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Periictal electroclinical characteristics of postictal generalized electroencephalographic suppression after generalized convulsive seizures

Yingying Tang, MD[a], Wei Xia, MD[b], Bo Yan, MD[a], Lili Zhao, MD[a], Dongmei An, MD[a,*], Dong Zhou, MD[a,*]

Abstract

The aim of this study was to investigate the demographic, clinical, and electrophysiological characteristics of postictal generalized electroencephalography (EEG) suppression (PGES), thereby facilitating the recognition of PGES and providing clues regarding its risk factors, pathophysiology, and relationship with sudden unexpected death in epilepsy patients (SUDEP).

We retrospectively reviewed 237 generalized convulsive seizures (GCSs) in 126 patients during long-term video-EEG (VEEG) recordings. The associations of PGES and prolonged PGES (duration >20 seconds) with person- and seizure-specific variables were evaluated independently using SPSS software.

Eighty patients (63.5%, 80/126) exhibited PGES after 127 GCSs (53.6%, 127/237) with an average PGES duration of 41.31 ± 24.03 seconds. The tonic phase was significantly prolonged in patients with PGES and prolonged PGES. PGES was independently associated with ictal semiology, which was attributable to the different proportions of GCS type 1. After seizure termination, patients with PGES had a higher percentage of postictal unresponsiveness and immobility, including oropharyngeal immobility. Between prolonged and short-duration PGES, the former was more likely to phase out gradually followed by immediate body movement, whereas the latter tended to have an abrupt, evoked termination followed by delayed body movement.

Prolonged tonic duration, GCS type 1, postictal unresponsiveness, and immobility were more prone to occur with PGES, which might imply that hyperactivation of inhibitory neural networks underlies the pathophysiology of PGES and subsequent SUDEP. Any form of periictal bedside care, whether it constitutes effective medical intervention or not, is advisable due to its possible contribution to the interruption of PGES. Regardless of the PGES termination pattern, the neural network resuscitation process was progressive.

Abbreviations: AED = antiepileptic drug, CS = convulsive seizure, EEG = electroencephalography, GCS = generalized convulsive seizure, ILAE = International League Against Epilepsy, MRI = magnetic resonance image, PGES = postictal generalized electroencephalography suppression, SUDEP = sudden unexpected death in epilepsy patients, VEEG = video-electroencephalography.

Keywords: epilepsy, generalized convulsive seizure, postictal generalized electroencephalographic suppression, video-electroencephalography

[a] Department of Neurology, West China Hospital of Sichuan University,
[b] Department of Obstetrics and Gynecology, West China Second University Hospital of Sichuan University, Chengdu Sichuan, China.

* Correspondence: Dong Zhou, Professor of Neurology, Department of Neurology, West China Hospital of Sichuan University, No. 37 Guo Xue Lane Chengdu 610041, China (e-mail: zhoudong66@yahoo.de); Dongmei An, Associate Professor of Neurology, Department of Neurology, West China Hospital of Sichuan University, No. 37 Guo Xue Lane, Chengdu 610041 China (e-mail: andongmei2010@gmail.com).

1. Introduction

The risk of sudden death is at least 20 times higher in people with epilepsy than in the general population.[1,2] The incidence of the most frequent epilepsy-related cause of death, namely, sudden unexpected death in epilepsy patients (SUDEP), is substantial in all types of epilepsy and ranges from approximately 0.81‰ to 9.3‰.[1–3] The public health burden of SUDEP is reportedly second only to that of stroke in terms of years of potential life lost.[3] Consequently, identifying the warning signs of SUDEP has become an issue of great concern to clinicians, researchers, and the public health community.

Bird et al[4] first reported a notable electroencephalography (EEG) phenomenon in a case of SUDEP in which seizure cessation was immediately followed by diffuse EEG flatness, after which the patient's pulse faded away. Thereafter, this characteristic EEG performance has been increasingly observed in video-EEG (VEEG)-recorded cases of SUDEP and near-SUDEP,[5–7] subsequently promoting the concept of postictal generalized EEG suppression (PGES)[8] and further inspiring speculation that PGES, as a reflection of "electrocerebral shutdown," might be a potential EEG warning sign of SUDEP.[2,6,8]

However, this conclusion should be drawn with caution due to challenges from subsequent studies. Surges et al,[9] upon performing a matched-pair comparison between patients with

pharmacoresistant focal epilepsy who died from SUDEP and living controls, found no significant difference in either the incidence or the duration of PGES. Another review of VEEG recordings during convulsive seizures (CSs) demonstrated that PGES is not a consistent finding after each seizure attack and that, at the individual level, as more CSs were recorded, fewer cases of prolonged PGES (>20 seconds) occurred consistently.[10] A growing research effort on PGES has been triggered by the controversial role of PGES as a putative warning for SUDEP.

The risk factors for PGES have been evaluated in several studies with conflicting results,[8–20] which may be attributed to the different patient populations. Given that generalized convulsive seizure (GCS) is an acknowledged high-risk factor for SUDEP[1,2] and that PGES occurs mostly after GCS,[9,10,13,15,19] the current study retrospectively reviewed GCSs that occurred during long-term VEEG monitoring at a single epilepsy center in West China to explore the demographic and periictal electroclinical characteristics related to PGES. Due to the possible positive correlation between prolonged PGES and a high risk of SUDEP,[8,11,20] we also performed a subgroup analysis based on the duration of PGES. We hope that these results will provide new clues for PGES identification and early intervention as well as its relationship with SUDEP.

2. Subjects and methods

2.1. Participants

We retrospectively reviewed the archived medical records and VEEG data of consecutive patients from January 2015 to January 2017 at the Epilepsy Center of the Neurology Department at the West China Hospital of Sichuan University, China. This retrospective case-control study was approved by the local ethics committee at West China Hospital of Sichuan University. All these anonymized data are available by request from any qualified investigator.

