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RESEARCH ARTICLE

Focal electroclinical features in generalized tonic–clonic seizures: Decision flowchart for a diagnostic challenge

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Abstract

Objective: Bilateral tonic–clonic seizures with focal semiology or focal interictal electroencephalography (EEG) can occur in both focal and generalized epilepsy types, leading to diagnostic errors and inappropriate therapy. We investigated the prevalence and prognostic values of focal features in patients with idiopathic generalized epilepsy (IGE), and we propose a decision flowchart to distinguish between focal and generalized epilepsy in patients with bilateral tonic–clonic seizures and focal EEG or semiology.

Methods: We retrospectively analyzed video-EEG recordings of 101 bilateral tonic–clonic seizures from 60 patients (18 with IGE, 42 with focal epilepsy). Diagnosis and therapeutic response were extracted after ≥1-year follow-up. The decision flowchart was based on previous observations and assessed concordance between interictal and ictal EEG.

Results: Focal semiology in IGE was observed in 75% of seizures and 77.8% of patients, most often corresponding to forced head version (66.7%). In patients with multiple seizures, direction of head version was consistent across seizures. Focal interictal epileptiform discharges (IEDs) were observed in 61.1% of patients with IGE, whereas focal ictal EEG onset only occurred in 13% of seizures and 16.7% of patients. However, later during the seizures, a reproducible pattern of 7-Hz lateralized ictal rhythm was observed in 56% of seizures, associated with contralateral head version. We did not find correlation between presence of focal features and therapeutic response in IGE patients. Our decision flowchart distinguished between focal and generalized epilepsy in patients with bilateral tonic–clonic seizures and focal features with an accuracy of 96.6%.

Significance: Focal semiology associated with bilateral tonic–clonic seizures and focal IEDs are common features in patients with IGE, but focal ictal EEG onset is rare. None of these focal findings appears to influence therapeutic response. By assessing the concordance between interictal and ictal EEG findings, one can accurately distinguish between focal and generalized epilepsies.

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KEYWORDS
EEG, focal epilepsy, generalized epilepsy, semiology, tonic–clonic seizures

1 | INTRODUCTION

Patients presenting with bilateral tonic–clonic seizures and focal electroclinical features often raise a diagnostic challenge: is their seizure a generalized onset tonic–clonic seizure (GTCS) within the context of idiopathic/genetic generalized epilepsy (IGE), or a focal to bilateral tonic–clonic seizure (FBTCS) reflecting focal epilepsy. This has important therapeutic consequences, with generalized epilepsies at risk of not responding or even being aggravated by some antiseizure medication (ASM).[1–5] Focal electroencephalographic (EEG) abnormalities and seizure semiology suggesting focal onset are typically used to distinguish FBTCSs from GTCSs. Yet, such findings are observed in more than half of GTCSs,[6,7] and may lead to misdiagnosis.[1,2] Furthermore, video-EEG documentation of GTCSs in patients with IGE is scarce, as these patients are rarely referred to video-EEG monitoring.[8–10] Whether the presence of focal features in IGE influences the response to ASM remains controversial, with some series reporting higher risk of drug-resistance,[11–13] and others not.[14–17]

Previous studies assessed the presence of specific focal semiological signs and whether they differentiate between GTCSs and FBTCSs.[18,19] In our experience, although focal interictal epileptiform discharges (IEDs) are common in IGE, focal ictal EEG onset is rarely seen in GTCSs, and if present, it is not in the same location as the focal IEDs. Based on this observation, we proposed a decision flowchart to distinguish between GTCSs with focal semiology and FBTCSs.

We had the following goals: first, to provide a detailed analysis of focal IEDs and focal ictal electroclinical findings in IGE patients with GTCSs, using long-term video-EEG recordings from the epilepsy monitoring unit (EMU); second, to evaluate whether focal features in GTCSs are associated with therapeutic outcome (seizure-free or not); and third, to validate the decision flowchart that aims to distinguish between focal and generalized epilepsies in patients with bilateral tonic–clonic seizures (TCSs) and focal electroclinical features. We compared the accuracy of the flowchart with the accuracy of using seizure duration and head version time onset, previously proposed as classifying parameters.[19]

Key Points

- Focal semiology and interictal EEG are common in generalized tonic–clonic seizures and should not exclude IGE diagnosis.
- Focal ictal EEG onset of tonic–clonic seizures is rare in IGE, and when present, it points to different location than the IEDs.
- The most common focal semiological feature is forced head version
- Presence of focal features in IGE does not seem to affect the patient's therapeutic response.
- The flowchart assessing concordance between interictal and ictal EEG localization accurately classifies these difficult cases.

2 | MATERIALS AND METHODS

We performed a two-step retrospective observational study of patients with GTCSs or FBTCSs, admitted for long-term video-EEG monitoring, at the Danish Epilepsy Center. The first step consisted of reviewing the electroclinical data of patients with IGE and GTCSs. Inclusion criteria were (1) diagnosis of IGE based on International League Against Epilepsy (ILAE) classification guidelines,[20,21] (2) follow-up at our center ≥1 year after diagnosis of IGE, and (3) ≥1 GTCS recorded on video-EEG. The diagnosis was derived from all available data in the electronic health records, including detailed history, neuroimaging, and response to ASMs. The second step consisted in testing whether our decision flowchart distinguished patients with IGE and GTCSs (cases) from those with focal epilepsy and FBTCSs (controls). To this purpose, we used the IGE population selected for the first step, as well as patients with focal epilepsy and FBTCSs according to the following criteria: (1) diagnosis of focal epilepsy based on ILAE guidelines,[20,21] (2) ≥1 FBTCSs recorded on video-EEG, and (3) age and sex matched to the IGE cases. Patients gave their informed consent before admission to the EMU for data reuse for research. The study was approved by the regional ethics committee (SJ-793).

