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RESEARCH ARTICLE

Progressive slowing of clonic phase predicts postictal generalized EEG suppression

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Abstract

Objective: Postictal generalized electroencephalography (EEG) suppression (PGES) is a surrogate marker of sudden unexpected death in epilepsy (SUDEP). It is still unclear which ictal phenomena lead to prolonged PGES and increased risk of SUDEP. Semiology features of generalized convulsive seizure (GCS type 1) have been reported as a predictor of prolonged PGES. Progressive slowing of clonic phase (PSCP) has been observed in GCSs, with gradually increasing inhibitory periods interrupting the tonic contractions. We hypothesized that PSCP is associated with prolonged PGES.

Methods: We analyzed 90 bilateral convulsive seizures in 50 consecutive patients (21 female; age: 11–62 years, median: 31 years) recruited to video-EEG monitoring. Five raters, blinded to all other data, independently assessed the presence of PSCP. PGES and seizure semiology were evaluated independently. We determined inter-rater agreement (IRA) for the presence of PSCP, and we evaluated its association, as well as that of other ictal features, with the occurrence of PGES, prolonged PGES (≥20 s) and very prolonged PGES (≥50 s) using multivariate logistic regression analysis.

Results: We found substantial IRA for the presence of PSCP (percent agreement: 80%; beyond-chance agreement coefficient: .655). PSCP was an independent predictor of the occurrence of PGES and prolonged PGES ($p < .001$). All seizures with very prolonged PGES had PSCP. GCS type 1 was an independent predictor of occurrence of PGES ($p = .02$) and prolonged PGES ($p = .03$) but not of very prolonged PGES. Only half of the seizures with very prolonged PGES were GCS type 1.

Significance: PSCP predicts prolonged PGES, emphasizing the importance of gradually increasing inhibitory phenomena at the end of the seizures. Our findings shed more light on the ictal phenomena leading to increased risk of SUDEP. These phenomena may provide basis for algorithms implemented into wearable devices for identifying GCS with increased risk of SUDEP.

1 | INTRODUCTION

Sudden unexpected death in epilepsy (SUDEP) is one of the leading causes of death in patients with epilepsy. Its incidence rate is estimated at up to 9.3 per 1000 person-years in patients with drug-resistant epilepsy, and its public health burden is reportedly second only to that of stroke in terms of years of potential life lost.[1–3] Postictal generalized electroencephalography (EEG) suppression (PGES) has been proposed as a surrogate marker of SUDEP.[4–6] PGES was observed in all cases of SUDEP or near SUDEP in the MORTEMUS study.[7] Long PGES (>20 s and >50 s duration) was reported to be associated with SUDEP risk,[5] although this finding has been disputed by others.[8,9] However, the exact association mechanism between PGES and SUDEP remains elusive. The hypothesis of seizure propagation to the lower brainstem and hence an autonomic dysfunction and central hypoventilation has been proposed.[4,7]

It is still unclear whether ictal phenomena can predict the occurrence of SUDEP in the postictal phase. All patients in the MORTEMUS study had generalized convulsive seizures (GCSs).[7] Specific ictal semiology features, consisting of tonic-clonic GCSs with bilateral and symmetric tonic arm extension (GCS type 1) were found to be associated with the occurrence of PGES and prolonged PGES.[10]

A specific dynamic evolution of motor signs, consisting of a progressive slowing of the clonic phase, has been observed in GCSs (both in generalized tonic-clonic seizures and in focal-to-bilateral tonic-clonic seizures). After the initial tonic phase, the muscle activity is interrupted by inhibitory (silent) periods of gradually increasing duration, resulting in a deceleration of the clonic jerks, until the seizure eventually stops[11–15] (Figure 1A). We further refer to this progressively increasing duration of the silent period as a progressive slowing of clonic phase. As this aspect is not specified in the definition of GCSs (generalized tonic-clonic seizures and focal-to-bilateral tonic-clonic seizures) many clinicians, including epilepsy experts, include here all bilateral convulsive seizures consisting of a tonic phase, immediately followed by a clonic phase, regardless of its dynamics (Figure 1B).

