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Seizures in autoimmune encephalitis: specific features based on a systematic comparative study

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ABSTRACT

Objective. To highlight specific characteristics of seizure semiology and EEG features associated with different subtypes of autoimmune encephalitis (AE).

Methods. We systematically reviewed the seizure semiology and all the EEG recordings from patients with AE managed in a tertiary referral centre for epilepsy and a neuro-intensive care unit. Each characteristic across the different subtypes of AE was compared by post hoc analysis.

Results. We identified 66 patients with anti-neuronal antibody-mediated AE or Rasmussen's encephalitis (RE) experiencing seizures, which were the most frequent symptom at onset. Anti-NMDAR and anti-LGI1 AE accounted for the majority of patients; 41% and 24%, respectively. We isolated specific semiological features, such as early tonic-clonic seizures (TCS) in anti-NMDAR AE, early mesial temporal lobe seizures with emotional symptoms in anti-GAD AE, somatosensory seizures in RE, and a lower frequency of TCS in anti-LGI1 AE. EEG analysis also provided additional insights into distinguishing the subtypes based on: (1) generalized rhythmic delta activity, which was more sensitive than extreme delta brush in identifying anti-NMDAR AE among all subtypes; and (2) temporal interictal epileptiform activity and temporal seizures on EEG in anti-GAD AE. We identified a new EEG pattern consisting of temporal low-voltage and periodic spikes associated with ipsilateral hippocampal abnormalities on MRI, which could be a sign of inflammatory mesial temporal involvement.

Significance. Specific clinical and EEG features can be useful in guiding the diagnosis of a subtype of AE with acute symptomatic seizures, particularly before the results of anti-neuronal antibody testing are available.

Key words: autoimmune diseases, epilepsy, electroencephalography, anti-neuronal antibodies

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Temporal lobe seizures with acute or subacute onset associated with memory impairment and psychiatric and behavioural disorders have long been considered as highly suggestive of autoimmune encephalitis (AE) [1, 2]. These features are actually related to limbic encephalitis and do not reflect clinical presentations of extra-limbic encephalitis, which are increasingly reported [3]. In addition, some patients have isolated seizures at onset, which could make the diagnosis difficult [4]. Delayed diagnosis should

be prevented by a better understanding of the clinical spectrum of AE.

As seizures are frequent in AE and often occur in the early stage of the disease, they constitute a key element of the diagnostic procedure [5, 6]. Some features may suggest an underlying autoimmune disorder, such as acute or subacute onset, high seizure frequency at onset, new-onset refractory status epilepticus or drug resistance [7, 8]. In addition, seizure semiology may differ according to the type of anti-neuronal antibodies and could help to identify a particular subtype of AE [7].

Although temporal lobe seizures are reported in most subtypes of AE, their prevalence is highly heterogeneous. Mesial temporal lobe seizures (MTLS) are frequent in encephalitis associated with glutamic acid decarboxylase (GAD) antibodies and voltage-gated potassium channel (VGKC) complex antibodies (leucine-rich glioma-inactivated 1 [LGI1] and contactin-associated protein-like 2 [CASPR2]) [3, 7, 9-11]. In contrast, extra-limbic involvement leads to a highly varied seizure semiology. Faciobrachial dystonic seizures (FBDS) in LGI1-antibody encephalitis and epilepsia partialis continua in Hu-antibody encephalitis and Rasmussen's encephalitis highlight the motor cortex involvement in AE [12-22]. However, although some subtypes of AE have a specific – and sometimes even pathognomonic – seizure semiology, it is difficult to guide the diagnosis using only clinical features.

EEG features provide additional support to identify an AE and its subtype. Specific patterns were reported, such as extreme delta brush (EDB) and generalized rhythmic delta activity (GRDA) in N-methyl-D-aspartate receptor (NMDAR) antibody encephalitis, or the frontal slow wave preceding FBDS in LGI1-antibody encephalitis [12, 13, 23-27]. Apart from these specific features, common abnormalities (*e.g.* temporal and extra-temporal epileptiform activity) were also reported [28]. No systematic comparison of all EEG features between the different subtypes of AE has been undertaken.

Seizure semiology and EEG features have been described per subtype or based on a combination of different subtypes of AE [28-34]. A systematic comparative analysis of these features between the different subtypes of AE has never been reported. This would help to determine in which subtypes some clinical and EEG features are more prevalent, to guide diagnosis before results of antineuronal antibodies testing are available – and even if they are negative [35] –, in order to reduce delay in diagnosis and allow for earlier consideration of immunomodulatory drugs. In this study, we aimed to compare the specific characteristics of seizure semiology and EEG abnormalities between the different AE subtypes.

Methods

Patient selection

We screened all patients admitted to either the epilepsy unit or the neuro-intensive care unit of the Pitié-Salpêtrière Hospital (Paris, France), between January, 2006 and May, 2019, for a suspected central nervous system inflammatory disorder (*supplementary figure 1*). We selected patients with a confirmed AE defined by: (1) possible AE [35] and positive cell-surface or onconeuronal antibodies; or (2) Rasmussen's encephalitis [20]. Only patients with at least one clinical and/or electrical epileptic seizure were included.

We included Rasmussen's encephalitis in order to obtain a wider range of seizures associated with AE subtypes, whether they were antibody-mediated or T cell-mediated, and independently of the different time courses of the diseases. In addition, the clinical presentation of Rasmussen's encephalitis in adults is more heterogeneous than in children, and should therefore be included among the AE subtypes.

Data collection

We collected the clinical characteristics during the course of the encephalitis, and more specifically during the early phase (within four weeks after the first symptoms) and the late phase (after the first four weeks) of disease from medical reports. Symptoms suggestive of MTLS were sudden fear or anxiety, dreamy state, *déjà-vu* feeling or autonomic symptoms such as ascending epigastric, palpitations or flushing. CSF white blood cell count, protein and IgG synthesis were also collected.

All available EEG recordings (588 EEGs over at least 20 minutes and 111 consecutive days of continuous EEG monitoring in seven patients) were reviewed (LC) and compared to the previous interpretation (VL, VHNM, VF); in case of discrepancy, a third independent review was performed (VN).

All brain MRI was reviewed by an experienced neuroradiologist (NS).

Antibody identification

Detection of anti-neuronal antibodies was assessed in serum and/or cerebrospinal fluid samples (CSF) using

indirect immunofluorescence, ELISA (Euroimmun®, Germany) and cell-based assays [13]. Anti-neuronal antibody panels included: anti-GAD, anti-Yo, anti-Hu, anti-Ri, anti-CV2, anti-Tr, anti-LGI1, anti-CASPR2, anti-gamma-aminobutyric acid type B ($GABA_B$) receptor, anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid type 1 and 2 (AMPA1 and AMPA2) receptor and anti-NMDAR antibodies.