The patients' electroclinical findings were reviewed from the video-EEG recordings by two experts with >15 years of experience (S.B., P.R.). We retrieved demographic and clinical data, including family history and comorbidities, age at epilepsy onset, neurological status, seizure frequency, ASM, and magnetic resonance imaging (MRI) findings (3 T, with sequences according to the HARNESS-MRI protocol[22]). We assessed the presence and distribution of IEDs and evaluated the ictal electroclinical findings at onset, during propagation, and at termination

of GTCSs. EEGs were recorded using NicoletOne (Natus) or Brainquick (Micromed), with the standard EEG array of the International Federation of Clinical Neurophysiology[23] and four surface electromyographic (EMG) electrodes. Intermittent photic stimulation was done in all patients in the routine EEG and in the video-EEG monitoring in 16 patients with generalized and in 18 patients with focal epilepsy.

Focal IEDs were defined as unilateral spikes, sharp-waves, and polyspikes, in single discharge or in bursts. Bilateral synchronous IEDs were considered generalized. Semiological signs with unequivocal lateralizing value, typically seen in focal epilepsies and pointing toward a specific localization, were described as focal[24]: head version (defined as sustained, forced head deviation to one side), figure-of-four, asymmetric tonic posturing, asymmetric clonic or myoclonic jerks (when unilateral), and lateralized automatisms. Asymmetric seizure termination, defined as unilateral clonic jerks on video-EEG or EMG, was also included. Aura, ictal coughing, and head orientation (not forced version) were described but not reported as focal. According to the seizure timeline (sequence of symptoms), semiological features were grouped into onset, propagation, and seizure termination phases. In the postictal period, we evaluated palsy, aphasia, and postictal nose-wiping. Spearman correlation method was applied to evaluate possible relationships between categorical data.

We investigated the IGE population to test whether the presence of focal EEG or semiological signs was associated with therapeutic outcome (seizure-free or not). Seizure freedom was defined as no epileptic seizure after reaching maintenance dose of the ASM, after the video-EEG monitoring. We divided IGE patients into two groups: seizure-free and not seizure-free. We used *t*-test to compare the mean value of normally distributed data or the nonparametric Wilcoxon rank sum test to compare the median value of continuous data not following a normal distribution. For the whole IGE population, we performed a univariable logistic regression analysis for individual focal features and their relation to the outcome, adjusting afterward for the patient sex, age and epilepsy duration in a multivariable model. We adjusted for patients with repeated seizures, using the variance estimator subcommand in our statistical program ($p < .05$ was considered significant). The statistical analysis was performed in Stata/MP 17.0.

We developed a decision flowchart based on the following observations, derived from our clinical experience prior to this study: (1) patients with IGE have bilateral synchronous IEDs (with or without focal features) recorded in the EMU, (2) patients with bilateral synchronous ictal EEG onset of tonic–clonic seizures have IGE, and (3) patients with bilateral TCSs who have bilateral synchronous IEDs but focal ictal EEG onset have IGE if they do not have focal IEDs or the focal IEDs are in a different location than the ictal EEG onset. We summarized these in a flowchart (Figure 1). We tested the flowchart in the dataset described above (cases and controls).

To compare the performance of our flowchart with previously proposed classifiers, we measured seizure durations and we plotted receiver operating characteristic (ROC) curves to validate previous findings suggesting that seizure duration threshold of 86.5 s and head version onset time threshold of 7 s from ictal start may be discriminating factors.[19] Furthermore, we searched for better cutoff values in our dataset. The area under the curve (AUC), sensitivity, specificity, and accuracy were determined. Both EEG and semiology-based ictal duration were extracted and separately used for the calculations. To adjust for patients with multiple seizures, the mean seizure duration was calculated. The same was applied for head version onset. The previously published rating scale[19] was used to characterize the AUC results. Using Fisher exact test, we investigated whether the presence of a focal cluster, consisting of a combination of initiating automatisms, unilateral facial jerks, and a lateralized tonic mouth deviation, served as a discriminator, as previously suggested.[19] Seizures where the presence of the focal cluster could not be accurately determined were excluded from this calculation.

3 | RESULTS

Eighteen patients (10 females) with IGE fulfilled inclusion criteria and had a total of 24 GTCSs. Two patients (Patients 15 and 16) had three GTCSs, two patients (Patients 5 and 18) had two GTCSs, and the remaining patients had one GTCS each. Patients' mean age at epilepsy onset was 13.1 (SD = 3.0) years and at the time of video-EEG recording was 27.9 (SD = 12.4) years; median epilepsy duration was 11 years (interquartile range [IQR] = 6–19). Two patients had a family history of epilepsy, and none had previous febrile seizures. Two patients suffered from depression. All patients had normal MRI. Eight patients had juvenile myoclonic epilepsy (JME), three patients had IGE with GTCSs alone (GTCSA), and one patient had juvenile absence epilepsy (JAE). Two patients had photosensitive IGE, and four patients were diagnosed with IGE not further classified. Demographic and clinical characteristics for each patient are in Table 1.

Focal seizure semiology occurred during GTCSs in 77.8% (95% confidence interval [CI] = 51.4%–92%) of IGE patients and 75% of seizures (95% CI = 47.9%–90.7%). When asymmetric seizure termination was included, the proportion increased to 88.9% (95% CI = 62.2%–97.5%)