We hypothesized that the progressive slowing of the clonic phase is an independent risk factor for PGES and is associated with longer PGES duration. In addition, we aimed to assess the inter-rater agreement on the presence of progressive slowing of the clonic phase and to compare its occurrence between the different types of GCSs. For that purpose, we analyzed video-EEG recordings of consecutive patients with bilateral convulsive seizures in the epilepsy monitoring unit (EMU). The presence of progressive slowing of the clonic phase, the classification of seizure types, and the PGES were evaluated independently and blinded to the other data.

Key points

1. Postictal generalized electroencephalography (EEG) suppression (PGES) has been reported as surrogate marker of sudden unexpected death in epilepsy (SUDEP).
2. Progressive slowing of the clonic phase in generalized convulsive seizures is an independent predictor of PGES and long PGES.
3. This observation emphasizes the role of inhibitory phenomena at seizure end, providing new insight into PGES and SUDEP pathophysiology.
4. Progressive slowing of the clonic phase is a potential biomarker for high-risk generalized convulsive seizures.

2 | METHODS

2.1 | Patients and recordings

We analyzed video-EEG recordings of consecutive patients admitted to the EMU at the Danish Epilepsy Centre[16] for diagnostic evaluation (seizure classification or presurgical evaluation). Patients who had at least one bilateral convulsive seizure (defined as bilateral tonic or clonic jerks) were included. Patients younger than 1 year were excluded. The study was approved by the regional ethics committee (SJ-793), and patients gave their informed consent before admission to the EMU. EEG, including polygraphic channels, was recorded according to the standard electrode array of the International Federation of Clinical Neurophysiology, using NicoletOne (Natus Neuro) and Brainquick (Micromed).

2.2 | Analysis of ictal semiology

Two experts (PR, SB) with more than 15 years of experience in interpreting seizure semiology, analyzed the ictal video recordings, blinded to the other data. Discordance was resolved using consensus discussions. All included seizures had bilateral muscle contractions. As in previous studies, they were considered GCS when consistent with more than minimal involvement of both hemispheres.[10] Otherwise, they were considered focal motor seizures with bilateral muscle contractions. GCSs were classified according to Alexandre et al.,[10] as follows:

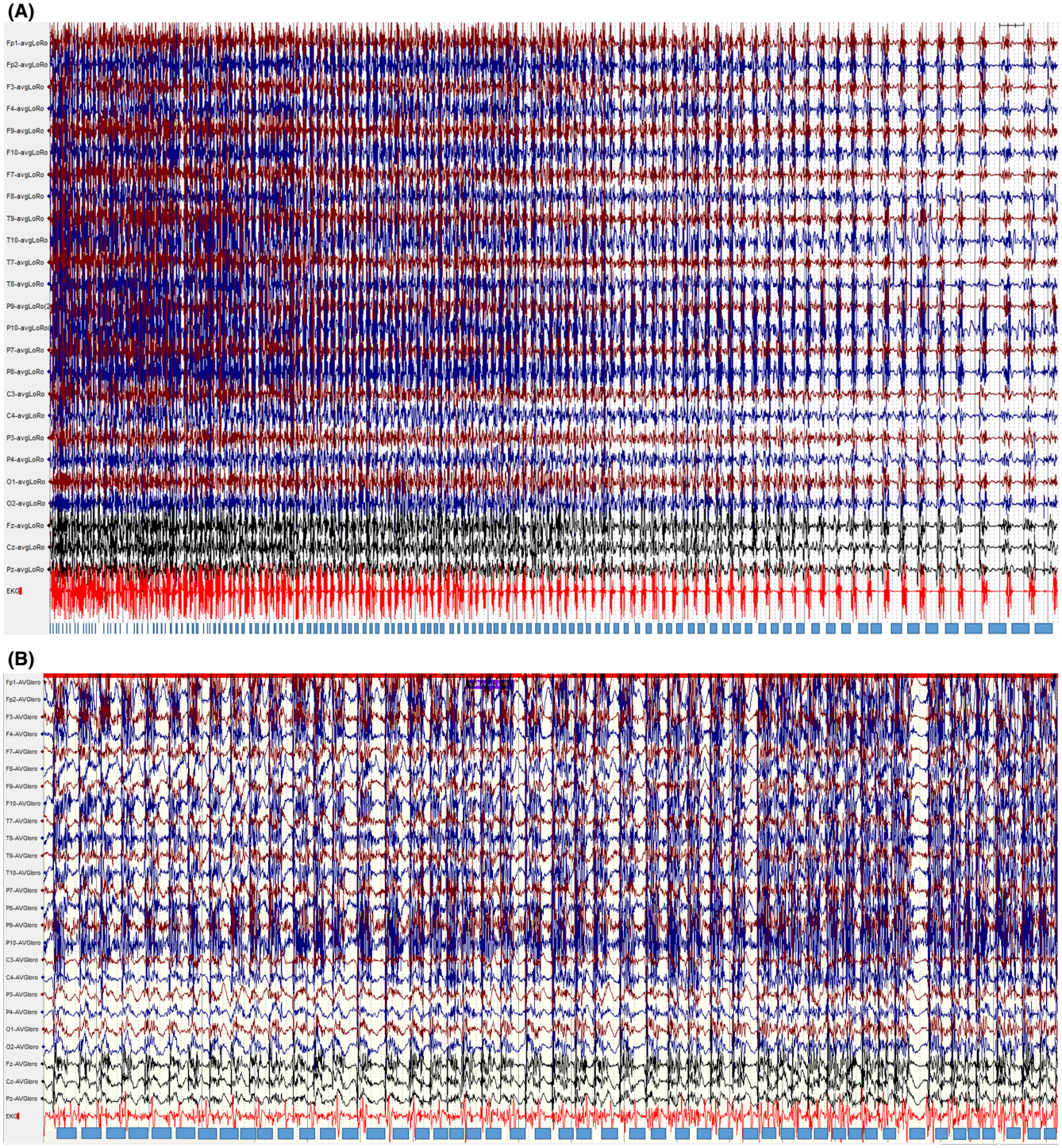

FIGURE 1 Dynamics of the clonic phase in generalized clonic seizures (GCSs). (A) Progressive slowing of clonic phase in a GCS. Please note the electromyography signals in the electroencephalography (EEG) and electrocardiography (ECG) channels. The tonic muscle activity is interrupted for longer and longer periods, resulting in a deceleration of the clonic jerks, until the seizure stops. The bar at the bottom of the figure illustrates the silent periods, with gradually increasing duration, interrupting the tonic muscle activity, generating the typical dynamic evolution of GCSs. (B) Quasi-rhythmic clonic phase, without progressive slowing. In contrast to the seizure shown in Figure 1A, the clonic phase shown in Figure 1B has a quasi-rhythmic frequency, without progressive slowing.

1. GCS type 1: Tonic-clonic GCS with bilateral and symmetric tonic arm extension at the onset of the tonic phase, followed by bilateral and symmetric clonic jerks in all limbs.

2. GCS type 2: Clonic GCS with bilateral and symmetric jerks in all limbs, without tonic arm extension or flexion.

3. GCS type 3: GCS with bilateral asymmetric tonic arm extension, unilateral tonic arm extension combined with

contralateral tonic arm flexion, bilateral tonic arm flexion, or unilateral tonic arm extension, followed by bilateral and symmetric jerks in all limbs. In addition, seizures for which the criteria of GCS type 1 or 2 could not be firmly ascertained because of the quality of the video were classified as GCS type 3. The two experts determined the duration of the tonic and clonic phases and the total seizure duration.

2.3 | Analysis of progressive slowing of clonic phase

Progressive slowing of the clonic phase was defined as gradually increasing silent periods (at least two consecutive changes in same direction) between the clonic jerks, until the seizure stops. In addition, the clonic phase had to follow a sustained (≥3 s) continuous muscle activity (i.e., the tonic phase). To blind the raters for other aspects of seizure semiology, the presence of progressive slowing of the clonic phase was evaluated based on the muscle artifacts in the EEG recordings, without using video data (Figure 1). Raters were blinded to all other data (including PGES). Five raters independently evaluated the presence/absence of the progressive slowing of the clonic phase. Table S1 shows the training and experience of the five raters. Figure S1 details the instructions given to the raters. Majority consensus scoring was used for subsequent analyses.

2.4 | Evaluation of postictal generalized EEG suppression

PGES was defined according to previously published criteria, as an abrupt generalized, severe attenuation of scalp EEG (amplitude <10 μV), during ≥10 s, apart from muscle, movements, respiratory and electrode artifacts, starting in the immediate aftermath or within 30 s after the ictal pattern termination.[5,10] Each recording was evaluated by two investigators (AAA and PR or SB). The average duration from the two raters was used for subsequent analyses. When present, PGES was further classified as prolonged (≥20 s) or very prolonged (≥50 s).