Statistical analysis

All statistical analyses were performed using R Statistical Software (version 3.6.1; https://www.r-project.org).

We conducted post hoc analyses using pairwise Fisher's exact test for comparisons of seizure semiology and EEG features between subtypes of AE. We used McNemar's test to compare seizure frequency between early and late phases of disease in each subtype. Only subtypes with a sufficient number of patients ($n \geq 5$) were analysed. All p values were adjusted for multiple comparisons using Benjamini-Hochberg procedure. Significant results that became insignificant after adjustment are indicated with an asterisk (*).

In order to compare the frequency of the different symptoms at onset, a generalized linear mixed model with binomial distribution and logit link was performed with symptom occurrence as dependent variable, type of symptoms (seizures, psychiatric disorders, cognitive impairment, movement disorders, vigilance impairment and dysautonomia) as fixed effect, and patient ID as random effect. All post hoc comparisons were estimated. The same approach was used to compare the frequency of abnormalities on diagnostic examinations (brain MRI, CSF analysis and EEG) with the occurrence of abnormalities as dependent variable, type of examination as fixed effect, and patient ID as random effect.

To compare GRDA and EDB on EEG, in order to identify NMDAR-antibody encephalitis, we tested whether the Youden index was different between the two methods (*i.e.* GRDA and EDB) using permutation tests. One thousand permuted samples were constructed by random permutations between values from both methods. The Youden index difference between both methods was then calculated on the permuted samples to estimate the distribution of this indicator under the null hypothesis that GRDA and EDB would lead to similar values. The observed Youden index difference in the raw data was compared to the estimated distribution in order to compute the p value.

Ethics

This study was conducted according to French legislation and authorized by the CNIL committee (No. 2211991). Patients were informed about the use of their anonymized data in this study.

Results

Study patients

Among 153 patients with suspected AE, we identified 84 patients with confirmed AE; 70 (83.3%) had at least one epileptic seizure, and a detailed description of seizures was available for 66 of these patients.

Our cohort included nine AE subtypes: patients with anti-NMDAR (n=27, 40.9%), anti-LGI1 (n=16, 24.2%), anti-GAD antibodies (n=8, 12.1%), Rasmussen's encephalitis (n=8, 12.1%), anti-Hu (n= 2), anti-VGKC (without anti-LGI1/CASPR2 antibodies) (n=2), anti-CASPR2 (n=1), anti-Ri (n=1) and anti-$GABA_B$R antibodies (n=1). Patients enrolled from the epilepsy unit (n=39) included two with anti-NMDAR AE, 15 with anti-LGI1 AE and all patients with anti-GAD, anti-Hu, anti-Ri, anti-CASPR2, anti-VGKC AE and with RE, while those from the neuro-ICU (n=27) included 25 with anti-NMDAR AE, one with anti-LGI1 AE and one with anti-$GABA_B$R AE. Their main characteristics are shown in *table 1*. The mean age at onset was 33.7 years (median: 26; min: 9, max: 80) and patients were predominantly female (66.7%). The mean follow-up period was 4.2 years (median: 2.3; min: 0.02, max: 16.1).

Apart from seizures, the most common symptoms were cognitive (n=55, 83.3%) and psychiatric disorders (n=44, 66.7%). CSF analysis showed an inflammatory profile (pleocytosis > 5 WBC/mm^3 and/or intrathecal IgG synthesis) in 59.1% (n=39) of patients. Brain MRI was considered pathological (atrophy and/or hyperintensity) in 65.2 % (n=43) of patients.

Specific clinical description of seizures (*table 2*)

Seizures were the most frequent symptom during the early phase (n=62, 93.9%) in comparison with cognitive impairment or psychiatric symptoms (n=35, 53% and n=37, 56.1%, respectively; all n<0.001). Antiepileptic drug-resistant seizures were reported in 71.2% of patients (n=47).

Focal motor seizures were very frequent (n=46, 69.7%), except for patients with anti-GAD AE (n=2, 25%). Clonic seizures were more suggestive of anti-NMDAR AE (n=15, 55.6%) and RE (n=4, 50%) than

▼ **Table 1.** Main clinical and biological data, therapeutics and outcome of patients.

	Total	Anti-NMDAR	Anti-LGI1	Anti-GAD	RE	Anti-Hu	Anti-VGKC*	Anti-CASPR2	Anti-Ri	Anti-$GABA_BR$
	n=66	*n*=27	*n*=16	*n*=8	*n*=8	*n*=2	*n*=2	*n*=1	*n*=1	*n*=1
Demographic characteristics										
Age at onset, mean (SD), min.-max., years	33.7 (±20.6), 9-80	25 (8.5), 14-41	58.9 (16.9), 21-79	24.5 (13.6), 14-48	18.8 (9.1), 9-34	14.5 (0.7), 14-15	37 (33.9), 13-61	30	80	19
Female, *n* (%)	44 (66.7)	22 (81.5)	5 (31.3)	7 (87.5)	5 (62.5)	2 (100)	1 (50)	0	1 (100)	1 (100)
Non-epileptic symptoms										
Prodromal symptoms, *n* (%)	25 (37.9)	11 (40.7)	8 (50)	3 (37.5)	1 (12.5)	1 (50)	0	0	1 (100)	0
Psychiatric symptoms, *n* (%)	44 (66.7)	25 (92.6)	8 (50)	5 (62.5)	3 (37.5)	1 (50)	1 (50)	0	0	1 (100)
Cognitive impairment, *n* (%)	55 (83.3)	27 (100)	12 (75)	7 (87.5)	4 (50)	1 (50)	2 (100)	1 (100)	0	1 (100)
Movement disorders, *n* (%)	23 (34.8)	21 (77.8)	2 (12.5)	0	0	0	0	0	0	0
Vigilance impairment, *n* (%)	12 (18.2)	11 (40.7)	1 (6.3)	0	0	0	0	0	0	0
Dysautonomia, *n* (%)	22 (33.3)	21 (77.8)	1 (6.3)	0	0	0	0	0	0	0
Cerebrospinal fluid analysis										
Pleocytosis (> 5 WBC/mm^3), *n* (%)	27 (40.9)	23 (85.2)	2 (12.5)	0	0	0	0	0	1 (100)	1 (100)
Elevated CSF protein (> 0.45g/L), *n* (%)	24/65 (36.9)	8/26 (30.8)	8 (50)	3 (37.5)	3 (37.5)	0	0	1 (100)	1 (100)	0
Intrathecal IgG synthesis, *n* (%)	23/58 (39.7)	10/20 (50)	0	6 (75)	4 (50)	2 (100)	0	0	1 (100)	NA
Blood tests										
Hyponatraemia related to SIADH, *n* (%)	8 (12.1)	0	7 (43.8)	0	0	0	0	0	1 (100)	0
Antinuclear antibodies (≥ 1/160), *n* (%)	16/56 (28.6)	5 (18.5)	5/15 (33.3)	2/6 (33.3)	1/5 (20)	1 (50)	2 (100)	0	NA	0
Positive anti-Tg antibodies, *n* (%)	8/34 (23.5)	5/13 (38.5)	1/7 (14.3)	1/6 (16.7)	0/2	0	1 (50)	0	NA	0
Positive anti-TPO, *n* (%)	6/37 (16.2)	5/14 (35.7)	0/8	1/6	0/3	0	0	0	NA	0
Brain MRI										
T2w-FLAIR hyperintensities, *n* (%)	39 (59.1)	11 (40.7)	9	6 (75)	8 (100)	2 (100)	1 (50)	1 (100)	1 (100)	0
Mesial temporal lobe, *n* (%)	26 (39.4)	4 (14.8)	10 (62.5)	6 (75)	2 (25)	1 (50)	1 (50)	1 (100)	1 (100)	0
Unilateral, *n* (%)	15 (22.7)	2 (7.4)	7 (43.8)	2 (25)	2 (25)	0	1 (50)	0	1 (100)	0
Bilateral, *n* (%)	11 (16.7)	2 (7.4)	3 (18.8)	4 (50)	0	1 (50)	0	1 (100)	0	0
Other locations, *n* (%)	18 (27.3)	8 (29.6)	0	0	8 (100)	1 (50)	0	0	1 (100)	0
Hippocampal atrophy, *n* (%)	16 (24.2)	4 (14.8)	7 (43.8)	2 (25)	3 (37.5)	0	0	0	0	0
Antiepileptic drugs										
Maximum number of antiepileptic drugs, mean (SD), min.-max.	2.6 (1.2), 1-6	2.3 (1), 1-5	1.9 (1), 1-5	2.4 (1.2), 1-4	4.3 (1), 3-6	3.5 (0.7), 3-4	2.5 (0.7), 2-3	2	5	3