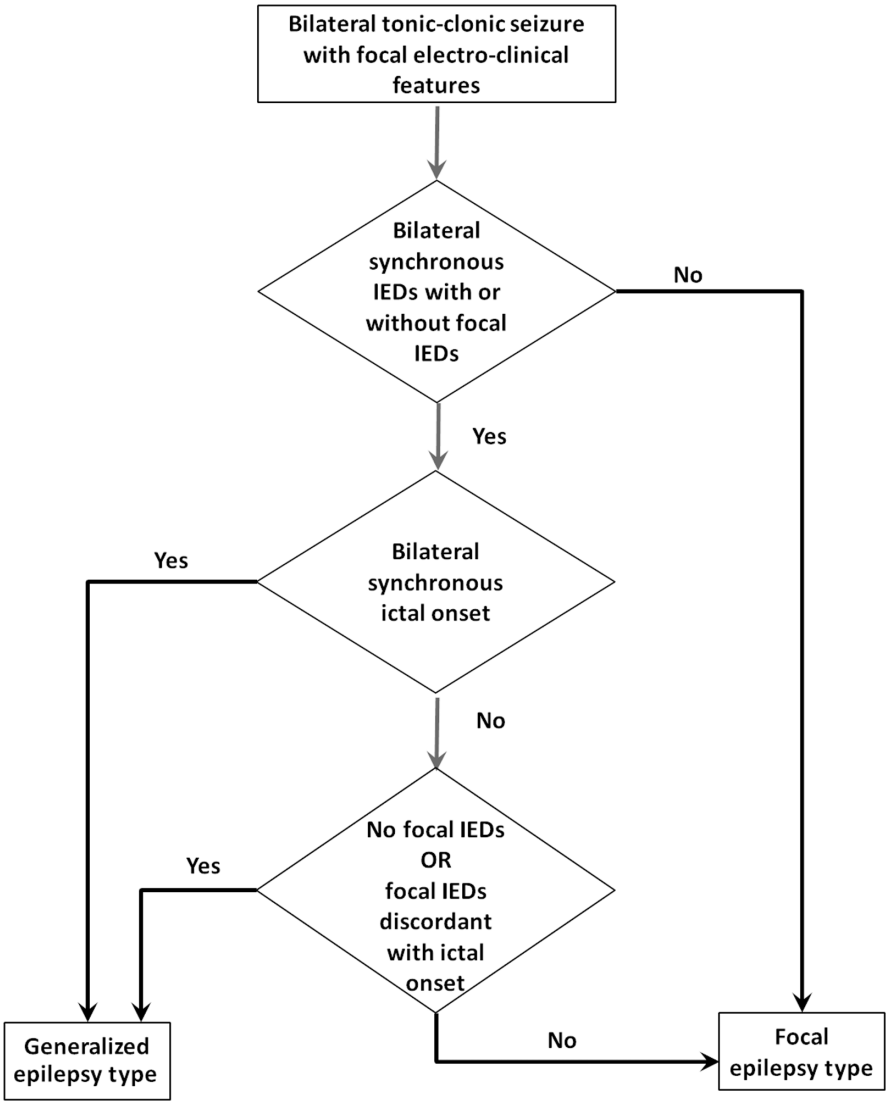

FIGURE 1 Decision flowchart to distinguish between focal and generalized epilepsy in patients with bilateral tonic–clonic seizures and focal electroclinical features. IED, interictal epileptiform discharge.

of IGE patients and 83.3% of seizures (95% CI = 54.6%–94.5%). The most common lateralizing feature was head version (Supplementary Document 1),[24,25] observed in 12 patients (66.7%, 95% CI = 41.1%–85.2%) and 16 seizures (66.7%, 95% CI = 40.3%–85.6%). In patients with multiple GTCSs and head version (Patients 15 and 16), direction of head version was consistent across seizures. Other lateralizing features were focal tonic (22.2% of patients, 95% CI = 7.95%–48.6%; 16.7% of seizures, 95% CI = 5.6%–40.1%), focal myoclonic (5.6% of patients, 95% CI = .7%–34%; 4.2% of seizures, 95% CI = .5%–29.1%), lateralized gestural automatisms (11.1% of patients, 95% CI = 2.5%–37.8%; 8.3% of seizures, 95% CI = 1.8%–30.6%), figure-of-four (11.1% of patients, 95% CI = 2.5%–37.8%; 8.3% of seizures, 95% CI = 1.7%–32.2%; Supplementary Document 2), and asymmetric seizure termination (27.8% of patients, 95% CI = 11.2%–53.9%; 20.8% of seizures, 95% CI = 7.5%–46.2%; Supplementary Document 3). Postictal lateralizing features were not found. Seizure semiology is presented in Table 2.

All IGE patients had generalized (bilateral synchronous) IEDs. Eleven IGE patients (61.1%, 95% CI = 36.2%–81.3%) also had focal IEDs, mostly multifocal or bilateral independent IEDs. Three patients had unifocal IEDs in the frontocentral and frontotemporal regions (Patients 2, 14, and 16). Importantly, there was no significant association between location of the IEDs and the focal semiological features. Examples of focal and generalized IEDs are shown in Figure 2. Background activity was normal in all IGE patients. Generalized photoparoxysmal response was recorded in five patients (27.78%) with generalized epilepsy and in none of the 42 patients with focal epilepsy ($p < .001$). Generalized photoparoxysmal response had a sensitivity of 27.78% (95% CI = 9.69%–53.48%), specificity of 100% (95% CI = 91.59%–100%), and overall accuracy of 78.33% (95% CI = 65.80%–87.93%).

Ictal EEG was obscured by artifacts in one patient.[9] Ictal EEG onset was bilateral synchronous in 15 of the 17 remaining patients (82.4%, 95% CI = 54.8%–94.7%) and in

TABLE 1 Demographic and clinical data.

Patient	Sex	Age, years	Onset age, years	Comorbidities	Family history	Febrile seizures	MRI	Final diagnosis	VEM duration, days— protocol[a]
1	Male	32	13	No	No	No	Normal	IGE with GTCS-only	4—IPS, HV, sleep deprivation
2	Female	26	16	No	No	No	Normal	IGE with GTCS-only	2—IPS, HV
3	Male	19	8	No	No	No	Normal	JME	5—IPS, HV
4	Female	19	9	No	No	No	Normal	JME	4—IPS, HV, cognitive test
5	Female	23	17	No	Yes	No	Normal	IGE	4—IPS, HV, sleep deprivation
6	Male	41	14	No	No	No	Normal	IGE	3—IPS, HV, sleep deprivation
7	Male	24	10	No	No	No	Partial rotation of left hippocampus (normal variant)	JAE	5—IPS, cognitive & motor tasks
8	Male	17	14	No	No	No	Normal	IGE	5—IPS, HV, sleep deprivation
9	Female	46	14	No	No	No	Normal	Photosensitive IGE with GTCS	1—IPS, sleep deprivation
10	Male	23	13	No	No	No	Normal	JME	1—sleep deprivation
11	Female	11	10	No	No	No	Normal	Photosensitive IGE with GTCS	1—IPS
12	Female	14	13	No	No	No	Normal	JME	1—IPS, sleep deprivation
13	Female	17	16	No	No	No	Normal	JME	1—sleep deprivation
14	Female	28	7	No	No	No	Normal	JME	1—IPS, HV, sleep deprivation
15	Female	51	14	Yes (previous depression)	No	No	Normal	IGE	3—IPS, HV, cognitive test
16	Female	28	16	No	Yes	No	Normal	IGE with GTCS-only	5—HV, cognitive test
17	Male	53	15	Yes (depression, not medically treated)	No	No	Normal	JME	5—IPS
18	Male	30	16	No	Unknown	No	Normal	JME	4—IPS, HV

Abbreviations: GTCS, generalized tonic–clonic seizures; HV, hyperventilation; IGE, idiopathic generalized epilepsy; IPS, intermittent photic stimulation; JME, juvenile myoclonic epilepsy; MRI, magnetic resonance imaging; VEM, video-electroencephalographic monitoring.