2.5 | Statistical analysis

For evaluation of inter-rater agreement on progressive slowing of clonic phase, we used Gwet agreement coefficient (AC1), to avoid the paradoxes of kappa.[17] Strength of agreement beyond chance was interpreted according to Landis and Koch criteria: poor (<0), slight (.01–.20), fair (.21–.40), moderate (.41–.60), substantial (.61–.80), and almost perfect (.81–1.00).[18] Wilcoxon-Mann- Whitney test was used to compare the PGES duration between seizures with and without progressive clonic slowing. We analyzed binary variables using Spearman's rho and Fisher's exact or chi-square tests, as appropriate. We calculated sensitivity, specificity, accuracy, and positive and negative predictive values of progressive slowing of the clonic phase and GCS type 1 for the presence of PGES, PGES ≥20 s, and PGES ≥50 s. Finally, we performed a logistic regression analysis to identify independent predictors of PGES. In the first step, univariate regression was performed for presence of progressive slowing of the clonic phase and for features previously reported to be associated with PGES: GCS type 1, seizure duration (total seizure duration, tonic and clonic phase durations) and seizures starting from sleep.[10,14,19–21] In addition, we aimed to address whether an asymmetric termination of the seizure is more likely to be associated with PGES, as well as with progressive slowing of the clonic phase. The latter was evaluated based on high-quality video of the seizure, where the patient's extremities were clearly visible and/or unequivocal signal of surface electromyography. Then, multivariable regression analysis was made using variables with significant association with PGES in the univariate analysis, to identify whether they were independent predictors for the PGES, as well as prolonged PGES ≥20 s and very prolonged PGES ≥50 s. For both analyses, we adjusted for patients with multiple seizures by using the variance–covariance estimator (vce cluster) subcommand in our statistical models. We calculated probabilities for PGES, PGES ≥20, and PGES ≥50 s occurrence in different combinations of progressive slowing of the clonic phase and GCS type 1 (presence/absence), as well as the corresponding odds ratios and 95% confidence intervals (CIs). The statistical analysis was performed with Stata version 17.0 statistical package.

3 | RESULTS

A total of 90 bilateral convulsive seizures from 50 consecutive patients (21 female) were recorded and analyzed. The patients´ mean age was 32.9 (median: 31 years, range: 11–62, interquartile range: 24–41). Twenty-nine patients had one seizure, eight patients had two seizures, eight patients had three seizures, three patients had four seizures, and two patients had five seizures each. Thirty-five seizures were GCS type 1, 23 were GCS type 2, 16 were GCS type 3, and 16 were focal motor seizures with bilateral muscle contractions.

PGES was identified in 67 seizures (74.4%, 95% CI 64.3–82.5). PGES ≥20 s was observed in 59 seizures (65.5%, 95% CI 55.1–74.7), and PGES ≥50 s in 14 seizures (15.5%, 95% CI 9.4–24.7). The mean duration of PGES, when present,

was 41.6 ±21.9 s (median 39, range 14–124, interquartile range 27.5–48). Adjusting for patients with multiple seizures, by calculating the average PGES duration for each patient gave similar results (median 40.3 s, interquartile range 29.5–54).

The observed percent agreement among the five raters for the presence/absence of progressive slowing of the clonic phase was 80% (95% CI 75%–85%; $p < .001$). The inter-rater agreement was substantial, with beyond-chance agreement coefficient of .655 (95% CI .56–.75; $p < .001$). For almost all seizures, the majority consensus for progressive slowing of the clonic phase was high (≥4) and there was only one seizure, where the majority consensus was based on three positive ratings. Among the 90 bilateral convulsive seizures, progressive slowing of the clonic phase was identified in 65 (72.2%, 95% CI 61.9%–80.5%).

Compared with seizures without dynamic clonic slowing, those with progressive slowing of the clonic phase had significantly higher occurrence of PGES (98.5% vs 12%; $p < .001$.), prolonged PGES≥20 s (87.8% vs 8%; $p < .001$) and very prolonged PGES≥50 s (21.5% vs 0%; $p = .009$), as well as longer duration of PGES (Wilcoxon test, $p < .001$). Spearman correlation analysis confirmed a significant positive correlation between the progressive slowing of the clonic phase and occurrence of PGES (rho = .88; $p < .001$), prolonged PGES≥20 s (rho = .75; $p < .001$), and very prolonged PGES≥50 s, (rho = .27; $p = .01$). Accordingly, the presence of progressive slowing of the clonic phase had a high positive predictive value and sensitivity for PGES and prolonged PGES≥20 s (Table 1). All seizures ($n = 14$) followed by very prolonged ≥50 s PGES had progressive slowing of the clonic phase, although not all seizures with this pattern had very prolonged ≥50 s PGES. Absence of this dynamic motor pattern excluded the occurrence of very prolonged ≥50 s PGES (negative predictive value of 100%).

