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Running title: PGES on SEEG

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Abstract

Objectives

We aimed to describe intracerebral aspects of post-ictal generalized EEG suppression (PGES) following focal to bilateral tonic-clonic ("secondarily generalized tonic clonic") seizures (GTCS) recorded using stereoelectroencephalography (SEEG), and to correlate these with electroclinical features.

Methods

Three independent observers scored semiological and SEEG features. Patient and epilepsy characteristics were collected. Descriptive statistics and multivariate analysis were performed. Operational definition of PGES on SEEG used strict criteria (absence of visible signal at 20µV/mm amplitude, in all readable channels). Post-ictal regional suppression (RS) was identified if only a subset of implanted electrodes showed absence of signal.

Results

We evaluated 100 seizures in 52 patients. Inter-observer agreement was good (Kappa 0.72 for clinical features and 0.73 for EEG features). PGES was present in 27/100 and RS without PGES present in 42/100 seizures. Region of RS included epileptogenic zone in 43/51 (86%). No effect of sampling (multi-lobar or bilateral exploration) was seen. Oral tonicity (mouth opening and/or tonic vocalization during tonic phase of GTCS) was associated with presence of PGES (p=0.029; negative predictive value (NPV) 0.91). Bilateral upper limb extension during tonic phase correlated with PGES (p=0.041; NPV 0.85). Association of both oral tonicity and bilateral upper limb extension had high NPV of 0.96.

Significance

SEEG recordings confirm true absence of signal during post-ictal EEG suppression. PGES is unlikely when both upper limb extension and oral tonicity are absent. We hypothesize that bilateral tonic seizure discharge at bulbar level brainstem regions is associated with production of oral signs and may relate to mechanisms of PGES.

Key words

Post-ictal generalized suppression; PGES; stereo-EEG

Introduction

Post-ictal electroencephalographic (EEG) suppression (PGES) is a pattern of generalized flattening on scalp EEG that may be observed post-ictally after focal to bilateral tonic-clonic seizures[1, 2], and rarely reported following focal seizures[3]. While recognizing the importance of terminology when describing seizure types[4], since the majority of existing PGES literature uses the earlier terminology of "secondarily generalized tonic-clonic seizures" (GTCS), we adopt this abbreviation here for clarity. A large study reported that all cases of electrophysiologically documented sudden unexpected death in epilepsy (SUDEP) or near-SUDEP were associated with PGES following GTCS[5]. An association between PGES measured using scalp EEG, and a specific semiological pattern of GTCS evolution has been reported, in which tonic posturing of upper limbs (UL) evolving to bilateral symmetric upper limb extension was associated with severe post-ictal EEG flattening[6]. Bilateral UL extension in this context, with its resemblance to decerebrate posture, likely represents brainstem involvement during the tonic phase of the GCTS.

Recording method is an important consideration, since deep electrical sources, subtle modulations and/or electrical changes occurring within a restricted volume of neural tissue are not usually visible on scalp recordings[7]. Subdural recordings, while informative, do not provide information on deeper structures and tend to be limited in spatial sampling in terms of number of lobes explored[8].

Here, we describe the clinical and electrical expression of focal to bilateral tonic clonic seizures in a series of patients undergoing intracerebral recording with stereoelectroencephalography (SEEG). We particularly wished to describe the characteristics of seizure termination and post-ictal EEG change as visualized using intracerebral recording, and assess whether any clinical or electrical features correlated with occurrence and duration of post-ictal EEG suppression.

Materials and Methods

Patient selection

Adults and children undergoing video-SEEG for presurgical evaluation in the Epilepsy Unit at Timone Hospital, Marseille between 2000 and 2015, with focal to bilateral tonic-clonic seizures, were identified. All consecutive GTCS were included, both spontaneous and electrical stimulation-evoked seizures. All patients had detailed clinical evaluation and magnetic resonance imaging (MRI), and underwent SEEG exploration following long-term video-EEG monitoring with scalp EEG and other non-invasive studies including magnetoencephalography and positron emission tomography. Placement of electrodes was based upon non-invasive information providing hypotheses about the localization of the epileptogenic zone (EZ). Clinical and epileptological features were collated for each patient in a spreadsheet. The institutional review board of Aix-Marseille University and Timone University Hospital approved the use of human subjects for this study.