[a]All patients had electromyographic and electrocardiographic electrodes as well.

TABLE 2 Semiological features.

Patient (seizure)	Onset semiology	Semiology propagation	Asymmetric seizure termination	Postictal clinical phenomena	Focal semiology signs
1	Bilateral myoclonic	Bilateral tonic–clonic	**Yes**, last clonic jerks L UL	Impaired consciousness	**AST**
2	Head to the midline (from R) → ictal cry	Bilateral tonic–clonic	No	Impaired consciousness	No
3	Ictal cry	**R head version** → symmetric clonic → symmetric tonic–clonic	No	Impaired consciousness	**Version**
4	Bilateral myoclonic	**L version** → **L tonic** (facial) → symmetrical tonic–clonic	No	Impaired consciousness	**Version, lateral tonic**
5 (a)	Aura? → ictal coughing	**L automatisms (gestural)** → **L version** → **L UL flexion** → bilateral tonic–clonic	No	Impaired consciousness	**Lateral automatisms, version, lateral tonic**
5 (b)	Ictal cry	Bilateral tonic–clonic	No	Impaired consciousness	No
6	Bilateral myoclonic (irregular)	Ictal vocalization → bilateral clonic → bilateral tonic–clonic	**Yes**, last clonic jerks R UL + LL	Impaired consciousness	**AST**
7	**L automatisms** (gestural)	**R automatisms** (gestural) → ictal cry → bilateral tonic–Clonic	**Yes**, last clonic jerks L UL	Impaired consciousness	**Lateral automatisms, AST**
8	**L myoclonic** (face) + still responsive	Nonresponsive → **L head version** → bilateral clonic → **figure-of-four** (L extension, R flexion) → bilateral tonic–clonic	**Yes**, last clonic jerks R LL	Impaired consciousness	**Lateral myoclonic, version, figure-of-four, AST**
9	Bilateral myoclonic	**R version** → bilateral tonic–clonic	No	Impaired consciousness	**Version**
10	**L version**	Bilateral tonic–clonic	No	Impaired consciousness	**Version**
11	Bilateral myoclonic	**L version** → bilateral tonic–clonic	No	Impaired consciousness	**Version**
12	**R elbow tonic/flexion**	Vocalization → bilateral tonic–clonic	No	Impaired consciousness	**Lateral tonic**
13	**L version**	**L UL elevation/tonic** → **vocalization** → **figure-of-four** (L extension, R flexion) → bilateral tonic–clonic	No	Impaired consciousness	**Version, lateral tonic, figure-of-four**
14	(At start: covered under the blanket) → **L version**	Bilateral tonic–clonic	**Yes**, last clonic jerks R LL	Impaired consciousness	**Version, AST**
15 (a)	Motor/behavioral arrest	**R version** → bilateral tonic–clonic	No	Impaired consciousness	**Version**
15 (b)	Motor/behavioral arrest	**R version** → bilateral tonic–clonic	No	Impaired consciousness	**Version**
15 (c)	Motor/behavioral arrest	**R version** → bilateral tonic–clonic	No	Impaired consciousness	**Version**
16 (a)	Motor/behavioral arrest	**L eye deviation** → **L version** → bilateral tonic–clonic	No	Impaired consciousness	**Version**
16 (b)	Motor/behavioral arrest	**L eye deviation** → **L version** → bilateral tonic–clonic	No	Impaired consciousness	**Version**

TABLE 2 (Continued)

Patient (seizure)	Onset semiology	Semiology propagation	Asymmetric seizure termination	Postictal clinical phenomena	Focal semiology signs
16 (c)	Motor/behavioral arrest	**L eye deviation → L version** → bilateral tonic–clonic	No	Impaired consciousness	**Version**
17	Bilateral myoclonic	**R version** → bilateral myoclonic (asymmetric R > L) → bilateral tonic–clonic	No	Impaired consciousness	**Version**
18 (a)	Eye opening	Ictal cry → bilateral tonic → symmetric tonic–clonic	No	Impaired consciousness	No
18 (b)	Eye opening	Ictal cry → bilateral tonic → symmetric tonic–clonic	No	Impaired consciousness	No

Note: The seizure timeline (sequence) is grouped into onset, propagation, and termination phases. Focal features are highlighted in bold.

Abbreviations: AST, asymmetric seizure termination; L, left; LL, lower limb; R, right; UL, upper limb.

20 of the 23 GTCSs (86.9%, 95% CI = 61.7%–96.5%). Three patients (Patients 13, 14, and 17) had focal ictal EEG onset: unilateral spike–waves, rhythmic delta activity, and rhythmic fast activity, respectively. Examples of ictal EEG onset are shown in Figure 3A,B. Focal ictal EEG activity occurred later during propagation phase in 10 patients (58.8%) and 15 seizures (65.2%). In these seizures, we observed a typical pattern of focal ictal EEG activity during propagation phase, consisting of lateralized 7-Hz (6.5–8-Hz) rhythmic discharge. In patients with multiple GTCSs (Patients 5, 15, and 16), this feature was consistent across all recorded seizures. Lateralized ictal 7-Hz activity was significantly associated with contralateral head version (Spearman rho = .72, $p < .001$). Conversely, localization of the interictal and ictal focal EEG features were discordant in the vast majority of patients with IGE. Detailed description of the EEG findings is provided in Supplementary Document 4 and a summary of the electroclinical focal features in Table 3.

One patient with IGE was lost to follow-up[4]; all other patients had follow-up of >1 year (median = 6 years, IQR = 3–7 years). Supplementary Document 6 shows the follow-up time for all patients. Of the 17 patients with follow-up data, 12 (70.6%) were seizure-free. There was no significant difference in age, sex, and duration of epilepsy between seizure-free and non-seizure-free patients. Univariable regression analysis for individual focal features did not show any correlation with therapeutic outcome. Multivariable analysis after adjusting for sex, age, and epilepsy duration did not show any correlation between focal features and outcome either (Supplementary Document 5). The patients' therapeutic outcome, seizure frequency, and current treatment are presented in detail in Supplementary Document 6.

