Seizures in autoimmune encephalitis: findings from an EEG pooled analysis

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Abstract

Purpose: Seizures are common in autoimmune encephalitis (AE), and an extensive work-up is required to exclude alternative etiologies. The aim of our study was to identify possible clinical/EEG peculiarities suggesting the immune-mediated origin of late-onset seizures.

Methods: Thirty patients diagnosed with AE (19 men, median age 68 years, 18 seronegative) were included. Overall 212 video-electroencephalographic (EEG) and 31 24-h ambulatory EEG (AEEG) recordings were retrospectively reviewed. Posterior dominant rhythm, interictal epileptiform discharges (IEDs), clinical (CSs) and subclinical seizures (SCSs) were analyzed.

Results: Six-hundred-nineteen ictal events were recorded in 19/30 subjects, mostly (568/619) during AE acute stage. Among ten patients with CSs other than faciobrachial dystonic seizures, 7 showed prominent autonomic and emotional manifestations. SCSs were detected in 11 subjects, mainly via AEEG (260/287 SCSs vs 150/332 CSs, $p<0.001$). Eight patients presented seizures during hyperventilation. IEDs, documented in 21 cases, were bilateral in 14 and focal temporal in 13. Multiple ictal EEG patterns were detected in 9/19 patients, 6 of whom had both CSs and SCSs, bilateral asynchronous seizures and ictal activities arising from temporal and extra-temporal regions. No correlation was found between the lateralization of MRI alterations and that of EEG findings.

Conclusion: Our study confirms that adult-onset, high frequency focal seizures with prominent autonomic and emotional manifestations should be investigated for AE. Multiple ictal EEG patterns could represent a 'red flag', reflecting a widespread neuronal excitability related to the underlying immune-mediated process. Finally, our work enhances the crucial role of long-lasting EEG monitoring in revealing subclinical and relapsing seizures.

Keywords: autoimmune encephalitis, 24-h ambulatory EEG, late-onset epilepsy, subclinical seizures, transient epileptic amnesia, amygdala

Abbreviations: AE: autoimmune encephalitis: AED: antiepileptic drug; AEEG: 24-h ambulatory EEG; AMPAR: alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor; CASPR2: contactin-associated protein-like 2; CNS: central nervous system; CSs: clinical seizures; DRE: drug-resistant epilepsy; CSF: cerebrospinal fluid; EDE: electrodecremental event; FBDS: faciobrachial dystonic seizures; GABAR: γ-aminobutyric acid receptor; GAD65: glutamic acid decarboxylase 65; GPDs: generalized periodic discharges; HV: hyperventilation; IEDs: interictal epileptiform discharges; LGI1: leucine-rich glioma-inactivated 1; mTL: mesial temporal lobe; MTLE: mesial temporal lobe epilepsy; NCSE: non convulsive status epilepticus; NMDAR: N-methyl-D-aspartate receptor; NREM: non Rapid Eye Movement; SCSs: subclinical seizures; SOX1: SRY-Box Transcription Factor 1; SSW: sequential spike/spike-and-slow wave; TLE: temporal lobe epilepsy; VEEG: video-EEG