All enrolled participants were diagnosed with epilepsy based on the International League Against Epilepsy (ILAE)-2017 criteria,[21] had at least 1 GCS (either generalized or focal onset)[22] recorded in >24 hours of long-term VEEG monitoring, and did not meet any of the following exclusion criteria: EEG data were obscured by significant electrode/muscle/breathing/ movement artifacts, and benzodiazepines were administered intravenously during seizure attacks.

On the basis of the definition of PGES that was previously published by Lhatoo et al (2010), namely, immediate generalized EEG activity suppression after seizure termination (within 30 seconds) with an amplitude $<10 \mu V$, all participants and their GCSs were divided into a PGES+ group and a PGES–group. Prolonged PGES was defined by PGES duration >20 seconds and was further filtered from the PGES+ group for subgroup analysis due to its association with a significantly increased incidence of SUDEP.[8,20]

2.2. VEEG data acquisition and review

Thirty-two-channel VEEG data were obtained using a digital system with Galileo NT software (EB Neuro S.p.A., Florence, Italy). Scalp electrodes were placed according to the International 10–20 system at Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fpz, Fz, Cz, and Pz referenced to linked ears. Bandpass filters were set at 0.3 to 70 Hz with a 70-Hz notch filter. A deltoideus electromyogram and single-channel electrocardiog-

raphy (ECG) were routinely recorded. Two experienced clinical neurophysiologists independently reviewed the VEEG records. In cases of disagreement, the VEEG records were checked by an additional clinical neurophysiologist, and a consensus was reached by discussion among all 3 reviewers.

2.3. Collection of variables

For each patient, data on sex, age, age at onset, epilepsy duration, GCS frequency, magnetic resonance image (MRI) lesions, risk factors, epilepsy category, and numbers of antiepileptic drugs (AEDs) were collected. Potential risk for SUDEP was assessed using the Revised SUDEP-7 Risk Factor Inventory, in which higher scores denoted a higher risk.[13,23]

For each GCS, the total seizure duration, seizure origin (focal/ generalized), and seizure termination (abrupt/gradual)[8] were determined by a combination of ictal clinical and EEG manifestations. The convulsive phase was picked up independently and further divided into the tonic phase (generalized body tonic stiffening associated with continuous EEG muscle artifacts) and the clonic phase (generalized rhythmic body jerking associated with intermittent EEG muscle artifacts).[18,24] The semiology of GCSs was classified into 3 types, as described previously[19]: type 1, tonic-clonic GCS with bilateral and symmetric tonic arm extension; type 2, clonic GCS without tonic arm extension or flexion; and type 3, GCS with unilateral or asymmetric tonic arm extension or flexion. Seizures that could not be classified firmly as type 1 or type 2 were included in type 3. After seizure, postictal responsiveness and motion were determined from medical records and VEEG data. Furthermore, postictal motion was detailed in terms of bodily and oropharyngeal activity, whether spontaneous or passive. Peri-ictal interventions from both caregivers and medical staff, including adjustment of the body position, consciousness and vital sign examination, airway clearance, and oxygen administration, were also recorded.

For each PGES, the occurrence, duration, and termination were determined strictly in accordance with the aforementioned definition of PGES. The termination of PGES was categorized as abrupt (sudden, generalized EEG recovery) or gradual (slow, intermittent EEG recovery alternating with brief PGES fragment). In the course of reviewing, we noticed that some instances of PGES termination were induced by the passive movement of patients by bedside caregivers, which included patting, rotating, dragging, swaying and any other forms of movement of the trunk, limbs, head, neck and mouth. Hence, we also categorized PGES termination as evoked, in which PGES ceased immediately following any form of passive body movement, or spontaneous. In addition, some PGES instances ended with immediate body movement, whereas others demonstrated delayed body movement after a time interval to PGES termination, and both were recorded in this study.

2.4. Statistical analysis

The SPSS software package (version 20.0 for Mac, http://www. spss.com/; SPSS Inc, Chicago, IL) was used for statistical analysis. We performed Student t test for continuous data with normal distribution, Mann–Whitney U test for continuous data without normal distribution, and Pearson χ^2 test for categorical data to compare the PGES+ group with the PGES–group and the PGES >20 seconds group with the PGES <20 seconds group. The

threshold of statistical significance was set at *P* value <.05. To determine which variables were independently associated with PGES and prolonged PGES, logistic regression analysis was performed with Bonferroni correction. In addition, a multiple linear regression model was applied to estimate the potential impacts of age, onset age, and tonic duration on PGES duration.

3. Results

A total of 126 patients with 237 GCSs were enrolled after excluding 2 patients with 6 seizures due to the absence or poor visibility of their videos. The duration of VEEG records ranged from 24 to 72 hours. Eighty patients (63.5%, 80/126) exhibited PGES after 127 GCSs (53.6%, 127/237), with an average PGES duration of 41.31 ± 24.03 seconds (34 seconds, 3–70 seconds). Among these 80 patients, 59 (73.7%, 59/80) had >2 GCSs during VEEG monitoring, and 10 (16.9%, 10/59) exhibited inconsistent PGES occurrence after each GCS. In the calculation of the PGES duration, 4 GCSs in 2 patients with <17 seconds of VEEG data were excluded for showing continuous PGES in the recording period but no definite time of termination. Ninety-nine (80.5%, 99/123) PGES episodes in 64 (82.1%, 64/78) patients lasted >20 seconds, and 24 (19.5%, 24/123) PGES episodes in 14 (17.9%, 14/78) patients ended within 20 seconds.

