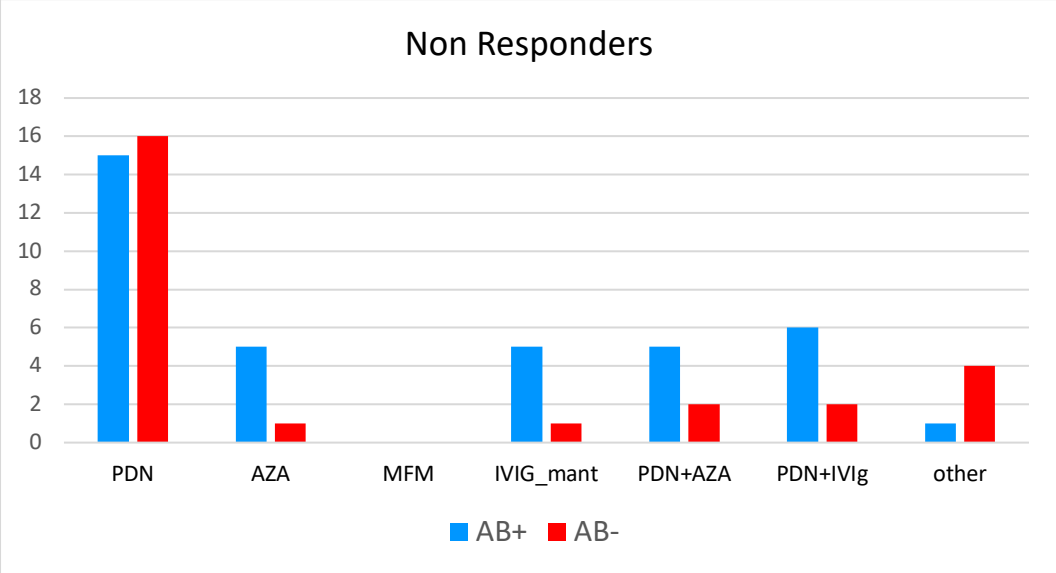
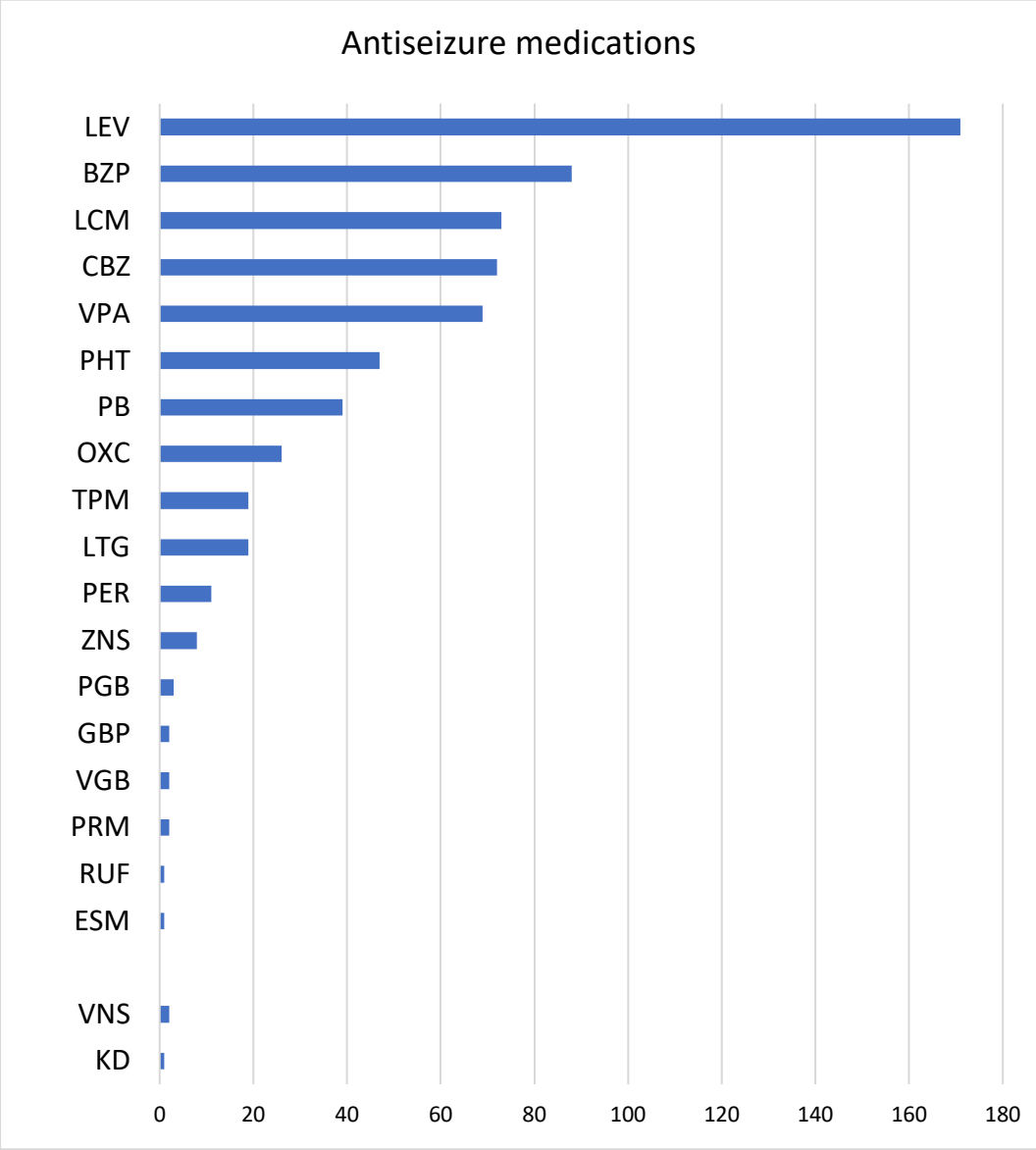