1. Introduction

Autoimmune encephalitis (AEs) encompasses a variable spectrum of clinical manifestations pointing to a widespread brain involvement, well beyond the limbic system alone [1]. Besides mental status alterations, cognitive deficits and behavioral/psychiatric disorders, seizures are part of the clinical core of AE [2], and often represent the most alarming and impressive sign at the disease onset, leading the patients to seek medical advice. The subacute onset of seizures, especially in elderly subjects, urges the need to investigate (and eventually rule out) numerous possible etiologies or mimics, ranging from vascular accidents and toxic-metabolic encephalopathies to neurodegenerative diseases. Although brain MRI might support AE suspicion, no abnormal findings are revealed in a significant proportion of cases, which makes a timely diagnosis extremely challenging, much more so when specific autoantibodies (against either intracellular or neuronal surface antigens) cannot be detected (the so-called "autoantibody-negative" AEs). Consequently, the diagnostic hypothesis is often made on clinical grounds alone, which justifies the ongoing search for peculiar signs suggestive of immune-mediated encephalitides.
As to the electro-clinical features of AE-related seizures and the possible diagnostic value of electroencephalographic (EEG) findings, investigations so far have been mainly focused on anti-N-methyl-D-aspartate receptor (NMDAR) and anti-leucine-rich glioma-inactivated 1 (LGI1) encephalitis [3-5], the most common among AEs. However, limited evidence is currently available on other, rarer forms [6], as well as seronegative cases, whose diagnosis is surely the most troublesome for clinicians. In addition, some patients with otherwise unexplained late-onset temporal lobe epilepsy (TLE) might actually harbor "smoldering" immune-mediated processes [7,8], so that their identification would have a great impact on both therapeutic approach and prognosis.
Considering the dearth of data on "autoimmune seizures", we reviewed the EEG exams undertaken by 30 patients with AE from diagnosis on, in order to investigate possible electro-clinical peculiarities and recognize "red flags" which might help and hasten the identification of an underlying immune-mediated seizure disorder.

2. Materials and Methods

2.1 Patient selection and general data collection

Through the review of both clinical charts and electronic databases, we retrospectively identified all the adult patients diagnosed with AE among those hospitalized in the Neurology Unit and/or followed at the epilepsy outpatient service of Policlinico "Umberto I" of Rome from January 2009 to February 2020. The study was developed in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Guidelines and approved by the local Ethics Committee. The diagnosis of AE was confirmed based on the recent criteria by Graus et al [2]. Only the subjects who had performed EEG exams in our neurophysiopathology lab at any time since the diagnosis were included in the study. All the participants presented seizures at the disease onset and about half of them had seizures recurring at some point during the follow-up.
The patients' demographics, clinical, laboratory and neuroimaging findings were collected. Autoantibody screening performed on either cerebro-spinal fluid (CSF) or serum included anti-onconeural antibodies (Abs anti-Hu, Yo, Ri, Amphiphysin, CRMP5/CV2, Ma2) and Abs against neuronal surface antigens (NMDAR, LGI11, contactin-associated protein-like 2 [CASPR2], alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor [AMPAR], γ-aminobutyric acid receptor $[GABAR]_B$). Anti-glutamic acid decarboxylase (GAD) 65, anti-$GABAR_A$ and anti- SRY-Box Transcription Factor 1 (SOX1) Abs were tested in a minority of subjects.

2.2 Analysis of EEG findings

At least one 30-minute video-EEG (VEEG) recording (Micromed System Plus, Treviso, Italy; Xltek®EEG, Oakville, Canada), with scalp electrodes placed according to the international 10–20 system (bipolar montage), was available for all the study participants. More than half of the population also had ≥ 1 24-h ambulatory EEG (AEEG) (Micromed System Plus, Treviso, Italy). Common activation procedures (i.e. intermittent photic stimulation and hyperventilation – HV) were systematically performed during VEEG.

Two neurologists with expertise in epilepsy (CDB, AM) independently inspected all the available tracings. In case of discordant assessments, the final decision was reached after discussion with an additional reviewer (ATG). The EEG exams were distinguished into those performed during the acute stage of AE (or within a month from immunotherapy administration) and the ones recorded during the follow-up.

The following interictal EEG features were collected and analyzed: posterior dominant rhythm (PDR); focal/diffuse slowing; interictal epileptiform abnormalities (IEDs); increase in IED rate during HV (within 60 seconds from its termination) and sleep.

In case of VEEG-recorded clinical seizures (CSs), the investigators directly evaluated the ictal semiology, whereas the patients' own description (as reported in their medical journal) was relied upon when seizures occurred during AEEG. The seizure type (aware focal, focal with impaired awareness, focal to bilateral tonic-clonic) was classified based on the latest ILAE proposal [9], while its semiology (i.e. autonomic, aphasic, emotional, cognitive, motor) was described according to the predominant ictal manifestation (not necessarily the earliest).