The PGES+ group demonstrated a longer duration of tonic phase (*P* = .001) and an older age (*P* = .024) than the PGES– group. The PGES >20 seconds group also demonstrated a longer duration of the tonic phase (*P* = .004) and an older age at onset (*P* = .006) than the PGES <20 seconds group. Further multiple linear regression showed a 0.97-second increase in the PGES duration for each 1-second increase in the tonic duration (*F* = 10.248, *P* < .001, Bonferroni correction). Surprisingly, a lower score on the Revised SUDEP-7 Risk Factor Inventory was observed in patients with prolonged PGES (*P* = .021). No significant differences in sex, epilepsy duration, GCS frequency, MRI lesion, number of AEDs, total seizure duration, convulsive duration, tonic duration, and so on were observed, and further

logical regression also rejected the independent association of these variables with PGES as well as prolonged PGES. See details in Tables 1–4 and Figure 1A and B.

Regarding ictal semiology, GCS type 3 accounted for a majority in both the PGES+ group and the PGES–group (64.6% vs 78.2%, odds ratio = 0.83, Table 2 and Fig. 1C); however, GCS type 1 was significantly more common in the PGES+ group than in the PGES– group (22.8% vs 4.5%, odds ratio = 5.07, Table 2 and Fig. 1C). Further multivariate regression analysis confirmed that the ictal semiology of GCS was independently associated with the occurrence of PGES (odds ratio = 2.296, *P* = .001, Bonferroni correction; Table 5). This predictive effect of ictal GCS semiology was not replicated in the prolonged PGES group (Table 4).

Various peri-ictal medical interventions were provided for 165 (69.6%) of 237 seizures, although no significant differences were found between either the PGES+ and PGES–groups or the PGES >20 seconds and PGES <20 seconds groups. Postictal unresponsiveness (98.4% vs 30.0%, *P* < .001) or immobility was significantly more commonly observed in patients with PGES than in those without PGES, including both body movements (90.6% vs 30.9%, *P* < .001) and oropharyngeal activity (96.1% vs 73.6%, *P* < .001). However, subgroup differences among the patients with different durations of PGES were mainly observed in the termination of PGES, rather than in postictal responsiveness and motion. In the PGES <20 seconds group, the termination of PGES tended to be abrupt (87.5%, *P* = .023) and induced by the passive movement of patients from bedside caregivers (41.7%, *P* = .023), followed by delayed body movement (54.2%, *P* = .019). In contrast, in the PGES >20 seconds group, a higher percentage of PGES episodes phased out gradually (36.1%, *P* = .023) and spontaneously (80.4%, *P* = .023) with immediate body movement at the endpoint of PGES (71.1%, *P* = .019). See details in Tables 1–4 and Figure 1D and E.

4. Discussion

PGES, as a potential EEG marker of SUDEP, has attracted increasing concern in recent years. However, the electroclinical

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Table 1

Association of PGES and patient-specific variables.

Patient-specific variables	PGES+ group N = 80	PGES–group N = 46	P
Sex, male: female	37:43	18:28	.438
Age, y, mean ± SD	25.60 ± 11.53	20.13 ± 8.36	.024[*]
Age at onset, y, mean ± SD	15.51 ± 11.69	10.96 ± 7.56	.051
Epilepsy duration, y, mean ± SD	10.11 ± 8.65	9.25 ± 7.56	.709
GCS frequency, no./y, mean (range)	70.08 (1–2190)	151.09 (1–2008)	.211
History of febrile convulsions, no:yes	66:14	42:4	.174
Birth history, no:yes	72:8	42:4	.81
History of head trauma or intracranial infection, no:yes	57:23	30:16	.481
Family history, no:yes	79:1	45:1	.69
Brain MRI[†], negative:positive	39:40	19:27	.383
No. of AEDs, mean (range)	1.88 (0–4)	1.96 (0–4)	.618
Epilepsy category, idiopathic:symptomatic:cryptogenic	10:47:23	2:31:13	.302
SUDEP-7 score[‡], mean (range)	3.44 (2–7)	3.63 (2–6)	.13

Continuous data with a normal distribution were given as mean ± SD, and those without a normal distribution were given as mean (range). Categorical data were given as numbers.

AEDs = antiepileptic drugs, GCS = generalized convulsive seizure, MRI = magnetic resonance imaging, No = number, PGES = postictal generalized electroencephalographic suppression, SD = standard deviation, SUDEP = sudden unexpected death in epilepsy patients.

[*] The statistical threshold was set at *P* < .05.

[†] Brain MRI information was absent for 1 of 126 patients.