Figure 4b: Maintenance therapy in non-responders according to the antibody findings



PDN: prednisone; AZA: azathioprine; MFM: mycophenolate mofetil

Figure 5: 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.

Table 1: 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]
Family history			
• Neurologic diseases, N (%)	17 (10.18%)	13 (13.54%)	0.26[b]
• Epilepsy, N (%)	7 (4.19%)	5 (5.21%)	0.46[b]
• Autoimmune diseases, N (%)	11 (6.59%)	10 (10.42%)	0.19[b]
Personal history			
• Neurologic diseases, N (%)	30 (17.96%)	10 (10.42%)	0.07[b]
• Epilepsy, N (%)	4 (2.4%)	0 (0%)	0.16[b]
• Autoimmune diseases, N (%)	29 (17.37%)	13 (13.54%)	0.26[b]
• Tumor within 5 years, N (%)	28 (16.77%)	12 (12.50%)	0.22[b]
• Prodromal symptoms, N (%)	31 (18.56%)	29 (30.21%)	**0.02[b]**
APE2 score	7 (IQR 5-9, range 2-13)	6 (IQR 4-7, range 3-12)	**0.0002[a]**
APE2 score ≥ 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 ≥ 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]**
Seizure frequency			
• Daily, N (%)	114 (68.26%)	62 (64.58%)	0.31[b]
• Weekly, N (%)	24 (14.37%)	15 (15.62%)	0.45[b]
• Monthly, N (%)	14 (8.38%)	8 (8.33%)	0.59[b]
• Sporadic, N (%)	15 (8.98%)	11 (11.46%)	0.32[b]
Seizure duration			
• Seconds, N (%)	40 (23.95%)	9 (9.38%)	**0.002[b]**
• Minutes, N (%)	99 (59.28%)	62 (64.58%)	0.23[b]
• Prolonged, N (%)	28 (16.77%)	25 (26.04%)	0.05[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	162 (97.1%)	83 (86.46%)	**0.002[b]**

onset, N (%)			
Median number of associated symptoms	3 (IQR: 2-4; range: 0-8)	2 (IQR: 1-3; range: 0-6)	**< 0.001[a]**
• Regression, 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 disintegration, N (%)	39 (23.35%)	14 (14.58%)	0.06
• Movement disorders, N (%)	54 (32.34%)	18 (18.75%)	**0.01[b]**
• Psychiatric 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]**
CSF findings			
• CSF alteration consistent with inflammation, N (%)	92 (55.09%)	52 (54.17%)	0.49[b]
• CSF cell count >5 cells/dl, N(%)	48 (28.74%)	22 (22.92%)	0.18[b]
• CSF protein > 50 mg/dl, N (%)	54 (32.34%)	26 (27.08%)	0.22[b]
• CSF Specific OCB >4, N (%)	44 (26.35%)	26 (27.08%)	0.5[b]
Interictal EEG findings			