A subclinical seizure (SCS) was defined as the occurrence of a paroxysmal electrographic pattern consistent with a seizure (i.e. showing a plausible electrographic field and a proper temporal-spatial evolution in frequency, amplitude and morphology) that was not associated with identifiable clinical manifestations other than very subtle signs (i.e. micro-arousals, unreported changes in the heart rate).

Facio-brachial dystonic seizures (FBDS) were also observed (exclusively in subjects with anti-LGI1encephalitis, as expected) and carefully analyzed. In some patients, FBDS were either isolated or set in a complex sequence of other motor events (e.g. myoclonic jerks, clonic head deviation, tonic limb/axial posturing, perioral and gestural automatisms). Since it was not possible to consider these phenomena separately, we decided to group them together under the term of "FBDS *plus*" (FBDS+).

All the ictal electrographic patterns (both clinical and subclinical) were inspected with particular focus on the following features: lateralization, localization, circadian distribution and trigger factors (e.g. HV, specific stimuli). The term bilateral was used when distinct seizures arising asynchronously from both hemispheres were observed in the same patient, whereas those without a clearly lateralized onset were labelled as not-lateralizable. Seizures arising outside of the temporal lobe or involving areas beyond the temporal region alone from the very beginning were considered as "extra-temporal", as were FBDS+. Moreover, all the ictal events were further classified into the following categories according to the predominant rhythm/activity observed at seizure onset: 1. theta activity (4-7 Hz) onset, 2. delta activity (1-3 Hz) onset, 3. sequential spike/spike-and-slow-wave (SSW) onset, 4. electrodecremental event (EDE), 5. generalized periodic discharges (GPDs). In the patients presenting morphologically distinct patterns, they were considered separately.

2.3 Statistical analysis

Data were tested for normal distribution using the Shapiro–Wilk test, resulting in generalized non-normal distribution, and therefore were presented as median and interquartile range (IQR).

Categorical variables were presented as frequency (count) and compared across the relevant groups – namely, CSs, SCSs and FBDS+ – through the Fisher's exact test or the chi-square test. Group tests were two-sided with $P < 0.05$ considered statistically significant.

3. Results

3.1 Patient demographics and general data

Thirty patients (19 men, 11 women) were included in the study, with a median age at first observation of 68 years (IQR 55.75-70, range 26-76). The median diagnostic delay was 4 months (IQR 0.5-9.25, range 0.2-48), and the median follow-up was 22 months (IQR 9.75-48, range 3-108).The search for specific autoantibodies yielded no results in more than 50% of cases (18/30). Twenty-four patients were hospitalized at disease onset for generalized tonic-clonic seizures and/or rapidly progressive awareness impairment (15/24), or due to the subacute onset of high frequency focal seizures (9/24). None of them required intensive care unit.

All but two subjects received immunotherapy at the time of diagnosis, and 26 (86.7%) were treated with antiepileptic drugs (AEDs) (1-4) as well. Among 21 patients with a clinical follow-up ≥ 12 months, 6 (4 anti-LGI1, 1 anti-CASPR2, 1 NMDAR) were withdrawn from AEDs due to persistent seizure remission, although 2 of them stayed on long-term immunomodulatory treatment. As to the remaining 15 subjects, 5 developed drug-resistant epilepsy (DRE) [10], whereas 10 showed a satisfactory seizure control (no seizures or occasional ones) on anti-epileptic monotherapy.

Further clinical, laboratory and neuroimaging findings are illustrated in Table 1.

3.2 Clinical and EEG findings

Overall 243 EEG recordings (212 VEEG, 31 AEEG), evenly distributed between acute stage and follow-up (124 and 119, respectively), were reviewed. All participants underwent ≥1 VEEG exam (range 1-35, median 4, IQR 3-9), whereas 22 (73.3%) had ≥ 1 AEEG exam (range 0-3, median 1, IQR 0-2). The median duration of the EEG follow-up was 9 months (range 0-104, IQR 2-30).

Six-hundred-nineteen ictal events were recorded in 19/30 (63.3%) patients (median number per subject 16, range 1-262), mostly during the acute stage of the disease (568/619, 91.8%).

Ten out of 19 patients were seronegative, five had anti-LGI1 encephalitis and two had anti-CASPR2 encephalitis, whereas anti-NMDAR, anti-SOX1 and anti-Hu/Ri Abs were detected in one case each.