▼ **Table 1.** Main clinical and biological data, therapeutics and outcome of patients (*continued*).

	Total	Anti-NMDAR	Anti-LGI1	Anti-GAD	RE	Anti-Hu	Anti-VGKC*	Anti-CASPR2	Anti-Ri	Anti-$GABA_BR$
	n=66	*n*=27	*n*=16	*n*=8	*n*=8	*n*=2	*n*=2	*n*=1	*n*=1	*n*=1
Immunomodulatory and immunosuppressive drugs										
Number of lines of therapy, mean (SD), min.-max.	1.9 (0.8), 0-3	2.3 (0.7), 1-3	1.3 (0.7), 0-3	2.1 (0.8), 1-3	1.6 (0.7), 1-3	2 (1.4), 1-3	2 (1.4), 1-3	1	1	1
Preventive maintenance treatment, *n* (%)	15 (22.7)	8 (29.6)	2 (12.5)	2 (25)	1 (12.5)	0	1 (50)	0	0	1 (100)
Evolution										
Follow-up, median, years	2.4	1.9	3.1	3.45	9.1	6.7	5.1	2.2	6.3	1.9
Complete remission, *n* (%)	36 (54.5)	20 (74.1)	14 (87.5)	0	0	0	0	1 (100)	0	1 (100)
Relapse, *n* (%)	5 (7.6)	3 (11.1)	1 (6.3)	1 (12.5)	0	0	0	0	0	0
No recovery, *n* (%)	25 (37.9)	4 (14.8)	1 (6.3)	7 (87.5)	8 (100)	2 (100)	2 (100)	0	1 (100)	0
Hospitalization in ICU, *n* (%)	32 (48.5)	21 (77.8)	3 (18.8)	0	4 (50)	1 (50)	1 (50)	0	1 (100)	1 (100)
Death[1], *n* (%)	6 (9.1)	3 (11.1)	1 (6.3)	0	0	0	1 (50)	0	1 (100)	0
Paraneoplastic syndrome										
Associated neoplasia[2], *n* (%)	10 (15.2)	8 (29.6)	1 (6.3)	0	0	0	0	0	1 (100)	0
Thymic hyperplasia, *n* (%)	4 (6.1)	0	0	1 (12.5)	1 (12.5)	2 (100)	0	0	0	0

*Anti-VGKC-complex seropositive patients without anti-LGI1/CASPR2 antibodies.
[1]Death was caused by sepsis-associated acute respiratory distress syndrome (*n*=3), cardiac arrest due to autonomic dysfunction (*n*=1), persistent vegetative state and palliative care (*n*=1) and complications associated with intensive care support (*n*=1).
[2]Associated neoplasia included ovarian teratomas (*n*=8 with anti-NMDAR AE), thyroid cancer (*n*=1 with anti-LGI1 AE) and breast adenocarcinoma (*n*=1 with anti-Ri AE).

anti-LGI1 AE (*n*=0; *p*=0.004 and *p*=0.007*, respectively). Myoclonic seizures were only described in RE (*n*=3, 37.5%) and anti-Hu AE (*n*=1, 50%). Brief FBDS were exclusively reported in anti-LGI1 AE (*n*=15, 93.8%; *p*<0.01 for all).

MTLS were found in 34.8% (*n*=23) of patients. These symptoms were more frequent in anti-GAD (*n*=8, 100%) and anti-LGI1 AE (*n*=9, 56.3%) than in anti-NMDAR AE (*n*=2, 7.4%; *p*< 0.05 for all) or RE (*n*=0; *p*=0.006 and *p*=0.05, respectively). During the early phase, sudden anxiety or fear – as MTLS symptoms – tended to be more suggestive of anti-GAD AE (*n*=4, 50%) than anti-LGI1 AE (*n*=1, 6.3%, *p*=0.03*).

Somatosensory seizures were only reported in RE (*n*=7, 87.5%; *p*<0.05 for all).

Bilateral tonic-clonic seizures (TCS) with an unknown onset were more prevalent in anti-NMDAR AE (*n*=23, 85.2%) than in anti-LGI1 AE (*n*=3, 18.8%; *p* = 0.002), RE (*n*=1, 12.5%; *p*=0.009) or anti-GAD AE (*n*=3, 37.5%; *p*=0.02*). TCS in anti-NMDAR AE became considerably less frequent during the late phase than during the early phase of the disease (from 85.2% to 18.5%; *p*=0.002).

Focal or generalized status epilepticus occurred in 40.9% of patients (*n*=27), mostly with anti-NMDAR AE or RE.

Specific EEG features (*table 3, figure 1*)

At least one EEG with pathological findings was recorded in 60 patients (90.9%). Pathological findings were more frequently identified on EEG than on either brain MRI (atrophy or hyperintensity in 65.2 % of patients; *p*<0.005) or CSF analysis (inflammatory profile in 59.1% of patients; *p*<0.005).