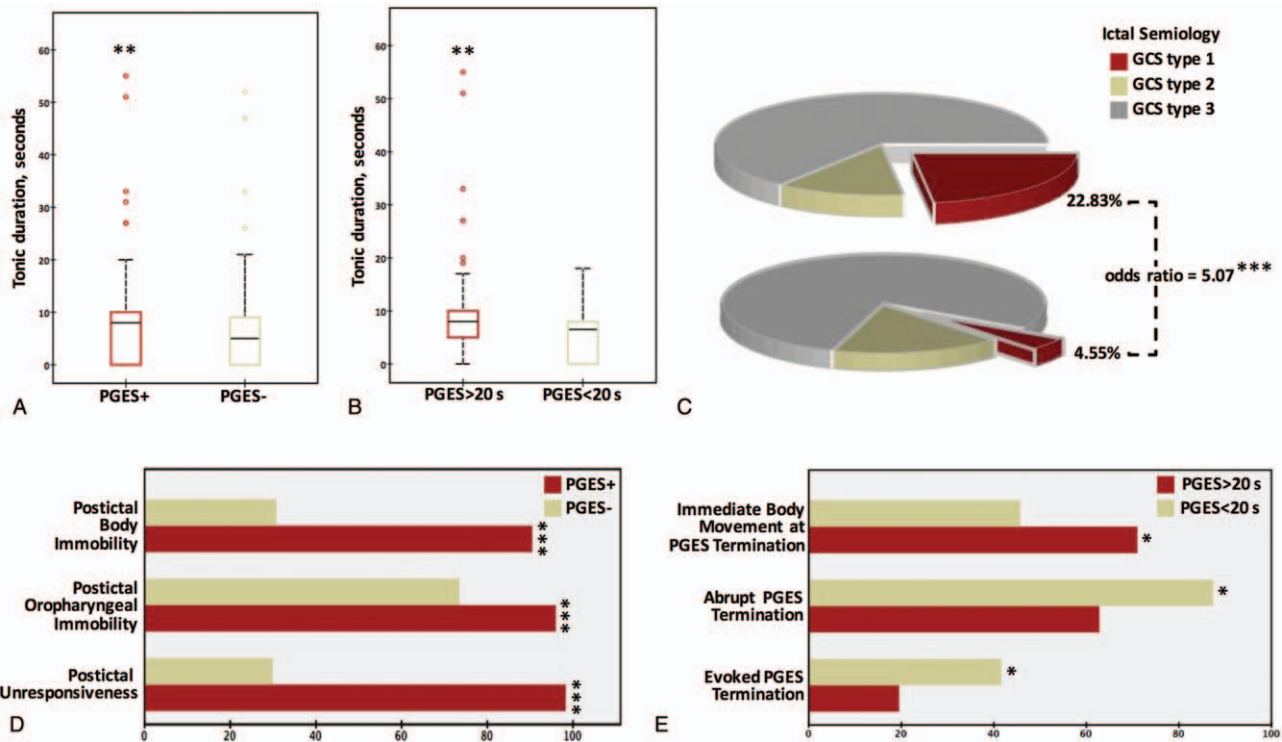[‡] Application of the Revised SUDEP-7 Risk Factor Inventory.

Figure 1. Main electroclinical findings in patients with PGES and prolonged PGES. (A) Duration of the tonic phase in patients with and without PGES. (B) Duration of the tonic phase in patients with PGES >20 seconds and PGES <20 seconds. (C) GCS ictal semiology in patients with and without PGES (GCS type 1 accounted for 22.8% vs 4.5%, respectively; odds ratio = 5.07). (D) Postictal performance in patients with and without PGES. (E) Features of PGES termination in patients with PGES >20 seconds and PGES <20 seconds. $^{***}P<.001$, $^{**}P<.01$, $^{*}P<.05$. GCS = generalized convulsive seizure, PGES = postictal generalized electroencephalographic suppression.

Table 2

Association of PGES and seizure-specific variables.

Seizure-specific variables	PGES+ group N = 127	PGES–group N = 110	P
Season, spring:summer:autumn:winter	27:19:44:37	34:19:36:21	.185
Timing, nocturnal:diurnal	68:59	60:50	.877
State of wakefulness, asleep:awake	72:55	69:41	.345
Seizure origin, generalized:focal	61:66	46:64	.338
Preictal position, side-lying:supine:sitting:others	43:59:25:0	41:53:15:1	.446
Postictal position, side-lying:supine:sitting:others	28:94:4:1	17:91:2:0	.362
Ictal semiology, GCS type1:type 2:type 3	29:16:82	5:19:86	<.001[*]
Postictal responsiveness, no:yes	125:2	33:77	<.001[*]
Postictal oropharyngeal movement, no:yes	122:5	81:29	<.001[*]
Postictal body movement, no:yes	115:12	34:76	<.001[*]
Postictal passive body movement, no:yes	77:50	73:37	.361
Periictal intervention, no:yes	34:93	38:72	.194
Adjustment to recovery position, no:yes	61:66	62:48	.200
Consciousness evaluation, no:yes	61:66	62:48	.200
Vital sign evaluation, no:yes	93:34	87:23	.292
Airway clearance, no:yes	112:15	103:7	.150
Oxygen administration, no:yes	120:7	102:8	.579
Seizure termination, gradual:abrupt	59:68	49:61	.768
Total seizure duration, s, mean (range)	131.94 (40–2425)	91.48 (21–394)	.216
Convulsive duration, s, mean (range)	53.20 (25–128)	58.06 (4–348)	.372
Tonic duration, s, mean (range)	8.24 (0–55)	6.07 (0–52)	.001[*]
Clonic duration, s, mean (range)	44.96 (0–128)	52.00 (3–342)	.803

Categorical data were given as numbers. Continuous data were given as mean (range) due to their non-normal distribution.

EEG = electroencephalography, GCS = generalized convulsive seizure, PGES = postictal generalized electroencephalographic suppression.

[*] The statistical threshold was set at $P<.05$.

Table 3

Association of prolonged PGES and patient-specific variables.

Patient-specific variables	PGES >20 s N = 64	PGES <20 s N = 14	P
Sex, male: female	31:33	5:9	.387
Age, y, mean ± SD	26.14 ± 10.82	21.71 ± 12.54	.087
Age at onset, y, mean ± SD	16.22 ± 11.31	9.93 ± 12.88	.006*
Epilepsy duration, y, mean ± SD	9.93 ± 7.85	11.85 ± 11.94	.825
GCS frequency, no./y, mean (range)	77.11 (1–2190)	44.57 (1–243)	.582
History of febrile convulsions, no:yes	53:11	11:3	.708
Birth history, no:yes	57:7	13:1	.672
History of head trauma or intracranial infection, no:yes	47:17	9:5	.491
Family history, no:yes	63:1	14:0	.638
Brain MRI[†], negative:positive	33:30	6:8	.519
No. of AEDs, mean (range)	1.84 (0–4)	2.07 (0–4)	.405
Epilepsy types, idiopathic:symptomatic:cryptogenic	8:36:20	2:9:3	.766
SUDEP-7 score[‡], mean (range)	3.34 (2–7)	4.00 (2–6)	.021*

Continuous data with a normal distribution were given as mean ± SD, and those without a normal distribution were given as mean (range). Categorical data were given as numbers.