As in previous studies[10,14] we found that GCS type 1 had significantly higher occurrence of PGES (97.1% vs 60%; $p < .001$) and prolonged PGES≥20 s (91.4% vs 49.1%; $p < .001$), compared with other types of bilateral convulsive seizures. However, there was no significant difference in the occurrence of very prolonged PGES≥50 s between GCS type 1 and the other bilateral convulsive seizures (20% vs 12.3%; $p = .38$). This was also confirmed by the presence of significant positive correlation between the presence of GCS type 1 and the occurrence of PGES (rho = .42; $p < .001$) and prolonged PGES≥20 s (rho = .43; $p < .001$), but no significant correlation with very prolonged PGES≥50 s (rho = .1; $p = .36$). GCS type 1 occurred in half ($n = 7$) of the seizures followed by very prolonged ≥50 s PGES. In accordance with previous studies, no significant association was found between patient's age or sex with PGES presence ($p = .79$ and $p = .09$, respectively). Table 1 summarizes the diagnostic accuracy measures of progressive slowing of the clonic phase and of GCS type 1 for PGES.

TABLE 1 Diagnostic accuracy measures of progressive slowing of the clonic phase and GCS type 1 for PGES

	PGES	PGES≥20 s	PGES≥50 s
Progressive slowing of the clonic phase			
Sensitivity	95.5 (87.5–99.0)	96.6 (88.3–99.6)	100 (76.8–100)
Specificity	95.7 (78.1–99.9)	74.2 (55.4–88.1)	32.9 (22.5–44.6)
PPV	98.5 (90.4–99.8)	87.7 (79.7–92.8)	21.5 (19.0–24.3)
NPV	88.0 (70.7–97.5)	92.0 (74.4–97.9)	100[a]
Accuracy	95.6 (89.0–98.8)	88.9 (80.5–94.5)	44.3 (32.9–54.2)
GCS type 1			
Sensitivity	50.8 (38.2–63.2)	54.2 (40.8–67.3)	50.0 (23.0–77.0)
Specificity	95.7 (78.1–99.9)	90.3 (74.3–98.0)	63.2 (51.3–73.9)
PPV	97.1 (83.1–99.6)	91.4 (78.0–97.0)	20.0 (12.1–31.3)
NPV	40.0 (34.0–46.3)	50.9 (43.4–58.4)	87.3 (79.8–92.3)
Accuracy	62.2 (51.4–72.2)	66.7 (56.0–76.3)	61.1 (50.3–71.2)

Note: 95% CI are given in parentheses.

Abbreviations: EEG, electroencephalography; GCS, generalized clonic seizure; NPV, negative predictive value; PGES, postictal generalized EEG suppression; PPV, positive predictive value.

[a]Cannot be calculated, as number of false negatives = 0.

Univariate logistic regression analysis (Table S2) showed that progressive slowing of the clonic phase was a very strong predictor for PGES and prolonged PGES≥20 s ($p < .001$). Because all seizures with very prolonged PGES≥50 s had progressive clonic termination, it was not possible to perform regression analysis for this subgroup. GCS type 1 was also a significant predictor of PGES and prolonged PGES≥20 s in the univariate analysis ($p = .004$ and $p = .001$, respectively). Seizures for which the criteria of GCS type 1 or 2 could not be firmly ascertained were classified as type 3.[10] After excluding these seizures from the analysis ($n = 14$), the results remained the same (Table S3). Sleep-onset seizures, seizure duration (total, tonic, or clonic), as well as asymmetric seizure termination were not found to significantly predict PGES in our series (Table S3). Regarding asymmetric termination, nine seizures were excluded from the analysis due to insufficient video or electromyography (EMG) quality. Among the remaining 81, there were 29 seizures that terminated asymmetrically. Nineteen of these (65.5%) presented progressive slowing of the clonic phase, whereas 39 (75%) among the 52 seizures with bilateral, symmetric termination presented that feature. The logistic regression analysis, after adjusting for patients with repeated seizures did not show statistical significant difference (odds ratio [OR] .63, 95% CI .23 to 1.72; $p = .37$).