Slowing of background activity was more frequent in patients with anti-NMDAR AE (*n*=21, 77.8%) than in other patients (*p*=0.02 for all).

▼ Table 2. Specific semiology of seizures.

	Anti-NMDAR (&)	Anti-LGI1 ($)	Anti-GAD (§)	RE(#)	Anti-Hu	Anti-VGKC*	Anti-CASPR2	Anti-Ri	Anti-$GABA_BR$
	n=27	*n*=16	*n*=8	*n*=8	*n*=2	*n*=2	*n*=1	*n*=1	*n*=1
Focal-onset seizures, *n* (%)	18 (66.7) ($)	16 (100) (&)	8 (100)	8 (100)	2 (100)	2 (100)	1 (100)	1 (100)	1 (100)
Motor, *n* (%)	16 (59.3) $	16 (100) &§	2 (25) $(#)	7 (87.5) (§)	1 (50)	1 (50)	1 (100)	1 (100)	1 (100)
Clonic, *n* (%)	15 (55.6) $(§)	0 &(#)	1 (12.5) (&)	4 (50) ($)	0	1 (50)	0	1 (100)	0
Myoclonic, *n* (%)	0 (#)	0 (#)	0	3 (37.5) ($&)	1 (50)	0	0	0	0
Dystonic, *n* (%)	1 (3.7) $	15 (93.8) &§#	0 $	1 (12.5) $	1 (50)	0	0	0	1 (100)
Faciobrachial dystonic seizures, *n* (%)	0 $	15 (93.8) &§#	0 $	0 $	0	0	0	0	0
Manual automatisms, *n* (%)	0 (§)	1 (6.3)	2 (25) (&)	1 (12.5)	0	0	1 (100)	0	0
Tonic, *n* (%)	0 (#)	0	0	2 (25) (&)	0	0	0	0	0
Versive, *n* (%)	2 (7.4)	1 (6.3)	0	3 (37.5)	0	0	0	1 (100)	0
Sensory, *n* (%)	1 (3.7) #(§)	1 (6.3) #	3 (37.5) (&)	7 (87.5) &$	1 (50)	0	0	0	0
Somatosensory, *n* (%)	0 #	0 #	0 #	7 (87.5) &$§	1 (50)	0	0	0	0
Olfactory, *n* (%)	1 (3.7)	1 (6.3)	2 (25)	0	0	0	0	0	0
Visual, *n* (%)	0	0	0	1 (12.5)	0	0	0	0	0
Auditory, *n* (%)	0	0	1 (12.5)	0	0	0	0	0	0
Cognitive, *n* (%)	2 (7.4) §($)	6 (37.5) (&§)	7 (87.5) &($#)	1 (12.5) (§)	1 (50)	1 (50)	0	1 (100)	0
Déjà-vu feeling or memory impairment, *n* (%)	0 $§	6 (37.5) &	6 (75) &(#)	0 (§)	1 (50)	1 (50)	0	1 (100)	0
Dreamy state, *n* (%)	1 (3.7)	0	1 (12.5)	0	0	1 (50)	0	0	0
Aphasic, *n* (%)	1 (3.7)	0	1 (12.5)	1 (12.5)	0	0	0	0	0
Emotional: Anxiety or fear, *n* (%)	1 (3.7) (§)	2 (12.5)	4 (50) (&)	0	1 (50)	0	0	0	0
Autonomic, *n* (%)	1 (3.7) $§	7 (43.8) &	5 (62.5) &(#)	0 (§)	1 (50)	1 (50)	1 (100)	0	0
Impaired awareness, *n* (%)	10 (37)	4 (25) (#)	4 (50)	6 (75) ($)	0	1 (50)	1 (100)	1 (100)	1 (100)
MTLS, *n* (%)	2 (7.4) $§	9 (56.3) &(#)	8 (100) &#	0 §($)	1 (50)	1 (50)	1 (100)	1 (100)	0
Bilateral tonic-clonic seizures, *n* (%)	25 (92.6) $	4 (25) &(#)	5 (62.5)	6 (75) ($)	1 (50)	0	1 (100)	0	1 (100)
Identified focal onset, *n* (%)	5 (18.5) (#)	1 (6.3)	2 (25)	5 (62.5) (&)	1 (50)	0	0	0	1 (100)
Unknown onset, *n* (%)	23 (85.2) $#(§)	3 (18.8) &	3 (37.5) (&)	1 (12.5) &	0	0	1 (100)	0	0
Status epilepticus, *n* (%)	13 (48.1) $(§)	3 (18.8) &#	0 #(&)	7 (87.5) $§	1 (50)	1 (50)	0	1 (100)	1 (100)
Focal, *n* (%)	7 (25.9) ($)	1 (6.3) #(&)	0 (#)	5 (62.5) $(§)	1 (50)	1 (50)	0	1 (100)	0
Epilepsia partialis continua, *n* (%)	0 (#)	0 (#)	0	3 (37.5) ($&)	1 (50)	0	0	0	0
Other, *n* (%)	7 (25.9)	1 (6.3)	0	2 (25)	0	1 (50)	0	1 (100)	0
Generalized convulsive, *n* (%)	8 (29.6)	1 (6.3)	0	3 (37.5)	0	0	0	0	1 (100)

Post hoc comparisons were conducted between anti-NMDAR, anti-LGI1, anti-GAD AE and RE.
The following signs indicate significant difference between AE subtypes: &: subtype differs from anti-NMDAR AE; $: subtype differs from anti-LGI1 AE; §: subtype differs from anti-GAD AE; #: subtype differs from RE.
Signs in parentheses indicate significant results before the Benjamini-Hochberg procedure, but not after.
*Anti-VGKC-complex seropositive patients without anti-LGI1/CASPR2 antibodies.
MTLS: mesial temporal lobe seizures.

Diffuse delta waves were more prevalent in anti-NMDAR AE (*n*=24, 88.9%) than in other subtypes ($p<0.01$ for all), and were often characterized by a generalized rhythmic delta activity (GRDA). Interestingly, GRDA was more effective than EDB in identifying patients with anti-NMDAR AE among all patients (sensitivity=0.67, specificity=0.97, Youden index=0.64 versus sensitivity=0.41, specificity=1, Youden index=0.41; $p=0.03$).

Unilateral focal slowing, especially in frontal lobes, and frontal interictal epileptiform activity were significantly more frequent in RE (*n*=7, 87.5% and *n*=5, 62.5%) than in anti-NMDAR (*n*=2, 7.4%; $p<0.05$ for all) and anti-LGI1 AE (*n*= 1, 6.3%; $p=0.01$ and *n*=0; $p=0.05$). Temporal interictal epileptiform activity and seizures tended to be more frequent in patients with anti-GAD AE (*n*=5, 62.5% and *n*=4, 50%) than in patients with anti-NMDAR (*n*=2, 7.4%; $p=0.003$* and *n*=2, 7.4%; $p=0.02$*) and anti-LGI AE (*n*=4, 25%; $p=0.09$* and *n*=2, 12.5%; $p=0.03$*). Frontal slow waves preceding FBDS were only recorded in patients with anti-LGI1 AE (*n*=11, 68.8%; $p<0.05$ for all).