SEEG recordings

Recordings were performed using intracerebral multi-contact electrodes (10–15 contacts, length: 2mm, diameter: 0.8 mm, 1.5 mm apart) placed intracerebrally according to Talairach's stereotactic method. A post-operative computerized tomography (CT) scan was then used to verify the absence of bleeding and the position of electrodes.

Signals were recorded on a 128 or 256 channel Deltamed^{TM} system, were sampled at 256, 512 or 1024 Hz depending on the period of recording, and recorded on a hard disk (16bits/ sample) using no digital filter. Two hardware filters were present in the acquisition procedure:

a high-pass filter (cut-off frequency equal to 0.16Hz at -3dB), and an anti-aliasing low-pass filter (cut-off frequency equal to 97 Hz at 256 Hz, or 170 Hz at 512Hz or 340 Hz at 1024 Hz).

Antiepileptic drug (AED) reduction or withdrawal was undertaken in all patients from onset of SEEG recording.

Semiological analysis of GTCS

The main focus of this study was the transition phase of focal to bilateral tonic-clonic seizure, beginning with first sign of onset of "generalization" (e.g. early forced head deviation, early forced eye deviation, vocalization, or asymmetric forced facial contraction, as per Jobst et al[9]). Criteria for diagnosis of focal to bilateral tonic-clonic seizures was in keeping with those proposed in the most recent ILAE position paper on seizure classification[10]. The various clinical stages were assessed, with particular attention paid to the final (stable) upper limb posture attained at the end of the tonic phase[11]. This was scored independently by 2 experienced epileptologists blinded to other clinical data (AMcG and AM), following the classification proposed by Alexandre et al[6]: Type 1, characterized by bilateral upper limb (UL) extension; Type 2, characterized by no significant tonic posture and only clonic jerks of UL; Type 3, characterized by asymmetric UL posture.

Seizures which could not be fully scored because of poor visibility of video (e.g. patient under sheets) were scored as Type 3, following the same methodology as Alexandre et al[6].

However, any seizure which could be clearly visualized but that did not fit into this scheme was classed as Type 4. In case of disagreement between observers, a third blinded review was performed by an experienced epileptologist (SR) and the consensual result was retained. We also noted presence/absence of vocalization, mouth opening, clinical seizure duration and whether seizure arose from sleep. We scored presence/absence of tonic mouth opening, which could be symmetric or asymmetric, and tonic vocalization. These signs could be observed

separately or together in the course of the tonic phase of GTCS and we collectively termed these "oral tonicity" as suggested by Xu et al[12]. Seizures in which the mouth could not be clearly visualized (n=8) and in whom no audible vocalization occurred were scored as negative for mouth opening.

Electrophysiological (SEEG) analysis of GTCS

Interictal activity and seizure patterns were analyzed visually in bipolar montage and in some cases also using quantified signal analysis (Epileptogenicity Index; see Bartolomei et al[13])). SEEG interpretation of seizures was based on anatomical-electroclinical correlations[14]. Stimulation studies were performed as indicated for each case, for functional mapping and/or additional definition of EZ. SEEG traces were examined by 2 experienced epileptologists blinded to other clinical data (AMcG and AM). Any channels evidently contaminated by artefact were excluded from analysis.

Since no pre-existing diagnostic electrophysiological criteria existed for the appearance of post-ictal suppression on SEEG recording, we proposed the following operational definition for **PGES**:

- Generalized flattening of SEEG occurring within 30 seconds of clinical end of GTCS. The term "generalized" is clearly relative since the cerebral data is limited to sampled areas but means in this context that all readable contacts of all implanted electrodes simultaneously show flattening.
- No signal visible when looking at SEEG at 20µV/mm; low frequency filter 0.3 sec; high frequency filter 70Hz (representing marked increase in gain compared to usual parameters for reviewing SEEG data, to maximize the chance of detecting low amplitude activity).