To assess the accuracy of our decision flowchart in distinguishing between focal and generalized epilepsy in patients with bilateral TCSs and focal electroclinical features, we included and analyzed 42 consecutive patients (47.6% female) with focal epilepsy who had bilateral tonic–clonic seizures in the EMU and who were age- and sex-matched with the IGE group. The mean age of this patient population was 31.5 (SD = 15.9) years. There was no significant difference between the IGE and focal group regarding sex distribution ($p = .57$) and mean age ($p = .39$). The average number of recorded bilateral TCSs in the focal group was 1.8; 24 patients presented only one seizure. Eighteen patients (42.9%) had temporal lobe epilepsy, seven (16.7%) had frontal lobe epilepsy, three (7.1%) had posterior epilepsy, and 14 (33.3%) had multifocal epilepsy.

We applied the flowchart to 59 cases and controls, 17 with IGE (after excluding Patient 9, whose ictal EEG onset was obscured by artifacts) and 42 with focal

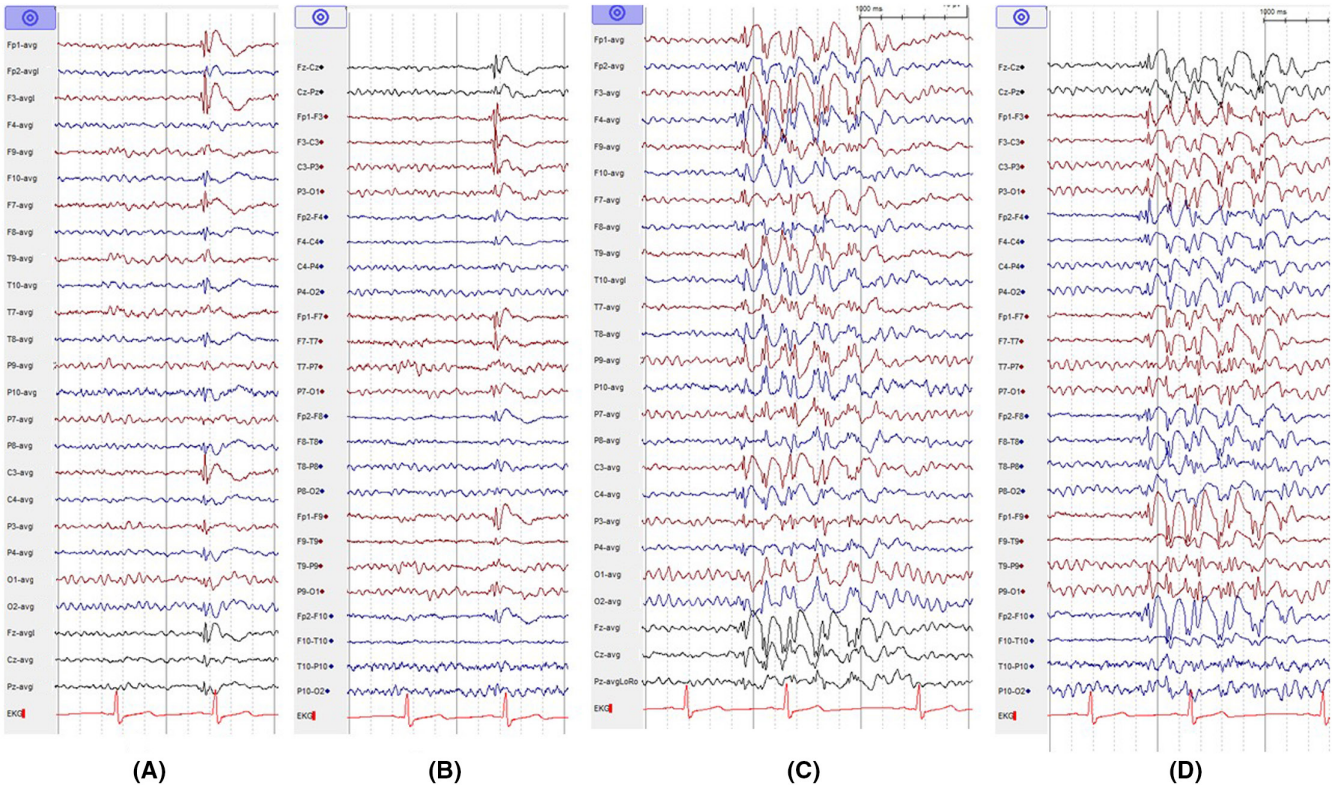

FIGURE 2 (A) Focal interictal epileptiform discharges (IEDs), common average montage. (B) Focal IEDs, longitudinal bipolar montage. (C) Generalized IEDs, common average montage. (D) Generalized IEDs, longitudinal bipolar montage.

epilepsy. All patients had bilateral TCSs and focal EEG or clinical features. The flowchart correctly classified 57 patients (accuracy: 96.6%, 95% CI = 88.3%–99.6%, sensitivity: 94.1%, 95% CI = 71.3%–99.9%, specificity: 97.6%, 95% CI = 87.4%–99.9%). One patient with focal epilepsy was misclassified as generalized, and one patient from the IGE group was misclassified as having focal epilepsy by the flowchart.

In concordance with previously published data,[19] we found a significant group difference in seizure duration between GTCSs and FBTCSs (both based on duration determined using EEG and seizure semiology). Median GTCS duration based on EEG was 73.7 s (IQR = 66.7–92), whereas the median FBTCS duration was 97.4 s (IQR = 81.3–143; Wilcoxon rank sum test $p < .001$). Similarly, based on semiology, the median GTCS duration was 73.8 s (IQR = 66.7–92), whereas the median GBTCS duration was 94.3 s (IQR = 80–117; Wilcoxon rank sum test $p = .02$). However, no significant difference was found on the presence or not of head version between the generalized and focal groups in our dataset (66.67% vs. 59.52%, respectively; χ^2 test $p = .6$). We found, however, a significant difference in the head version onset time during the seizure; the median version onset in the generalized group (based on the EEG seizure onset) was 10.3 s (IQR = 7–19.5), whereas in the focal group this was 25 s (IQR = 15–54; Wilcoxon rank sum test $p = .001$). The results were similar for version time onset based on the semiologic seizure onset.