• Preserved Background, N (%)	16 (9.58%)	6 (6.25%)	0.24[b]
• Diffuse slowing, N (%)	29 (17.37%)	22 (22.92%)	0.17[b]
• Focal slowing, N (%)	122 (73.05%)	68 (70.83%)	0.40[b]
• 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,	150 (89.82%)	83 (86.46%)	0.26[b]

N (%)			
• 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]
Relapses, N (%)	17 (10.18%)	5 (5.21%)	0.11[b]
Chronic epilepsy, 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]

[a]Mann-Whitney *U*-test, [b]chi-square of Fisher's exact test,

^T2/FLAIR hyperintensity compatible with inflammation

Table 2: Comparison between responders and non-responders patients among those 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]
Family history			
• Neurologic diseases, N (%)	15 (10.42%)	12 (13.48%)	0.30[b]
• Epilepsy, N (%)	5 (3.47%)	6 (6.74%)	0.20[b]
• Autoimmune diseases, N (%)	8 (5.56%)	12 (13.48%)	**0.03[b]**
Personal history			
• Neurologic diseases, N (%)	17 (11.81%)	17 (11.81%)	0.06[b]
• Epilepsy, N (%)	1 (0.69%)	3 (3.37%)	0.15[b]
• Autoimmune diseases, N (%)	14 (9.72%)	22 (24.72%)	**0.002[b]**
• Tumor within 5 years, N (%)	20 (13.89%)	14 (15.73%)	0.41[b]
• Prodromal symptoms, N (%)	33 (22.92%)	21 (23.60%)	0.51[b]
Antibody findings			
• Antibody positive, N (%)	98 (68.06%)	52 (58.43%)	0.09
• Antineuronal surface antibody, N (%)	87 (60.42%)	35 (39.33%)	**0.001[b]**

• GAD65, N (%)	5 (3.47%)	11 (2.36%)	**0.01[b]**
• Onconeuronal antibody, N (%)	6 (4.17%)	7 (7.87%)	0.18[b]
APE2 score	7 (IQR 5-9, range 2-13)	6 (IQR 5-8, range 2-11)	0.11[a]
APE2 score ≥ 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 ≥ 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]
Seizure frequency			
• Daily, N (%)	101 (70.14%)	55 (61.80%)	0.12[b]
• Weekly, N (%)	19 (13.19%)	18 (20.22%)	0.10[b]
• Monthly, N (%)	11 (7.64%)	9 (10.11%)	0.33[b]
• Sporadic, N (%)	13 (9.03%)	7 (7.87%)	0.48[b]
Seizure duration			

• Seconds, N (%)	31 (21.53%)	11 (12.36%)	0.05[b]
• Minutes, N (%)	83 (57.64%)	63 (70.79%)	**0.03[b]**
• Prolonged, N (%)	30 (20.83%)	15 (16.85%)	0.28[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]**
• Regression, 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 disintegration, N (%)	33 (22.92%)	18 (20.22%)	0.37
• Movement disorders, N (%)	47 (32.64%)	20 (22.47%)	0.06[b]
• Psychiatric 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]**
CSF findings			
• CSF alteration consistent	80 (55.56%)	48 (53.93%)	0.45[b]

with inflammation, N (%)			
• CSF cell count >5 cells/dl, N(%)	45 (31.25%)	19 (21.35%)	0.06[b]
• CSF protein > 50 mg/dl, N (%)	40 (27.78%)	30 (33.71%)	0.20[b]
• CSF Specific OCB >4, N (%)	41 (28.47%)	41 (28.47%)	0.46[b]
Interictal EEG findings			
• Preserved Background, N (%)	8 (5.56%)	6 (6.74%)	0.45[b]
• Diffuse slowing, N (%)	34 (23.61%)	13 (14.61%)	0.06[b]
• Focal slowing, N (%)	102 (70.83%)	70 (78.65%)	0.12[b]
• 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	2 (IQR: 1-3;	3 (IQR: 2-4;	**<0.001[b]**

acute phase	range 0-8)	range 0-12)	
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]**
Relapses, N (%)	11 (7.64%)	10 (11.24%)	0.24[b]
Seizure freedom at last available follow-up, N (%)	118 (81.94%)	15 (16.85%)	**<0.001[b]**
Other Symptoms freedom at last follow-up, N (%)	50 (34.72%)	21 (23.60%)	0.05[b]

[a]Mann-Whitney *U*-test, [b]chi-square of Fisher's exact test,

^T2/FLAIR hyperintensity compatible with inflammation

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