3.2.1. Clinical features of EEG-documented seizures

Among 332 electro-clinical events documented in 15 patients, 137 were FBDS+ (recorded in five anti-LGI1 encephalitis cases). Most of the other CSs (165/195, recorded in 7/10 patients) showed prominent autonomic manifestations. In particular, pilomotor seizures (overall 146) were observed in two subjects (one of whom, already reported, had olfactory stimulus-induced ictal piloerection)[11]. Another one had seizures characterized by aphasia and coughing, a most uncommon epileptic manifestation. Non convulsive status epilepticus (NCSE) was documented in a single case. Quite curiously, only one patient with anti-LGI1 encephalitis showed seizures other than FBDS+.

Eleven subjects (36.7%) presented overall 287 SCSs. Interestingly, almost 10% of them (28/287) were associated with sinus tachycardia, unreported by the patients and detected though concomitant EKG recording. Subclinical events occurred more often during sleep (216 out of 287), and were mostly documented via AEEG (260/287, 90.6%), contrarily to clinical ones (150/332, 45.2%)

(p<0.001) (Figure 1 and 2). In addition, two patients had SCSs detected at follow-up despite their (apparent) long-lasting (≥ 5 years) seizure remission.
Eight patients out of 19 (42.1%) presented ictal events during HV. The proportion of HV seizures (defined as the ratio between seizures recorded during HV and all awake seizures) showed that awake FBDS+ were significantly more likely to occur during HV compared with clinical and subclinical seizures (10/66 FBDS+ vs 12/192 clinical seizures vs 3/72 SCSs, p=0.042) (Figure 2).

3.2.2 Interictal EEG findings

A background slowing was observed during the acute stage of the disease in 10/30 subjects, but it was marked only in three of them, presenting with a concomitant severe impairment of awareness. IEDs, which were detected in 21 patients (70%), appeared bilaterally in 14 cases, were focal temporal in 13, regional in five (involving the temporal area plus fronto-central, centro-parietal or vertex derivations), unilateral hemispheric in one and widespread in two. As expected based on previous results, IEDs were documented in only one out of five anti-LGI1 patients, a significant smaller proportion compared with the other study participants (p=0.008). Finally, a consistent increase in the IED rate was observed during sleep in six cases (20%), and during HV in three (10%).

3.2.3 Ictal EEG findings

The recorded ictal activities were unilateral in nine patients and bilateral in five. As to the seizure localization, nine subjects had a temporal ictal onset, whereas in five patients seizures arose from wider territories beyond the temporal region alone (centro-temporal in one, fronto-temporal and temporo-parietal-occipital in two each). Finally, the ictal activity clearly localized outside of the temporal lobe in two cases (on the parieto-occipital and vertex derivations in one each). No lateralizing nor localizing value could be attributed to EEG changes associated with FBDS, which were preceded by a global/hemispheric attenuation (EDE) in only two cases.
As regards the ictal activity classification, two distinct EEG patterns could be clearly identified in nine subjects, who more often presented both clinical and subclinical seizures (6/9) than those exhibiting a single pattern (1/10) (p=0.02). Indeed, in the six patients from the "multiple pattern" group showing both CSs and SCSs, only one of the recorded patterns could be either clinical or subclinical (e.g. during sleep), whereas the other was never associated with a clinical correlate (Table 2).
The different EEG activities observed at seizure onset and their distribution are illustrated in Figures 3 and 4.

3.3 Anatomo-EEG correlations

When comparing IED lateralization with brain MRI findings, it appeared that unilateral parenchymal alterations were equally associated with either unilateral or bilateral IEDs, whereas bilateral brain involvement was detected only in cases with bilateral IEDs or no IEDs at all (p=0.004). The latter finding might be justified by the absence of IEDs in all but one patient with anti-LGI1 encephalitis, whose MRI scan showed bilateral mesial temporal involvement. Similarly, no significant correlation was found between the lateralization of the ictal activities and that of MRI alterations. Besides, bilateral IEDs were observed in patients with unilateral seizures as well.
In addition, the lateralization and localization of the ictal events significantly differed according to the number of identifiable paroxysmal EEG patterns. Indeed, among nine patients with 'multiple pattern', six had bilateral asynchronous seizures (*vs* 0/10 with a single pattern, p=0.002), and six also showed both temporal and extra-temporal ictal onset, compared with none of those of the 'single pattern' group (p=0.001).