AEDs = antiepileptic drugs, GCS = generalized convulsive seizure, MRI = magnetic resonance imaging, No = number, PGES = postictal generalized electroencephalographic suppression, SD = standard deviation, SUDEP = sudden unexpected death in epilepsy patients.

* The statistical threshold was set at $P < .05$.

[†] Brain MRI information was absent for 1 of 126 patients.

[‡] Application of the Revised SUDEP-7 Risk Factor Inventory.

characteristics of PGES have remained controversial across studies due to the heterogeneity of the patient population. The consensus is that PGES occurs far more frequently after GCS than after any other type of seizure.[9,10,13,15,19] In this context, we performed a retrospective case–control study of epilepsy patients who presented GCS during long-term VEEG monitoring, detecting demographic, and peri-ictal electroclinical variables

Table 4

Association of prolonged PGES and seizure-specific variables[†].

Seizure-specific variables	PGES >20 s N = 99	PGES <20 s N = 24	P
Season, spring:summer:autumn:winter	22:12:34:31	5:6:8:5	.401
Timing, nocturnal:diurnal	54:45	12:12	.689
State of wakefulness, asleep:awake	54:45	16:8	.282
Seizure origin, generalized:focal	46:53	12:12	.756
Preictal position, side-lying:supine:sitting:others	35:41:23	7:15:2	.122
Postictal position, side-lying:supine:sitting:others	20:75:3:1	7:16:1:0	.743
Ictal semiology, GCS type 1:type 2:type 3	25:10:64	3:6:15	.096
Postictal responsiveness, no:yes	98:1	23:1	.273
Postictal oropharyngeal movement, no:yes	94:5	24:0	.261
Postictal body movement, no:yes	89:10	23:1	.361
Postictal passive body movement, no:yes	56:43	18:6	.098
Periictal intervention, no:yes	27:72	5:19	.519
Adjustment to recovery position, no:yes	47:52	10:14	.609
Consciousness evaluation, no:yes	49:50	10:14	.491
Vital sign evaluation, no:yes	74:25	15:9	.229
Airway clearance, no:yes	88:11	21:3	.848
Oxygen administration, no:yes	93:6	24:0	.216
Seizure termination, gradual:abrupt	44:55	12:12	.624
Total seizure duration, s, mean (range)	143.21 (40–2425)	94.96 (47–132)	.089
Convulsive duration, s, mean (range)	52.83 (25–128)	54.08 (33–83)	.777
Tonic duration, s, mean (range)	9.06 (0–55)	6.50 (0–18)	.004*
Clonic duration, s, mean (range)	43.77 (0–128)	49.58 (24–83)	.104
PGES duration, s, mean (range)	47.83 (21–127)	13.17 (2–19)	<.001*
PGES termination, spontaneous:evoked[‡]	78:19	14:10	.023*
PGES termination, gradual:abrupt[‡]	35:62	3:21	.023*
Immediate body movement at PGES termination, no:yes[‡]	28:69	13:11	.019*

Continuous data with a normal distribution were given as mean ± SD, and those without a normal distribution were given as mean (range). Categorical data were given as numbers.

EEG = electroencephalography, GCS = generalized convulsive seizure, PGES = postictal generalized electroencephalographic suppression.

* The statistical threshold was set at $P < .05$.

[†] Four of 127 GCSs were excluded for inadequate VEEG data showing a continuous PGES in the recording period but no definite time of termination.

[‡] In the PGES >20 s group, 2 GCSs with VEEG data preserved to 29 s and 42 s after seizure termination were not included because the PGES persisted in the recording period but detailed information on the PGES termination were absent.

Table 5

Logistic regression analysis of variables related to PGES and prolonged PGES.

	PGES			PGES > 20 s		
	OR	95% CI	P	OR	95% CI	P
Age, y	0.963	0.924–1.004	.075	0.929	0.850–1.015	.102
Sex (male)	1.481	0.797–2.751	.214	1.229	0.355–4.254	.744
Age at onset, y	0.992	0.952–1.034	.712	0.969	0.884–1.061	.491
GCS frequency, no./y	1.001	1.000–1.002	.028	1.001	0.999–1.003	.282
No. of AEDs	1.269	0.878–1.834	.205	1.239	0.651–2.361	.514
Ictal semiology (GCS type 1)	2.296	1.405–3.754	.001*	1.467	0.631–3.414	.374
Total seizure duration, s	0.997	0.99–1.004	.428	0.999	0.995–1.004	.779
Convulsive duration, s	1.008	0.996–1.020	.207	0.981	0.943–1.019	.319
Tonic duration, s	0.964	0.929–1.000	.049	0.891	0.794–1.000	.051
PGES termination (evoked)	—	—	—	4.448	1.217–16.265	.024

AEDs = antiepileptic drugs, CI = confidence interval, GCS = generalized convulsive seizure , No = number, OR = odds ratio, PGES = postictal generalized electroencephalographic suppression, SD = standard deviation.

* The threshold was set by Bonferroni correction, and the significance level was $P < .05$ ($\alpha = 0.05/10 = 0.005$).

that were associated with not only the occurrence but also the prolonged duration of PGES.