Multivariate analysis (Table S4) showed that GCS type 1 was an independent predictor of PGES occurrence ($p = .03$), but not of prolonged PGES ≥20 s ($p = .08$) or very prolonged PGES ≥50 s ($p = .94$). In contrast, the presence of progressive slowing of the clonic phase was an independent predictor both for PGES ($p < .001$) and prolonged PGES ≥20 s ($p < .001$). Because all seizures with very prolonged PGES ≥50 s presented gradual clonic termination, it was not possible to perform regression analysis for this outcome. After excluding the 14 equivocal seizures (originally classified as GCS type 3) from the multivariate analysis, GCS type 1 became a significant independent predictor also for the prolonged PGES ≥20 s ($p = .03$), whereas the other results remained unchanged (Table S4).

Finally, we calculated PGES, PGES≥20 s, and PGES≥50 s probabilities and ORs based on different combinations of presence/absence of dynamic clonic slowing and GCS type 1. The combination of progressive slowing of the clonic phase and GCS type 1 had the highest probability and OR of PGES compared with all other combinations (Table 2).

Among the 25 seizures without progressive slowing of the clonic phase, the most frequent pattern (18 seizures; 72%) was a quasi-rhythmic clonic phase. The rest of the seizures showed rhythmic (two seizures) or arrhythmic jerks (five seizures) superimposed on the tonic contractions, at the end of the seizures.

4 | DISCUSSION

Although the underlying pathogenetic mechanisms of SUDEP remain unclear, PGES has attracted considerable attention as a SUDEP surrogate marker, after it was observed in all SUDEP or near-SUDEP cases during long-term EEG monitoring.[5,7] Moreover, prolonged PGES duration has been reported to be associated with increased SUDEP risk.[5,22] Thus the identification of robust clinical biomarkers associated with PGES, and especially prolonged PGES, may support the recognition of epilepsy patients with higher SUDEP risk.

We found that the progressive slowing of the clonic phase in convulsive seizures, with gradually increasing silent periods, is an independent predictor of prolonged PGES. Absence of this feature excludes the occurrence of very long PGES≥50 s with a negative predictive value of 100%. Interrater agreement was substantial.

Several previous studies attempted to determine putative electroclinical PGES predictors.[6,10,14,19,22–24] However, controversial results with significant variability have been demonstrated, presumably due to heterogeneity of the studied populations. One of the parameters that may have impacted previous results is the different seizure phenotypes. GCS type 1 was identified as independent PGES risk

TABLE 2 Probabilities and odds ratios (ORs) for occurrence of postictal generalized EEG suppression (PGES), prolonged PGES≥20 s and very prolonged PGES≥50 s, depending on the presence of progressive slowing of the clonic phase (PSCP) and of generalized clonic seizure (GCS) type 1

Combinations		PGES			PGES≥20 s			PGES≥50 s		
PSCP	GCS type 1	% (95% CI)	OR (95% CI)	*p* value	% (95% CI)	OR (95% CI)	*p* value	% (95% CI)	OR (95% CI)	*p* value
Yes	Yes	100 (89, 100)	43 (2.5, 737)	<.001	93.8 (79.2, 99.2)	15 (3.2, 68.7)	<.001	21.9 (9.2, 40)	2.04 (.6, 6.5)	.23
Yes	No	97 (84.2, 99.9)	20.1 (2.5, 157)	<.001	81.8 (64.5, 93)	3.5 (1.3, 9.8)	.02	21.2 (9.2, 40)	1.9 (.6, 6.1)	.27
No	Yes	66.7 (9.4, 99.2)	.68 (.05, 7.8)	.75	66.7 (9.4. 99.2)	.7 (.06, 8.2)	.77	0 (0, 70.8)[a]	.72 (.04, 14.8)	.83
No	No	4.6 (.12, 22.8)	.0014 (.0001, .02)	<.001	0 (0, 15.4)[a]	.0035 (.0002, .06)	<.001	0 (0, 15.4)[a]	.08 (.005, 1.46)	.09

[a]Based on one-sided 97.5% CI.

factor,[10] a finding that was replicated in later studies.[14,20] Seizures arising during sleep or being unattended were previously also associated with PGES.[19,21,22] Furthermore, recent surface EMG study detected among other quantitative parameters that the slope of the gradual increase in time of the silent periods between the clonic jerks of convulsive seizures, correlated positively with prolonged PGES ≥20 s. This may be indicative of an association between the dynamic lengthening of silent periods and PGES pathophysiology.[14]

In accordance with the previous studies, we found that GCS type 1 was a significant predictor of PGES and prolonged PGES ≥20 s. However, only half of the very prolonged PGES ≥50 s had GCS type 1, although all these seizures showed progressive slowing of the clonic phase.