AUC for EEG-based seizure duration was fair (.77). The previously proposed cutoff value of 86.5 s in our dataset gave specificity of 69% (95% CI = 52.9%–82.4%), sensitivity of 68.4% (95% CI = 40.9%–86.7%), and accuracy of 68.3% (95% CI = 55%–79.7%). We identified a different elbow point in our ROC curve, at 92 s. This gave specificity of 62% (95% CI = 45.6%–76.4%), sensitivity of 77.8% (95% CI = 52.4%–93.6%), and accuracy of 66.7% (95% CI = 53.3%–78.3%). The results were similar when semiology-based ictal duration was taken into account. Regarding head version onset time, the AUC was .96 (outstanding), with the 7-s cutoff showing high specificity of 92.3% (95% CI = 74.9%–99.1%), but a low sensitivity of 33.3% (95% CI = 9.9%–65.1%) and accuracy of 73.7% (95% CI = 57.9%–86.6%). A different threshold appeared in our ROC curve, and its elbow point was 15 s, showing a specificity of 73.1% (95% CI = 57.1%–91%), sensitivity of 66.7% (95% CI = 34.9%–90.1%), and accuracy of 71.1% (95% CI = 53.4%–84.5%). More details on this are available in Supplementary Documents 7 and 8. The presence of the focal cluster was possible to evaluate in 53 patients (18 with IGE, 35 with focal epilepsy), and it was significantly more common in the focal group (two-sided Fisher exact test $p = .01$; 31.43% of the focal

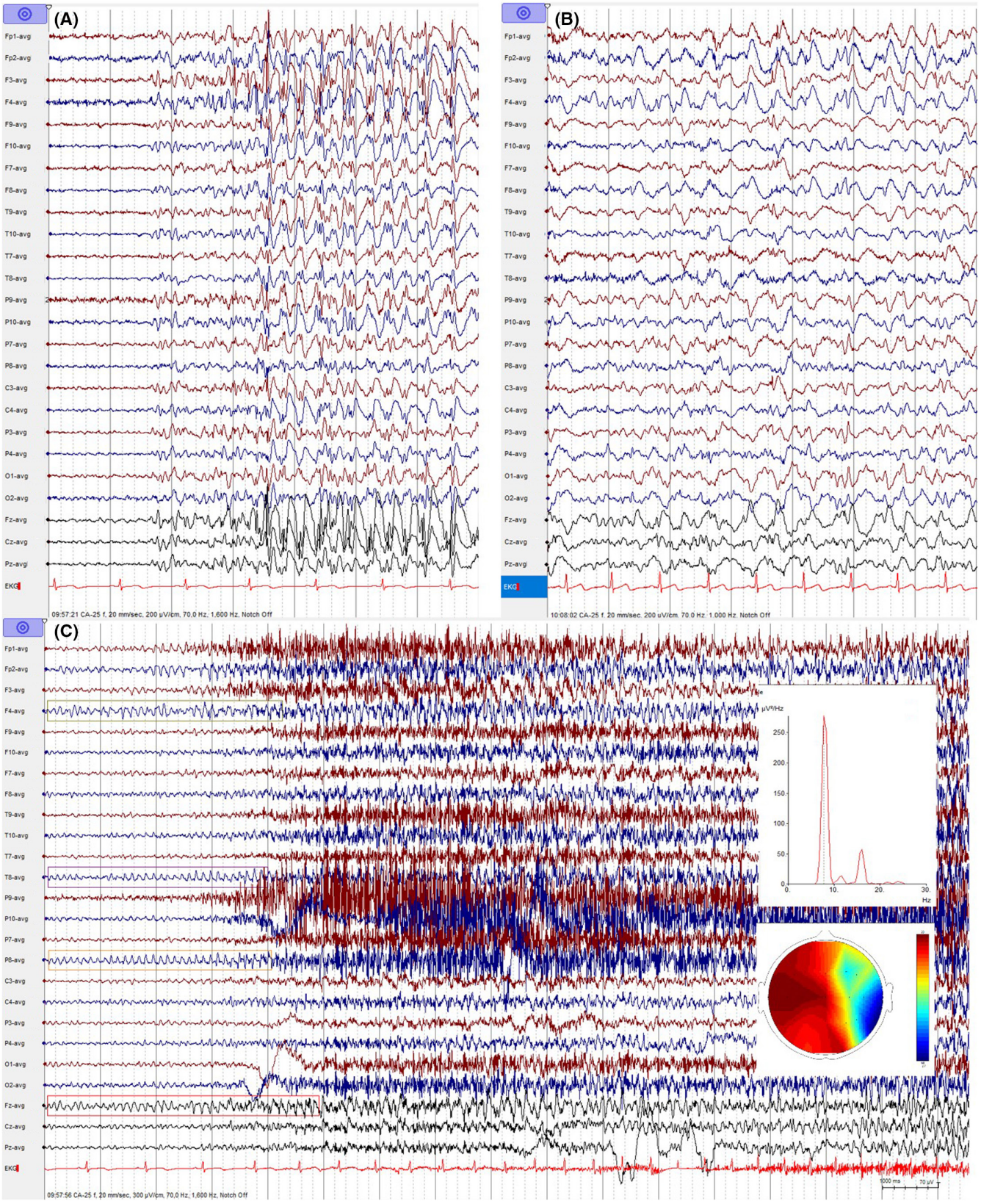

FIGURE 3 Ictal electroencephalograms. (A) Generalized onset. Observe the bilateral synchronous and symmetrical onset (F3 vs. F4) at the end of the second number 2. Common average montage is shown. (B) Focal onset. Observe the buildup of spike–wave activity in F4, while background activity continues undisturbed during the first 3 s in F3. Common average montage is shown. (C) Lateralized 7-Hz activity during the later (propagation) phase of the generalized onset tonic–clonic seizure. The inserts show frequency analysis and voltage maps.