This study demonstrated an older age in patients with PGES and a later age at onset in patients with prolonged PGES. Lamberts et al and Xu et al reported the same phenomenon[20,25] and referred to it as a possible proxy for the different etiologies among different age groups.[25] Freitas et al and Pavlova et al also corroborated that PGES, especially of prolonged duration, occurred more often in adults than in children,[11,13,14] for which the explanation might be the immature inhibitory neuronal network in pediatric patients.[26,27] Nevertheless, other previous investigations did not note a significant relationship between age/onset age and PGES,[11,16,18–20,28] probably due to their inclusion of seizure types other than GCS[11,16,28] or the age restrictions they used.[13,19]

Throughout the course of GCS, we found that the tonic phase lasted longer in patients with PGES as well as in patients with prolonged PGES, such that each 1-second increase in tonic duration was associated with a 0.97-second increase in PGES duration. This independent predictive role of prolonged tonic duration in PGES occurrence has been recognized in previous studies.[9,11,18,20] Another retrospective study further corroborated the positive correlation between tonic phase duration and PGES duration in both adults and children.[18] The tonic component has been postulated to represent the most pronounced ictal hypersynchronous neuronal excitation and apnea, presumably followed by severe postictal hypersynchronous neuronal inhibition[29,30] and hypoxemic effects on the brain,[16,18] which might be a possible explanation for the pathogenesis underlying PGES and its persistence.

However, this result was not replicated in other studies,[10,12,24] showing that PGES was not significantly associated with tonic duration. Lamberts et al[10] attributed these discrepancies to the diversity of the semiological characteristics of GCSs across studies. Consequently, an innovative classification based on the ictal semiology of GCSs was conducted in a prospective multicenter cohort[19] and indicated that the risk of PGES varied among the assigned 3 types of GCS. GCS type 1, which is characterized by symmetric bilateral tonic arm extension, was found to be the most relevant semiology to PGES. The manifestation of GCS type 1 that resembles the symptoms of decerebrate response was conjectured to suggest the involvement of the inhibitory neural network located in the brainstem.[19] Our results partially supported the above theory that the incidence of

GCS type 1 would be higher in the PGES+ group than in the PGES–group. The finding that GCS type 3 accounted for the highest proportion in both the PGES+ group and PGES–group in this study was possibly due to the admission mainly of epileptic patients with focal onset warranting a preoperative evaluation.

Following GCS, patients with PGES are more likely to be unresponsive and immobile and have a longer duration than those without PGES.[15,17,18,24] Our results reconfirmed this finding and further refined postictal immobility into the oropharynx, such as chewing, swallowing, and phonating. Postictal impaired consciousness and mobility have been considered signs of inhibitory neural network activation underlying PGES, causing the inability to adjust harmful postictal positions (ie, the prone position) and consequent airway obstruction.[17,18,24] The newly detected postictal immobility in the oropharynx, acting as an additional obstacle to reopening the airway, might further exacerbate peripheral hypoventilation and hypoxemia. These findings coincided with previous observations that seizure-related respiratory depression had a high rate of occurrence in patients with PGES[13,16,24] as well as in SUDEP cases[28] and might provide clues to the possible contribution of hypoventilation to the pathophysiology of PGES and SUDEP.

Another intriguing phenomenon that was noticed here for the first time was the termination pattern of PGES. The patients with shortened PGES developed an abrupt termination of PGES induced by the passive movement of patients from bedside caregivers; however, no significant difference in any peri-ictal medical intervention was demonstrated. Previous investigations merely presented evidence supporting medical care, such as oxygen administration, to reduce PGES presence and shorten its duration.[19] Our results further suggest that any form of peri-ictal interference action from a nearby witness might interrupt the pathophysiology of PGES, regardless of whether their actions constitute an effective medical intervention or even consist only of patting or moving the patient's body. Given that increasingly intelligent biometric techniques have been applied to monitor and optimize interventions for disorders,[31,32] it is reasonable to expect that PGES could enable early warning and intervention in seizures with PGES based on EEG pattern recognition.

Patients whose PGES terminated abruptly on intervention presented a shortened PGES duration, but they showed delayed body movement after an interval following PGES termination. On the contrary, patients with prolonged PGES were predisposed to display spontaneous gradual PGES termination following

immediate body movement. One can easily conclude that it would take time to proceed from PGES termination to body movement. Given that PGES is a sign of enhanced inhibitory neuronal network activity,[8,29,33] its termination represents inactivation of the inhibitory neuronal network. Our findings suggest that the inactivation of the inhibitory neural network and the arousal of the activating neural network, represented by motion, as well as the switching between these 2 systems, might undergo a progressive process.

The role of PGES in the pathophysiology of SUDEP is still a matter of debate.[8,10,17,28,33] Lhatoo et al[8] reported that prolonged PGES appears to identify patients at high risk for SUDEP. However, we obtained a relatively lower risk score for SUDEP in patients with prolonged PGES. The Revised SUDEP-7 Risk Factor Inventory, which was used in this study, has exhibited preliminary feasibility in children by showing an elevated risk of SUDEP in patients with PGES,[13] but has not been applied to adults. Moreover, this inventory does not include high-risk factors for SUDEP of current interest, such as nocturnal seizure and prone position, in the grading criteria.[34] Thus, caution should be taken when directly equating a high score in this screening inventory with a high risk of SUDEP. The exact relationship between PGES and SUDEP cannot be determined

simply by the Revised SUDEP-7 Risk Factor Inventory but warrants further investigation.