Finally, the autoantibody status did not appear to influence seizure electro-clinical features beyond the association between anti-LGI1 encephalitis and FBDS+.

5. Discussion

Over the last few decades, the complex mutual relationship between seizures, epilepsy and inflammation has been the object of intense investigations, fueled by its potential therapeutic implications. Seizures can activate brain-resident innate immune cells (i.e. microglia and astrocytes), causing an inflammatory cascade which widely affects neuronal excitability, synaptic function, neurogenesis and blood-brain barrier permeability, potentially igniting epileptogenesis [12,13]. In addition, both systemic and CNS inflammation can precipitate epileptic seizures [12]. In such intricate scenario, AEs have recently provided a peculiar model of seizures related to aberrant adaptive immunity [14], and are supposed to account for a large proportion (reportedly, up to 40%) of late-onset epilepsy cases [15].

We retrospectively reviewed the EEG recordings of 30 patients diagnosed with AE, with the aim of identifying peculiar clinical and EEG features which might help clinicians suspect seizure immune etiology. Of the 619 ictal events documented in 19/30 (63.3%) subjects, 568 (91.8%) were recorded during the acute stage of the disease, with a number per patient per day ranging from one to 262. Our findings are in accordance with published data, reporting that 33-100% of AE cases present with seizures, which tend to be exceedingly frequent during the "encephalitic" phase [13], as clearly seen in our population. A double, synergistic mechanism, involving both direct autoantibody effects on synaptic receptors and neuroinflammation-induced remodeling, has been advocated to justify seizure generation in AE and their remarkable burden [16]. During the follow-up, ictal events were documented in only seven (23.7%) of our patients, in line with other studies revealing the limited risk (around 10-15%) of developing epilepsy after AE, which has been supposed to be antibody-specific [17]. However, our own previous work suggested that a 'subtle' clinical onset (i.e. low seizure frequency, absence of IEDs and memory deficits) might correlate with seizure persistence past the acute stage, likely due to the prolonged diagnostic and therapeutic delay [18].

In seven out of 10 cases with recorded clinical seizures, the ictal semiology was highly suggestive for temporal lobe origin, as expected. Autonomic manifestations were the prominent ictal feature in all these patients (the most common being rising epigastric sensation, followed by sinus tachycardia). Ictal piloerection, generally considered an exceedingly rare phenomenon [19], was VEEG-documented in two subjects (one seronegative, one with anti-SOX1 Abs). So, in line with previous works [20,21], our data further support the association between pilomotor seizures and immune etiology, regardless of the autoantibody specificity. Along with vegetative manifestations, four patients also described ictal negative affective symptoms (i.e. agitation/anxiety and fear), with or without concomitant affective behavior. Conversely, none of the study participants showed ictal limb dystonia, which is rather unexpected, since dystonic posturing (supposedly related to the propagation of the ictal discharge to the basal ganglia) is observed in a high proportion (20-74%) of mesial TLE (MTLE) cases [22,23], and it is one of the few ictal features significantly more common in mesial than in lateral (neocortical) TLE [22,24]. This observation is even more puzzling when considering the well-acknowledged involvement of the basal ganglia in anti-LGI1 encephalitis [25]. In our population, the concomitant occurrence of autonomic and negative affective manifestations supports the hypothesis of an underlying temporo-frontal ('limbic') epileptogenic network, in which a potentially crucial role in determining seizure semiology might be played by the amygdala, whose involvement in AE has been already hypothesized based on neuroimaging studies [26]. Interestingly, the absence in our patients of somatosensory, opercular

and auditory/visual symptoms appears in contrast with the "perisylvian model" proposed in post-encephalitic and other immune-mediated epilepsies [27-29]. However, such discrepancy might depend on the fact that most of our patients' seizures were recorded during AE acute stage, whereas the involvement of the perisylvian structures in the epileptogenic zone, favored by tight anatomical connections, could occur later in the disease course, due to the dynamic remodeling of the seizure-generating network. However, the gradual spread of the underlying unextinguished immune-mediated process could also play a role.