Low-voltage periodic spikes

We identified an unusual pattern in four patients (anti-LGI1 AE, *n*=2; anti-Hu AE, *n*=1; anti-GAD, *n*=1) consisting of unilateral temporal low-voltage (<50 µV) repetitive (over a period of 300-1,000 ms) spikes. While a single sequence was observed in one patient (anti-GAD AE), periodic spikes were consistently identified for the three other patients, along their successive EEG (*figure 2*). Sequences of periodic spikes showed various durations sometimes in the same patient (few seconds to several minutes),and increased during lower vigilance stages. All these patients experienced clinical MTLS. Besides, low-voltage periodic spikes (LVPS) were always associated with ipsilateral hippocampal abnormalities on MRI (*figure 2*). Hippocampal T2-weighted (T2w) fluid-attenuated inversion recovery (FLAIR) hyperintensity (without associated atrophy on T1-weighted sequences) and LVPS were concurrently highlighted in three patients – two of whom subsequently developed a hippocampal sclerosis and persistent LVPS. Hippocampal sclerosis and LVPS were concomitantly observed in the fourth patient, and no EEG was available before the diagnosis of hippocampal sclerosis.

Relationship with MRI features

Symptoms suggestive of MTLS and temporal seizures on EEG were more frequent in patients with mesial temporal lobe (MTL) T2w-FLAIR hyperintensity on MRI (*n*=16/26, 61.5% and *n*=9/26, 34.6%) than in patients without MTL hyperintensity (*n*=7/40, 17.5%; $p=0.01$ and *n*=1/40, 2.5%, $p=0.02$). Interestingly, patients with MTL hyperintensity had fewer focal status epilepticus than others (3.8% vs 35% of patients; $p=0.03$) and less frequently diffuse delta waves on EEG (23.1% vs 62.5%; $p=0.03$).

Myoclonus, tonic seizures and focal motor status epilepticus were more common in patients with frontal hyperintensity on MRI than others (*n*=3/7, 42.9% vs *n*=1/59, 1.7%, $p=0.01$; *n*=3/7, 42.9% vs *n*=16/59, 27.1%, $p=0.04$; and *n*=6/7, 85.7% vs *n*=9/59, 15.3%, $p=0.005$, respectively). Frontal interictal activity and seizures on EEG tended to be more frequent in patients with frontal hyperintensity (*n*=4/7, 57.1% and *n*=3/7, 42.9%) than others (*n*=7/59, 11.9%, $p=0.01$* and *n*=4/59, 6.8%, $p=0.02$*).

Relationship with CSF analysis

While bilateral TCS were more frequent in patients with pleocytosis (*n*=24/27, 88.9%, $p=0.009$), MTLS were less common (*n*=4/27, 14.8%, $p=0.04$). EEG features suggestive of anti-NMDAR AE (slowing of background activity, diffuse delta waves, GRDA) were also more often reported in patients with pleocytosis (all $p=0.001$).

No association was found between other CSF findings (elevated protein or IgG synthesis) and clinical or EEG features.

Discussion

Our study highlights that seizures, when reported, often occur early during the course of AE. Moreover, EEG more frequently showed abnormal findings than either brain MRI or CSF. Our findings underline the major contribution of seizure semiology and EEG features to the early diagnosis of AE, which can sometimes be possible before the results of anti-neuronal antibodies testing are available (see the proposed decision tree in *figure 3*).

We conducted a comparative analysis of clinical and EEG manifestations according to different subtypes of AE in order to highlight specific features that could guide the diagnosis and avoid delays. To our knowledge, this is the first systematic comparative study of seizure semiology and EEG features between different subtypes of AE.

First, our study confirmed findings from previous case reports or cohorts of a single AE subtype. Our semiological analysis corroborated some specific features, such as focal myoclonic seizures in RE and anti-Hu AE [16-21, 36], focal clonic seizures in anti-NMDA AE [37] and MTLS – including autonomic, emotional and dysmnesic symptoms – in anti-GAD and anti-LGI1 AE [9-11, 13, 14]. While all patients

▼ Table 3. Specific EEG features.

	Anti-NMDAR (&)	Anti-LGI1 ($)	Anti-GAD (§)	RE (#)	Anti-Hu	Anti-VGKC*	Anti-CASPR2	Anti-Ri	Anti-$GABA_BR$
	N=27	*N*=16	*N*=8	*N*=8	*N*=2	*N*=2	*N*=1	*N*=1	*N*=1
Number of EEG per patient, mean (SD)	8	5.5	3.5	5	8.5	10.5	4	62	7
Background slowing < 7 Hz, *n* (%)	21 (77.8) $§#	5 (31.3) &	1 (12.5) &	1 (12.5) &	1 (50)	1 (50)	0	1 (100)	1 (100)
Diffuse delta waves, *n* (%)	24 (88.9) $§#	3 (18.8) &	1 (12.5) &	0 &	1 (50)	1 (50)	0	0	1 (100)
Polymorphic, *n* (%)	16 (59.3) $#(§)	2 (12.5) &	1 (12.5) (&)	0 &	1 (50)	1 (50)	0	0	1 (100)
Monomorphic, *n* (%)	18 (66.7) $§#	1 (6.3) &	0 &	0 &	0	0	0	0	1 (100)
Generalized rhythmic delta activity, *n* (%)	18 (66.7) $§#	1 (6.3) &	0 &	0 &	0	0	0	0	0
Extreme delta brush, *n* (%)	11 (40.7) $(§#)	0 &	0 (&)	0 (&)	0	0	0	0	0
Focal slow wave activity, *n* (%)	2 (7.4) #	1 (6.3) #	3 (37.5)	7 (87.5) &$	1 (50)	1 (50)	0	1 (100)	0
Frontal, *n* (%)	0 (#)	1 (6.3)	0	3 (37.5) (&)	2 (100)	1 (50)	0	0	0
Temporal, *n* (%)	1 (3.7)	0	2 (25)	2 (25)	1 (50)	1 (50)	0	1 (100)	0
Fronto-temporal, *n* (%)	1 (3.7)	0	1 (12.5)	1 (12.5)	0	0	0	0	0
Hemispheric, *n* (%)	0	0	0	1 (12.5)	0	0	0	0	0
Interictal epileptiform activity, *n* (%)	6 (22.2) #(§)	5 (31.3) (#)	6 (75) (&)	7 (87.5) &($)	2 (100)	2 (100)	1 (100)	1 (100)	0
Frontal, *n* (%)	2 (7.4) #	0 (#)	1 (12.5)	5 (62.5) &($)	2 (100)	1 (50)	0	0	0
Temporal, *n* (%)	2 (7.4) (§)	4 (25)	5 (62.5) (&)	3 (37.5)	1 (50)	1 (50)	1 (100)	1 (100)	0
Central, *n* (%)	1 (3.7)	1 (6.3)	0	2 (25)	1 (50)	0	0	0	0
Hemispheric, *n* (%)	0	0	0	1 (12.5)	0	0	0	0	0
Multifocal, *n* (%)	1 (3.7)	0	0	0	1 (50)	0	0	0	0
Diffuse, *n* (%)	0	0	0	0	0	1 (50)	0	0	0
Seizure, *n* (%)	5 (18.5) $	14 (87.5) &(#)	4 (50)	3 (37.5) ($)	2 (100)	1 (50)	0	1 (100)	0
Focal, *n* (%)	4 (14.8) $	11 (68.8) &	4 (50)	3 (37.5)	2 (100)	1 (50)	0	1 (100)	0
Frontal, *n* (%)	2 (7.4)	1 (6.3)	0	2 (25)	1 (50)	0	0	1 (100)	0
Temporal, *n* (%)	2 (7.4) (§)	2 (12.5) (§)	4 (50) (&$)	1 (12.5)	1 (50)	0	0	1 (100)	0
Central, *n* (%)	0	0	0	1 (12.5)	0	0	0	0	0
Hemispheric, *n* (%)	0	0	0	0	0	1 (50)	0	0	0
FSW preceding FBDS, *n* (%)	0 $	11 (68.8) $§#	0 $	0 $	0	0	0	0	0
Generalized, *n* (%)	3 (11.1)	0	0	0	0	0	0	0	0
Subclinical seizure, *n* (%)	3 (11.1)	1 (6.3)	2 (25)	1 (12.5)	1 (50)	0	0	1 (100)	0