Feature	% per patient (95% CI)	% per seizure (95% CI, adjusted for patients with multiple seizures)
Focal IEDs	61.1 (36.2–81.3)	–
Focal ictal EEG pattern		
Onset	17.6 (5.3–45.2)	13.0 (3.5–38.3)
Propagation	58.8 (33.4–80.2)	65.2 (36.9–85.8)
Termination	0	0
Focal semiology		
Onset	33.3 (14.8–58.9)	25.0 (9.7–50.8)
Propagation	61.1 (36.2–81.3)	62.5 (36.5–83.9)
Termination	27.8 (11.2–53.9)	20.8 (7.5–46.2)
Postictal	0	0

TABLE 3 Focal EEG and semiological features in idiopathic generalized epilepsy.

Abbreviations: CI, confidence interval; EEG, electroencephalographic; IED, interictal epileptiform discharge.

group, 0% of the IGE group). The presence of focal cluster showed a specificity of 100% (95% CI = 73.5%–100%) for focal epilepsy, but with a relatively low sensitivity of 42.9% (95% CI = 21.8%–66.0%) and accuracy of 63.6% (95% CI = 45.1%–79.6%).

4 | DISCUSSION

We found that the vast majority of patients with IGE show focal semiology during GTCSs, most often forced head version. Similar to the focal IEDs, these are common findings in patients with IGE, and may lead to misdiagnosis and inappropriate therapeutic choice. Focal electroclinical features were not associated with therapeutic outcome in our series. Ictal EEG onset was rarely focal in patients with IGE. However, lateralized 7-Hz activity often occurred during seizure propagation, time-locked to contralateral head version. A flowchart assessing bilateral synchrony and concordance between interictal and ictal EEG accurately distinguishes between focal and generalized epilepsies in patients with bilateral TCS and focal electroclinical features. Although at group level, GTCSs seem to be significantly shorter, and head version, if present, occurs earlier compared to FBTCs, the cutoff values do not distinguish between the two seizure types at patient level (neither the previously published cutoff nor the one found in our dataset). The presence of generalized photoparoxysmal response reliably indicates generalized epilepsy. However, this occurs only in approximately one of four patients.

Although the classic dichotomy of generalized and focal epilepsy is useful in clinical practice, an increasing number of studies have challenged it, and demonstrated the overlapping features between focal and generalized seizures, often leading to misclassification and suboptimal treatment. Various hypotheses have been proposed for the focal EEG abnormalities in IGE, including development of focal cortical pathology and a state of hyperexcitability in localized, low-threshold brain structures, subjected to repeated spike–wave activity.[26] However, this remains speculative. The position paper on seizure classification from the ILAE attempts to resolve the contradiction between terminology and pathophysiology; generalized seizures are defined as "originating at some point within, and rapidly engaging, bilaterally distributed networks."[20,21] Although individual seizure onsets can appear localized, it was hypothesized that "the location and lateralization are not consistent from one seizure to another." However, our findings of consistent lateralization in patients with multiple seizures seem to contradict this, and emphasize the diagnostic challenge in such cases.

In our series, >60% of the patients presented at least one focal EEG sign, either interictal or ictal. This is concordant with previous studies reporting 30%–70% of IGE patients showing focal EEG.[1,15,27–29] Furthermore, previous studies reported focal slowing in IGE patients as well. However, the recent ILAE position paper by Hirsch et al.[30] specifies focal EEG slowing as an exclusion criterion for JME and GTCSA. Accordingly, we have not found focal slowing in IGE patients.

Focal semiology in GTCSs of patients with IGE is more the rule than the exception (77.8% of patients and 75% of seizures). Although GTCSs are rarely recorded in the EMU, because IGE patients are rarely referred to long-term video-EEG monitoring, previous studies found similarly high incidence of focal features in GTCS; 66% had forced head version,[9] 15% figure-of-four sign,[8] and 41% asymmetric seizure-termination.[31] These are typically considered signs indicating focal epilepsy.[24,32] Lateralized gestural automatisms are typically seen in ipsilateral temporal lobe focus.[33]

Lateralized limb automatisms have been documented in absence seizures,[34,35] but only rarely in video-EEG studies of GTCSs,[36] as well as in a single survey study suggesting their presence in this seizure type.[7] Two of our patients with IGE (11.1%) presented lateralized limb automatisms. A higher incidence of unilateral myoclonic jerks reported by other authors (42%–61.5% vs. 5.6% in our series) derives from the different study populations with exclusively JME patients in those studies.[10,37]

Postictal nose-wiping and hemiparesis were previously reported in 10% and 5% of patients, respectively, in a single study.[38] None of our patients presented these postictal lateralizing phenomena. Moreover, none of our patients presented ictal aphasia.[24,39] Aphasia was mentioned as one of the most common (15.6%) focal semiological features in IGE patients with GTCSs in a survey study.[7] The authors used an epilepsy interview questionnaire, where the patients reported their ictal symptoms based on open- and closed-ended questions. This method is less reliable than a video-EEG recording with simultaneous patient testing to identify ictal aphasia, which otherwise may be difficult to distinguish from consciousness impairment.[40]

The recent ILAE position paper on IGE[30] indicates that focal features should be "red flags" and alert the clinician regarding the diagnosis, or even exclude IGE. According to the position paper, a consistent unifocal semiology at seizure onset can rarely be seen, and consistent focal EEG patterns are considered as exclusionary criteria for JAE, JME, and GTCSA. However, in our series, consistent lateralizing semiology was observed in two of the four patients with multiple GTCSs in the EMU. Previous studies have also reported consistent focal semiology in IGE, such as head version, figure-of-four sign, or circling seizures.[5,37,41] Regarding focal IEDs, these were distributed in both hemispheres or were multifocal in most of the patients. However, three patients had unifocal IEDs. Lombroso reported that 56% of 58 patients with IGE who had multiple EEG recordings (average = 39 EEGs per patient) had consistent focal features in 65% of the EEGs.[26]