As in other studies on acute encephalitides [30], we found that 36.6% (11/30) of our patients had SCSs, a much higher percentage than those observed in both the general epileptic population (5.3%) and TLE cases (8.3%) [31,32]. Seventy-five% of the recorded SCSs occurred during sleep, and about 90% were documented by means of AEEG. These findings confirm the need for long-lasting EEG monitoring, not only to increase the chance to detect seizures (which might support the diagnosis and help identify subtle relapses), but also to properly quantify them. The quantitative assessment of the ictal discharges - especially during sleep - appears crucial, since they could contribute *per se* to the patients' cognitive impairment. Indeed, although SCSs have not been specifically investigated, they might compare to IEDs, which also increase during Non-Rapid Eye Movement (NREM) sleep [33], and have been proved to affect memory consolidation by interfering with sleep-related thalamo-cortical-hippocampal coupling [34]. Besides, SCSs arising from the mesial temporal lobe (mTL) could hypothetically manifest as a transient pure amnesic syndrome, difficult to disclose due to its brief duration. With respect to this hypothesis, it is interesting that multiple daily bitemporal SCSs have been documented during NREM sleep in patients diagnosed with Transient Epileptic Amnesia and complaining of interictal memory impairment [35]. Finally, SCSs could be substantially underdiagnosed, considering that intra-cranial EEG studies performed in drug-resistant TLE have demonstrated that scalp electrodes detect only a small proportion (10%) of all SCSs (especially if the ictal discharge is confined to the hippocampus) [36]. This might suggest that those of our patients who presented with numerous SCSs could actually have an enduring ictal activity - not recognizable with scalp EEG - resulting in a limbic status epilepticus, partly responsible for their "interictal" deficits [37].

With respect to the specific EEG activity observed at seizure onset, different patterns (theta onset, delta onset, SSW onset, GPDs) were documented not only in the whole population, but also within single subjects (9/19, 47.4%), which is rather unusual when using non-invasive recording techniques. The most common theta onset (detected in 13/19 cases) clearly pointed to the seizure mTL origin [38]. In two thirds of the patients with multiple EEG patterns, the morphologically distinct ictal activities also differed in terms of localization and lateralization. Based on these findings, it is possible to hypothesize that the inflammatory process underlying AE results in a multifocal neuronal hyperexcitability, which affects both hemispheres and extends beyond the limbic system alone. The lack of correlation between the lateralization of the EEG abnormalities (both ictal and interictal) and that of MRI alterations further supports a much wider brain involvement than detected through structural neuroimaging studies alone. However, we also found that in most of these cases (6/9) one "predominant" ictal EEG pattern was associated with clinical manifestations (mainly autonomic and emotional, as previously stated), whereas the other was subclinical. Such difference suggests that, alongside a "full-blown" epileptogenic network, there are other, probably more restricted hyperexcitable neural pathways not generating clinical manifestations. The prompt start of immunotherapy might abate inflammatory processes and hamper the progressive extension of these epileptogenic networks, whose dynamic remodeling

would otherwise justify the later involvement of the perisylvian structures [27,28] and the development of "chronic epilepsy".

This work has many limitations, including its retrospective design; the small sample size; the heterogeneity of the study population in terms of autoantibody status, diagnostic delay and follow-up duration, and the limited number of patients undergoing AEEG exams at follow-up. Moreover, some clinical observations here reported could be affected by the intrinsic limitations of scalp EEG and its interpretation.

6. Conclusion

In conclusion, our study confirms that an immune-mediated etiology should be suspected in adult and elderly patients developing high frequency focal seizures with prominent autonomic (in particular, pilomotor) and emotional manifestations, even more so when multiple ictal patterns are documented. However, further studies on larger samples are warranted to validate such hypothesis. Our work also highlights the crucial role of prolonged EEG recordings in revealing SCSs, which might have a negative impact on cognition. In this peculiar context, long-lasting EEG monitoring also allows to adequately evaluate the seizure burden during the acute stage of the disease, and to detect possible seizure persistence/relapse during the follow-up, providing clinicians with useful clues for the patients' therapeutic management.