Certain limitations of this study should be noted. First, although the total number of participants included might be sufficient, the sample size for conducting the subgroup comparison according to PGES duration appeared to be relatively small and might have reduced the ability to detect potential between-group differences. Second, of the patients who underwent VEEG monitoring in this study, those receiving a preoperative evaluation of focal onset GCS constituted a relatively large proportion of the total, which might have led to a possible selection effect. Third, we did not include variables such as AED withdrawal[10] and cardiorespiratory parameters,[4,5,11,13,16,24,28] which have been reported to be associated with PGES and its duration, due to the lack of detailed measurable documentation in the archived recordings. Last, periictal medical intervention was given at the discretion of bedside staff in this retrospective case-control study, acting as a possible confounder to postictal motion and responsiveness. A further prospective cohort study with a larger sample size, standardized periictal medical intervention, and synchronous cardiorespiratory monitoring data, or even the integration of an efficient biometric index for analysis,[31,32] would be optimal for
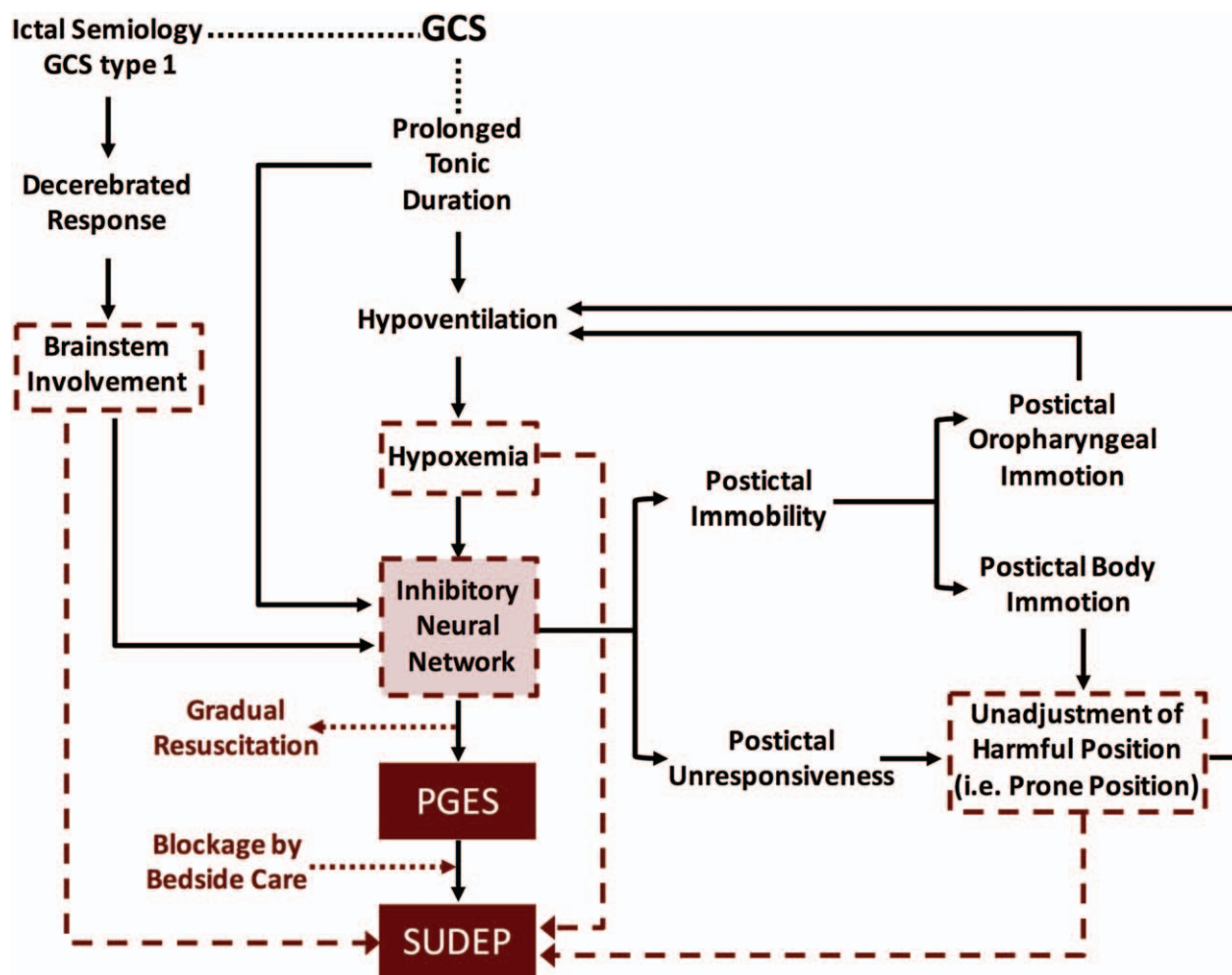

Figure 2. Schematic illustrating the hypothetical relationships among the inhibitory neural network, PGES, SUDEP and their precipitating factors. GCS = generalized convulsive seizure, PGES = postictal generalized electroencephalographic suppression, SUDEP = sudden unexpected death in epilepsy patients.

addressing these issues and deepening our insights into PGES and its relationship with SUDEP.

5. Conclusion

The conclusions are shown in Figure 2. GCS with an ictal semiology mimicking decerebrate extension or a prolonged tonic component had an increased likelihood of being followed by PGES and might facilitate PGES by involving and enhancing hyperactivation of the inhibitory neural network located in the brainstem. Postictal unconsciousness combined with immobility was a much more common manifestation in PGES, worsening airway obstruction by leaving the patient in a harmful position and driving a vicious cycle involving hypoxemia, the inhibitory neural network and PGES. All of these factors, including hypoxemia, harmful postictal position, and brainstem involvement, have been reported to contribute to SUDEP pathophysiology, suggesting an inherent relationship between PGES and SUDEP. However, the duration of PGES might be interrupted by any periictal interference from a nearby witness, regardless of whether it produces an effective medical intervention. In addition, regardless of the pattern of PGES termination, the resuscitation of the inhibitory neural network might be a gradually progressive process.

Author contributions

Yingying Tang: Analysis of clinical and video-EEG data, manuscript writing. Wei Xia: screening, acquisition and sort of clinical data. Bo Yan and Lili Zhao: acquisition and interpretation of video-EEG data. Dong Zhou: study concept and supervision, electroclinical and statistical result interpretation, and critical revision. Dongmei An: study design and supervision, video-EEG data interpretation and critical revision.