An interesting observation in our study was a significant correlation between head version and a contralateral ictal EEG pattern consisting of 7-Hz activity during the propagation phase of the seizure. A similar observation was made previously in two reports, describing rhythmic lateralized alpha activity contralateral to head deviation during versive seizures.[10,37] A specific ictal pattern during focal versive semiology of GTCSs is not yet recognized. In our study, most patients with lateralized 7-Hz activity during version presented this ictal pattern in the frontal–temporal regions in the contralateral hemisphere. Other studies reporting versive seizures in IGE[5,41,42] did not describe this EEG pattern. Although the focal propagation of generalized onset seizures has previously been highlighted,[36,43,44] the existing literature reports only a limited number of cases, with heterogeneous population/different generalized seizure types (absence, myoclonic, GTCS),[36] with epilepsy onset age before the first year of life,[43] or patients presenting with positive MRI findings or with cognitive impairment.[36] This ictal pattern was characterized as an uncommon phenomenon,[43] with some authors proposing that it might represent a distinct subgroup of genetic or idiopathic generalized epilepsy.[44] In accordance with our findings, the focal discharges were most often located at the temporal and frontal regions and mainly in the theta or frequency band.[36] Our study extends the existing observations, showing that ictal propagation of generalized onset seizures may be present in idiopathic generalized epilepsy syndromes, it is more common than previously described, and it may be associated with a focal clinical pattern of head version.

The impact of the focal features on therapeutic response is controversial. Some studies reported a less favorable outcome in IGE patients with focal findings.[11,12] Other studies, on specific IGE syndromes, as in CAE[16] and in JAE and JME,[15] did not find association between focal features and therapeutic outcome. In our series, the presence of focal EEG or semiology did not affect the therapeutic response. The discordant results may be due to variable reasons. It may reflect heterogeneity regarding the definition of the focal signs among the studies; for example, the inclusion of amplitude asymmetry or focal EEG slowing may in some cases lead to an overinterpretation or misclassification, affecting the evaluation of outcome. Moreover, there is important heterogeneity in the studied populations, comparing patients with different IGE syndromes, which may differ in terms of treatment response. The choice of ASM is also a crucial factor, as ASM not recommended for generalized epilepsies may affect the prognosis.[45] Additionally, the studies examining focal semiological features of GTCSs in IGE based on video-EEG often contain a limited number of patients, as capturing GTCSs in IGE patients is rare. The relatively small cohorts may also contribute to the remarkable variability. In our series, no significant difference was found in the outcome between patients with and without electroclinical focalities.

The overlap of focal signs in focal and generalized epilepsies and bilateral TCSs is significant. Our decision flowchart based on the concordance between interictal and ictal EEG findings in these patients (Figure 1) distinguished the two forms of bilateral TCS with high accuracy (96.6%). Lack of bilateral synchronous (generalized) IEDs identifies the vast majority of patients with focal epilepsy. However, patients with both focal and generalized IEDs may have either focal or generalized epilepsy. In these cases, presence of generalized ictal onset or focal onset

not concordant with the IEDs identifies the patients with generalized epilepsy, even in the presence of focal semiological features. This flowchart may serve as a useful additional tool for diagnostically challenging cases of patients with bilateral TCS and focal electroclinical features. In clinical practice, the challenging patients are those who report GTCSs with focal semiology and have focal IEDs. In our series, 11 of 18 patients with IGE and GTCSs with focal semiology were in this category. One of our main messages is that in these selected, difficult cases, video-EEG monitoring is needed for accurate and reliable classification. The main element in the flowchart is the ictal EEG, and one of the main messages in this paper is that although patients with IGE and GTCSs often have focal IEDs, the ictal onset rarely is focal, even in patients who have focal semiology. In the rare cases when the ictal onset is focal too, it is not congruent with the interictal focus. However, the latter observation is based on a small number of cases, which is an important limitation of that observation. Rarely, patients appear to have two separate seizure disorders, namely both IGE and a focal epilepsy. Although this is considered a rare phenomenon, accounting for <1% of IGE patients,[46] relevant literature evidence exists,[47,48] and clinicians should also bear this pitfall in mind.

Although at group level there is a significant difference in ictal duration between GTCSs and FBTCSs, as well as in the time onset of head version (if present), separation at patient level, sufficient for clinical application, is not achieved using these duration measures.[19] Changing the threshold to achieve a high sensitivity of >90% as previously reported comes at the cost of specificity, which in this case falls to <50% (see Supplementary Document 7). Only moderate sensitivity and specificity were found for seizure duration as classifying factor. To achieve a sensitivity level of >80% as previously reported, the specificity falls to approximately 50%.

Our work contributes further to awareness of the presence of focal electroclinical signs in IGE to avoid misclassification. An important strength of the study is the use of video-EEG recordings. The additional surface EMG is another important tool used in our study to assess motor phenomena, especially asymmetric seizure termination to avoid underreporting. Video-EEG studies investigating systematically both ictal and interictal signs, electrographic and clinical, as well as their possible association with patient outcome are scarce.

Our study has several limitations. Similar to previous works, the population size is relatively small, because of the rare occurrence in the EMU of GTCSs in IGE patients. Nevertheless, our study has the second largest sample size of patients with GTCSs and focal features documented in the EMU, reporting both semiology and EEG findings.[18,19] Moreover, our patients may represent a more complicated IGE group, as they were referred to our tertiary center due to diagnostic challenges, hence an overrepresentation of the focal findings may exist.

5 | CONCLUSIONS

The presence of focal findings, either electrographic or semiological, does not exclude IGE, and does not influence therapeutic response. Clinicians treating patients with epilepsy should be aware of this, to avoid erroneous diagnosis and inappropriate seizure management. Our simple decision flowchart, based on the interictal and ictal EEG findings, may help in difficult cases.

AUTHOR CONTRIBUTIONS

Maria Vlachou: Study design; formal analysis; investigation; methodology; visualization; writing–original draft preparation. **Philippe Ryvlin:** Conceptualization; formal analysis; investigation; supervision; writing–review & editing. **Sidsel Armand Larsen:** Investigation; methodology; data curation; resources; writing–review & editing. **Sándor Beniczky:** Conceptualization; investigation; formal analysis; methodology; project administration; supervision; visualization; writing–original draft preparation; writing: review & editing.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. 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.

DATA AVAILABILITY STATEMENT

Anonymized data and statistical analysis files will be available upon request to the authors for a 3-year period after publication from any qualified investigator.

Abbreviations: CI, confidence interval; EEG, electroencephalographic; IED, interictal epileptiform discharge.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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