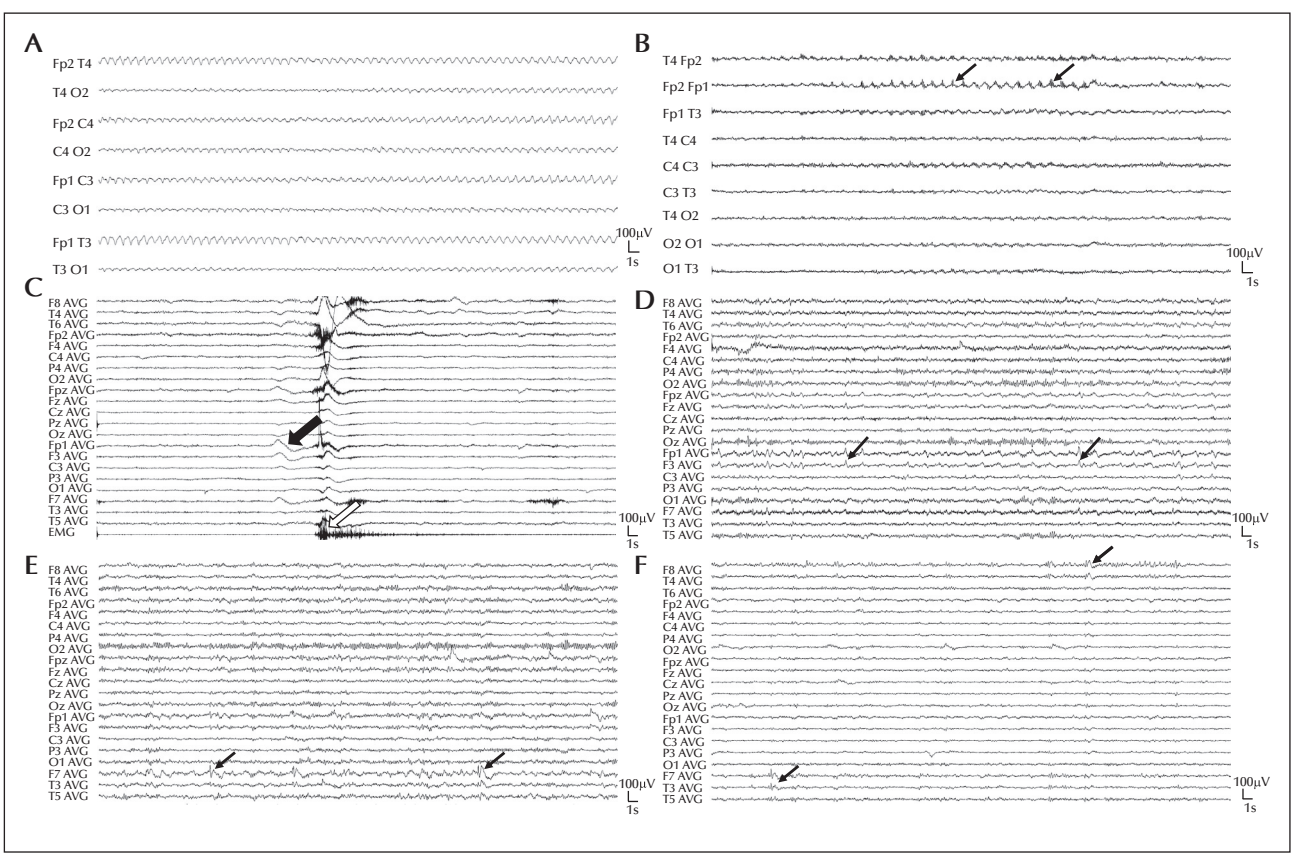
Post hoc comparisons were conducted between anti-NMDAR, anti-LGI1, anti-GAD AE and RE.
The following signs indicate significant difference between AE subtypes: &: subtype differs from anti-NMDAR AE; $: subtype differs from anti-LGI1 AE; §: subtype differs from anti-GAD AE; #: subtype differs from RE.
Signs in parentheses indicate significant results before the Benjamini-Hochberg procedure, but not after.
*Anti-VGKC-complex seropositive patients without anti-LGI1/CASPR2 antibodies.
FBDS: faciobrachial dystonic seizures; FSW: frontal slow wave.

with anti-GAD AE experienced MTLS, only half patients with anti-LGI1 AE showed such symptoms. The predominance of FBDS over MTLS in anti-LGI1 AE has already been reported [12, 13]. Besides, the EEG analysis confirmed that: (1) slowing of background activity and diffuse delta waves (particularly with GRDA and EDB) are highly suggestive of anti-NMDAR AE [23-26]; (2) FBDS preceded by a FSW are pathognomonic of anti-LGI1 AE [13, 27]; and (3) unilateral frontal slowing and interictal epileptiform activity are suggestive of RE [38].