Several mechanisms have been hypothesized for the development of PGES. Activation of neuromodulatory inhibitory networks, probably involved in seizure termination, may result in suppression of cortical activation and disruption of brainstem activity.[5] Similarly, the gradually longer "silent periods" between clonic jerks is also thought to be involved in the seizure termination mechanism.[11] Although still speculative, this may represent a pathophysiological connection between the progressive slowing of the clonic phase and PGES. Concerning bilateral tonic-clonic seizures without progressive slowing of the clonic phase, we speculate that these are focal seizures with bilateral motor manifestations, due to the involvement of the opercular/bilateral motor area, hence a different ictogenesis than generalized tonic-clonic seizures (or GTCS) and focal-to-bilateral tonic-clonic seizures (formerly known as secondary GTCS).

Another essential finding of the current study is the observation that the combination of progressive slowing of the clonic phase and GCS type 1 had the highest probability and OR of exhibiting PGES (in 100%) and prolonged PGES (in 93%) as compared to all other combinations ($p < .001$). Progressive slowing of the clonic phase was also associated with a 21.9% probability of very prolonged PGES ≥50 s. In other words, the gradual clonic slowing of GCS is necessary for the development of very prolonged PGES; yet it is not sufficient. Large, multicenter studies are needed to identify other factors that contribute to the development of very prolonged PGES, independent from progressive slowing of clonic jerks.

The new insights our findings provide into the possible PGES mechanisms could offer further opportunities in the domain of automatic seizure detection devices, and thus early detection of seizures with high risk for long PGES and possibly SUDEP. Such devices using surface electromyography or accelerometry signals to detect tonic-clonic seizures have been tested successfully already, presenting a high sensitivity.[25] Similar wearable devices based on algorithms that detect the progressive lengthening between clonic jerks could be a future research objective.

Our study has several limitations. Although PGES has been described as a surrogate marker for SUDEP, its accuracy is uncertain. Repeated seizures from the same subjects may bear a risk of bias toward the patients with several seizures. However we have adjusted our statistical calculations for intragroup correlations, as specified in the Methods section. The studied population originates from a highly specialized epilepsy center, thus an over-representation of PGES might exist, as most patients have a more complicated disease course than patients from the general epilepsy population. Yet our population might be more relevant to the study of PGES, given that both SUDEP and PGES are more frequent in populations with refractory seizures.[7,4,26] Furthermore, our rate of PGES in GCS (74.4%) is in accordance with that reported in the literature.[27,28] Nevertheless, a larger population size is needed to confirm our findings and obtain better insight into prolonged PGES risk factors.

Bearing these limitations in mind, our results shed more light on the importance of gradually increasing inhibitory phenomena at the seizure end, for the development of prolonged PGES and possibly an increased risk of SUDEP.

5 | CONCLUSIONS

The phenomenon of gradual deceleration of the clonic jerks is a strong predictor of prolonged postictal generalized EEG suppression (or PGES), a surrogate marker of SUDEP. Progressive slowing of the clonic phase may constitute the basis of biomarkers, implemented into wearable accelerometry or electromyography devices, to identify GCS that are at increased risk of SUDEP.

AUTHOR CONTRIBUTIONS

Maria Vlachou: formal analysis, original draft preparation, review and editing. Philippe Ryvlin: formal analysis supervision, review and editing. Anca A. Arbune: review and editing. Sidsel Armand Larsen: data curation, resources, review and editing. Annette Skræp Sidaros: formal analysis, review and editing. Melita Cacic Hribljan: formal analysis, review and editing. Martin Fabricius: formal analysis, review and editing. Sándor Beniczky: conceptualization, formal analysis, methodology, resources, project administration, original draft presentation, review and editing.

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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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