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Disclosure of conflicts of interest

None of the authors has any conflict of interest to declare

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

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Figure legend

Figure 1. The figure illustrates the different diagnostic yield of VEEG and AEEG in the acute stage of AE and during follow-up, according to the different seizure type. Abbreviations: AEEG: 24-h ambulatory EEG; CSs: clinical seizures; FBDS+: faciobrachial dystonic seizures *plus*; FU: follow-up; SCSs: subclinical seizures; VEEG: video-EEG.

Figure 2. The figure illustrates the seizure circardian distribution, which appears significantly different according to seizure type. CSs: clinical seizures; FBDS+: faciobrachial dystonic seizures *plus*; HV: hyperventilation; SCSs: subclinical seizures.

Figure 3. The figure provides examples of the different ictal EEG patterns observed at seizure onset. Panel A: the AEEG tracing shows a rhythmic theta (5 Hz) activity, arising from the left temporal and posterior regions, which gradually increases in amplitude and spreads to the homologous territories of the contralateral hemisphere, then evolving into a brief delta activity

intermingled with spikes well localized on the temporal derivations. Panel B: in the same patient, a rhythmic delta (3-3.5 Hz) activity with superimposed low-voltage beta frequencies was recorded on the right posterior regions, with early contralateral spread. Panel C: the seizure onset is characterized by a sequence of spike-and-slow waves arising from the left anterior and middle temporal lobe, evolving into a rhythmic theta/spiky (5-6 Hz) activity. Panel D: the EEG tracing shows a subcontinuous activity of GPDs at 1-1.5 Hz, intermingled with brief generalized flattening. Given the patient's concomitant awareness impairment, which improved after intravenous benzodiazepine administration, this pattern was interpreted as NCSE. Panel E: the video-EEG captured a left FBDS. The muscular activation detected through polygraphic recording (top trace: left orbicularis oris muscle, bottom trace: left deltoid muscle) was preceded by a brief EEG flattening over the right hemisphere (EDE). EEG settings: 21- and 8-channel digital recordings, bipolar longitudinal montage, HFF 70 Hz, LFF 1.6 Hz, sensitivity 100 μV/mm. Abbreviations: EDE: electrodecremental event; FBDS: faciobrachial dystonic seizures; GPDs: Generalized Periodic Discharges; NCSE: Non Convulsive Status Epilepticus.

Figure 4. The figure illustrates the proportion and the reciprocal associations of the different EEG patterns observed ad seizure onset. The "theta onset" clearly appears to be the most common pattern, documented in 13 subjects, who could also present seizures with either delta onset (4) or SSW onset (4) or EDE (1). EDE: electrodecremental event, GPD: generalized paroxysmal discharges, SSW: sequential spikes/spike-and-slow waves.

Table footnotes

Table 1
AE: autoimmune encephalitis; CSF: cerebrospinal fluid; GM: gray matter; IT: immunotherapy; mTL: mesial Temporal Lobe; NMDA: NPA: neuropsychological assessment; SE: status epilepticus; WM: white matter

Table 2
AI: awareness impairment, Autom: automatisms, Bilat: bilateral, CP: centro-parietal, Contralat: contralateral, EDE: electro-decremental event, F: frontal, FA: fast activity, FBDS: faciobrachial dystonic seizures, FBDS+: faciobrachial dystonic seizures *plus*, FC: fronto-central, FVR: focal voltage reduction, GPDs: generalized periodic discharges, Hallucin: hallucinations; He: hemispheric, IEDs: interictal epileptiform discharges, L: left, LA: low amplitude, mT: mesial temporal, PO: parieto-occipital, Post: posterior, R: right, S: spike, SW: sharp wave, SSW: sequential spikes/spike-and-slow waves, T: temporal, V: vertex, δ: delta, θ: theta