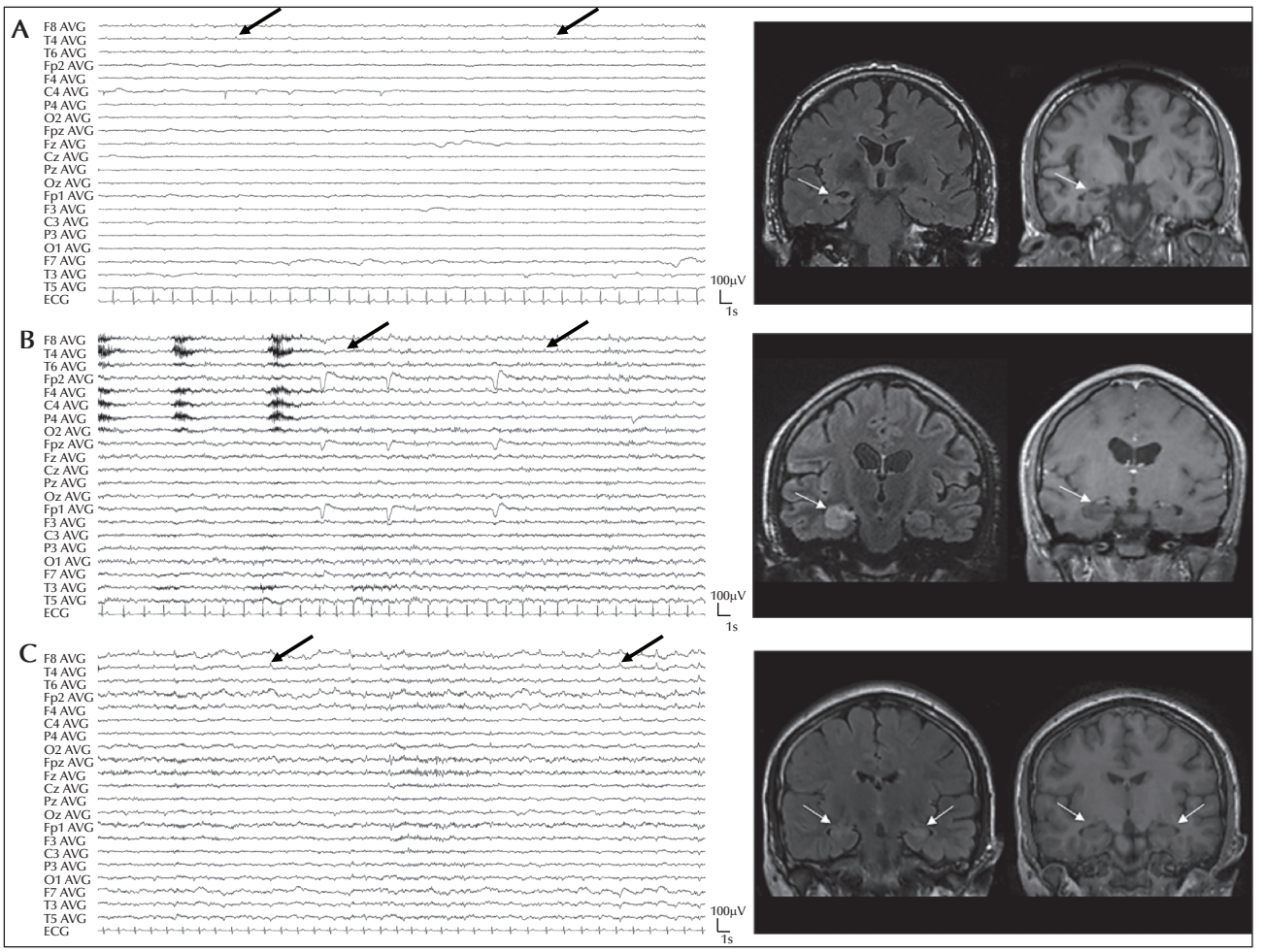
In addition, our systematic comparative approach helped to identify additional specific semiological features. Focal to bilateral TCS – particularly during the early phase – were highly suggestive of anti-NMDAR AE. MTLS with emotional symptoms (sudden fear or anxiety) during the early phase tended to be more common in anti-GAD AE and may help to distinguish anti-GAD from anti-LGI1 AE in cases of isolated MTLS. Moreover, unlike anti-LGI1 AE, patients with anti-GAD AE did not respond to immunomodulatory or immunosuppressive treatments, as reported in the literature [9, 10]. A lower frequency of TCS was also observed in anti-LGI1 AE. Somatosensory seizures were suggestive of RE.

EEG analysis also provided additional insight into distinguishing between the AE subtypes. GRDA was more sensitive than EDB in identifying anti-NMDAR AE among all patients. Patients with anti-GAD AE tended to have more frequent temporal interictal epileptiform activity and temporal seizures on EEG than the other patients.

We also identified a striking EEG pattern consisting of temporal low-voltage and periodic spikes, which were associated with clinical MTLS and ipsilateral hippocampal hyperintensity (with or without sclerosis) on MRI.



■ **Figure 1.** (A) Generalized rhythmic delta activity in anti-NMDA AE. (B) Extreme delta brush in anti-NMDA AE. (C) Left frontal slow wave (black arrow) preceding a faciobrachial dystonic seizure (muscle contraction of the right arm on electromyography; white arrow) in anti-LGI AE. D) Left frontal slowing and interictal epileptiform activity in Rasmussen's encephalitis. (E-F) Unilateral (E) and bilateral (F) temporal interictal epileptiform activity in anti-GAD AE.