References

[1] Devinsky O. Sudden, unexpected death in epilepsy. New Engl J Med 2011;365:1801–11.
[2] Shorvon S, Tomson T. Sudden unexpected death in epilepsy. Lancet 2011;378:2028–38.
[3] Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. Epilepsia 2014;55:1479–85.
[4] Bird J, Dembny K, Sandeman D, Butler S. Sudden unexplained death in epilepsy: an intracranially monitored case. Epilepsia 1997;38(suppl 11): S52–6.
[5] Lee M. EEG video recording of sudden unexpected death in epilepsy (SUDEP). Epilepsia 1998;39(suppl 6):123–4.
[6] McLean B, Wimalaratna S. Sudden death in epilepsy recorded in ambulatory EEG. J Neurol Neurosur Ps 2007;78:1395–7.
[7] So EL, Sam MC, Lagerlund TL. Postictal central apnea as a cause of SUDEP: evidence from near-SUDEP incident. Epilepsia 2000;41:1494–7.
[8] Lhatoo SD, Faulkner HJ, Dembny K, et al. An electroclinical case-control study of sudden unexpected death in epilepsy. Ann Neurol 2010;68: 787–96.
[9] Surges R, Strzelczyk A, Scott CA, et al. Postictal generalized electroencephalographic suppression is associated with generalized seizures. Epilepsy Behav 2011;21:271–4.
[10] Lamberts RJ, Gaitatzis A, Sander JW, et al. Postictal generalized EEG suppression: an inconsistent finding in people with multiple seizures. Neurology 2013;81:1252–6.
[11] Freitas J, Kaur G, Fernandez GB, et al. Age-specific periictal electroclinical features of generalized tonic-clonic seizures and potential risk of sudden unexpected death in epilepsy (SUDEP). Epilepsy Behav 2013;29:289–94.
[12] Lee A, Wu S, Zhou X, et al. Periictal autonomic dysfunction and generalized postictal EEG suppression in convulsive seizures arising from sleep and wakefulness. Epilepsy Behav 2013;28:439–43.
[13] Moseley BD, So E, Wirrell EC, et al. Characteristics of postictal generalized EEG suppression in children. Epilepsy Res 2013;106:123–7.
[14] Pavlova M, Singh K, Abdennadher M, et al. Comparison of cardiorespiratory and EEG abnormalities with seizures in adults and children. Epilepsy Behav 2013;29:537–41.
[15] Semmelroch M, Elwes RD, Lozsadi DA, et al. Retrospective audit of postictal generalized EEG suppression in telemetry. Epilepsia 2012;53: e21–24.
[16] Seyal M, Hardin KA, Bateman LM. Postictal generalized EEG suppression is linked to seizure-associated respiratory dysfunction but not postictal apnea. Epilepsia 2012;53:825–31.
[17] Seyal M, Bateman LM, Li CS. Impact of periictal interventions on respiratory dysfunction, postictal EEG suppression, and postictal immobility. Epilepsia 2013;54:377–82.
[18] Tao JX, Yung I, Lee A, et al. Tonic phase of a generalized convulsive seizure is an independent predictor of postictal generalized EEG suppression. Epilepsia 2013;54:858–65.
[19] Alexandre V, Mercedes B, Valton L, et al. Risk factors of postictal generalized EEG suppression in generalized convulsive seizures. Neurology 2015;85:1598–603.
[20] Xu J, Jin B, Yan J, et al. Postictal generalized EEG suppression after generalized convulsive seizures: A double-edged sword. Clin Neurophysiol 2016;127:2078–84.
[21] Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512–21.
[22] Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017; 58:522–30.
[23] Moseley BD, DeGiorgio CM. The SUDEP Risk Inventory: association with postictal generalized EEG suppression. Epilepsy Res 2015;117: 82–4.
[24] Kuo J, Zhao W, Li CS, et al. Postictal immobility and generalized EEG suppression are associated with the severity of respiratory dysfunction. Epilepsia 2016;57:412–7.
[25] Lamberts RJ, Laranjo S, Kalitzin SN, et al. Postictal generalized EEG suppression is not associated with periictal cardiac autonomic instability in people with convulsive seizures. Epilepsia 2013;54: 523–9.
[26] Hamer HM, Wyllie E, Luders HO, et al. Symptomatology of epileptic seizures in the first three years of life. Epilepsia 1999; 40:837–44.
[27] Korff C, Nordli DRJr. Do generalized tonic-clonic seizures in infancy exist? Neurology 2005;65:1750–3.
[28] Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013;12:966–77.
[29] Lado FA, Moshé SL. How do seizures stop? Epilepsia 2008;49: 1651–64.
[30] Yang L, Shklyar I, Lee HW, et al. Impaired consciousness in epilepsy investigated by a prospective responsiveness in epilepsy scale (RES). Epilepsia 2012;53:437–47.
[31] Samuel OW, Asogbon MG, Geng Y, et al. Intelligent EMG pattern recognition control method for upper-limb multifunctional prostheses: advances, current challenges, and future prospects. IEEE Access 2019;7: 10150–65.
[32] Zhang H, Wu W, Xu L, Zhang YT. Analysis of efficient biometric index using heart rate variability for remote monitoring of obstructive sleep apnea. Neuropsychiatry 2017;7:788–95.
[33] Rajakulendran S, Nashef L. Postictal generalized EEG suppression and SUDEP: a review. J Clin Neurophysiol 2015;32:14–20.
[34] Devinsky O, Hesdorffer DC, Thurman DJ, et al. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. Lancet Neurol 2016;15:1075–88.