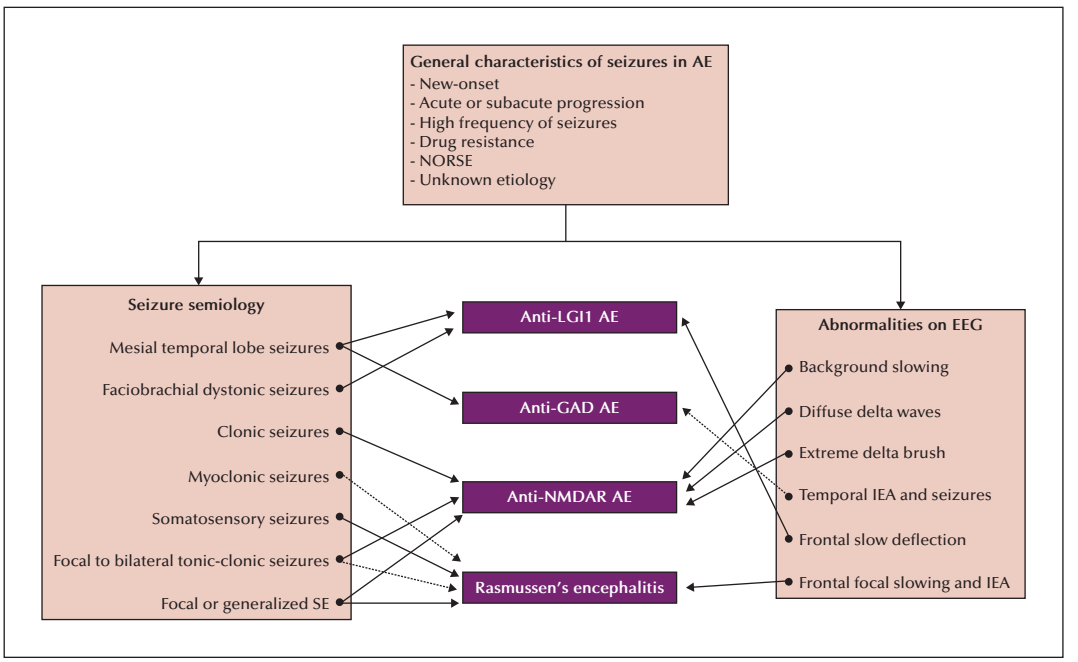


■ **Figure 2.** Unilateral temporal low-voltage (<50µV) repetitive spikes on EEG (average reference montage) were observed in patients with anti-LGI1 AE (A and B) and anti-Hu AE (C). This pattern was associated with ipsilateral hippocampal sclerosis (A), hippocampal hyperintensity and oedema (B) and hippocampal hyperintensity without sclerosis or oedema (bilateral involvement) (C) on brain MRI (coronal T2-weighted fluid-attenuated inversion recovery images on the left and coronal T1-weighted images are presented on the right for each patient).

These abnormalities could reflect the inflammatory or excitotoxic involvement of mesial temporal structures and may precede the development of hippocampal sclerosis. Of interest, this EEG finding always persisted at the stage of the hippocampal sclerosis. Although this pattern has already been reported in malformations of cortical development, especially focal cortical dysplasias, this is the first description in AE [39].

We found anatomical correlations between MRI hyperintensity and clinical or EEG features. The lower frequency of focal status epilepticus in patients with MTL hyperintensity may be explained by the smaller proportion of these radiological findings in patients with RE or anti-NMDAR AE (25% and 14.8%, respectively), in whom focal status epilepticus was mainly reported. Indeed, cortical and subcortical hyperintensity involving the perisylvian region is common in RE, while brain MRI is often normal in anti-NMDAR AE [40, 41]. Regarding the relationship between seizure semiology and CSF analysis, bilateral TCS were far more common and MTLS infrequent in patients with pleocytosis. This should be interpreted as reflecting the higher prevalence of pleocytosis among patients with anti-NMDAR AE (85.2%).

The two main subtypes of AE in our study (*i.e.* anti-NMDAR and anti-LGI1 AE) clearly had a different



■ **Figure 3.** Solid arrows highlight significant relationships between semiology, EEG characteristics and subtypes of AE. Dotted arrows indicate statistical trends. NORSE: new-onset refractory status epilepticus; SE: status epilepticus; IEA: interictal epileptiform activity.

prevalence according to care structure: anti-LGI1 AE was mainly managed in the epilepsy unit, whereas anti-NMDAR AE predominated in the neurological ICU. We did not include patients with autoantibody-negative AE, because they cannot be classified as a single group and might have heterogeneous characteristics. It would be interesting to analyse a larger cohort of autoantibody-negative patients in order to try to identify common clinical and EEG features.

Antiepileptic drug resistance was found in two thirds of patients. Several studies have already emphasized that seizures in AE are often refractory to antiepileptic drugs (AEDs) and may only respond to immunotherapy [42-45]. Therefore, several of our patients were treated by only one AED – in particular those with anti-LGI1 AE – and then by immunotherapy, because of a strongly suspected resistance to AEDs and an expected response to immunomodulatory and/or immunosuppressive medications. This could have underestimated the prevalence of antiepileptic drug resistance, which is defined as the failure of two (combined or not) AEDs.

Our study has several limits. First, as some patients were screened from an epilepsy unit database (n=39, 59.1%), the prevalence of seizures in AE is probably overestimated. On the other hand, 13.6% of patients in our cohort had subclinical seizures, suggesting that they may have been underestimated in other populations of AE and illustrating the advantages of long-term EEG monitoring [7, 26].

Second, in some AE subtypes, the number of patients was too small to perform statistical analyses, which could limit the generalizability of our findings. Nevertheless, our cohort provides an overall description of the prevalence of the different known subtypes of AE that could be seen in epilepsy and neuro-intensive care units and enabled us to refine the characteristics of the most frequent subtypes. Moreover, reports of AE subtypes with low prevalence allowed for a description of striking findings such as low-voltage periodic spikes in a patient with anti-Hu antibodies.

Third, as the delay between AE onset and the first available EEG, brain MRI or CSF analysis varied from one patient to another, we chose to report the EEG, MRI and CSF findings independently of the disease course. A longitudinal study of EEG patterns, MRI features and CSF findings would be interesting. Finally, the retrospective identification of seizure semiology may be inaccurate. However, as patients were often hospitalized in an epilepsy unit, medical reports provided rather exhaustive descriptions of seizures.

Conclusion

Our study refines the seizure semiology and EEG features of the most frequent subtypes of AE. These findings may guide clinicians in the diagnosis of a subtype of AE with acute symptomatic seizures, before the results of anti-neuronal antibody testing are available, and even if these results are negative [35]. ■

Supplementary material.
Supplementary figure and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

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TEST YOURSELF

(1) Which features are suggestive of anti-NMDAR autoimmune encephalitis (AE)?

A. Focal clonic and bilateral tonic-clonic seizures
B. Mesial temporal lobe seizures
C. Diffuse delta waves with rhythmic activity on EEG
D. Temporal interictal epileptiform activity on EEG
E. Slowing of background activity on EEG

(2) Which features are suggestive of anti-LGI1 AE?

A. Generalized myoclonic seizures
B. Faciobrachial dystonic seizures
C. Mesial temporal lobe seizures
D. Extreme delta brush on EEG
E. Unilateral frontal slowing

(3) Which of the following are true?

A. Mesial temporal lobe seizures are not common in anti-GAD and anti-LGI1 AE
B. Focal myoclonic seizures are suggestive of Rasmussen's encephalitis or anti-Hu AE
C. Temporal interictal epileptiform discharges on EEG are rarely observed in anti-GAD AE
D. Unilateral frontal slowing and interictal epileptiform discharges on EEG are suggestive of Rasmussen's encephalitis
E. Faciobrachial dystonic seizures are preceded by a frontal slow wave on EEG in anti-LGI1 AE

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.