- We did not specify a minimum duration, in contrast to previous studies using surface EEG[6], because of lack of predefined data on the appearance of PGES using SEEG and known discrepancies between surface and EEG recording[7].

When suppression was present in some but not all channels, we termed this **post-ictal regional suppression (RS)**, defined operationally using the same criteria as listed above for PGES.

We noted SEEG electrode placements and brain regions explored; unilateral/bilateral implantation; number of lobes explored (temporal, frontal, parietal, occipital, insular in each hemisphere); whether seizure arose from sleep; spontaneous/stimulation-triggered seizure; and presence, duration and type of post-ictal EEG suppression (PGES and/or RS). Epileptological data were recorded for all patients (age of epilepsy onset, etiology, etc.)

Statistical analysis

Kappa scores for degree of agreement between observers were calculated for determination of seizure types (1, 2, 3 or 4) and the presence of PGES. After establishing sufficient inter-observer agreement, descriptive univariate analysis of occurrence of PGES and/or RS in association with person- and seizure-specific variables was examined by Fisher's exact test, chi-square test, Kruskal-Wallis test or Mann-Whitney U test, as appropriate. Inferential multivariate analysis was performed using mixed logistic regression analysis with correction for individual effects and the varying number of seizures contributed by each person.

Results

Patient and seizure characteristics

Fifty-two patients were included with a total of 100 seizures. Age range at time of SEEG was 8-62 years, mean 30 years; 45 GTCS occurred in male patients and 55 GTCS in female patients. Duration of epilepsy prior to SEEG varied from 3-50 years (mean 19.2). Epilepsy localization following SEEG exploration was as follows: temporal lobe epilepsy (TLE) "plus": 16 patients (31%); TLE: 11 patients (21%); FLE 8 patients (15%); central region epilepsy 4 patients (8%); posterior cortex epilepsy 8 patients (15%); multi-focal epilepsy 5 patients (10%).

Fifty-six seizures were recorded with bilateral SEEG electrode placement and 44/100 unilateral. In terms of number of lobes explored (temporal, frontal, parietal, insular, occipital in each hemisphere), the following were noted: 2 lobes n=4; 3 lobes n=17; 4 lobes n=32; 5 lobes n=33; 6 lobes n=12; 8 lobes n=2. Thus, 53/100 seizures were recorded with 2-4 lobes explored and 47/100 seizures recorded with 5-8 lobes explored.

A total of 100 seizures, were analyzed, 90 spontaneous and 10 provoked by diagnostic cortical direct electrical stimulation. Twenty-three patients had >1 GTCS recorded during SEEG (range 2-6; mean 1.85). All patients also had habitual focal seizures without secondary generalization recorded during SEEG. Fifty-two GTCS occurred during sleep (stage not specified) and 48 during wakefulness. Seizure onset of initial focal discharge preceding generalization was right-sided in 46 seizures, left-sided in 39 and bilateral in 15. Oxygen administration was not routinely employed but given post-ictally in 18/100 seizures, in general >20 seconds after seizure offset.

GTCS semiology

Total GTCS duration was 14-140 seconds (median 50). Seizure types were scored as follows: 38/100 seizures had Type 1 semiology (bilateral UL extension at end of tonic phase), 3/100 seizures Type 2 (UL clonic jerks, no significant UL tonic posturing), 57/100 seizures Type 3 (asymmetric UL tonic posturing; 2/100 seizures Type 4 (Table 2). Both Type 4 seizures occurred in the same patient, who showed generalized hypertonicity without limb posturing and predominantly head and eyelid clonus, and thus did not fit into the classification proposed by Alexandre et al[6]. Of 9/23 with >1 GTCS and varying clinical pattern, 8/9 were either type 1 or type 3 generalization; 1/9 variably had type 1, 2 or 3 patterns. Oral tonicity (mouth opening and/or vocalization) was present in 68/100 (Table 2). While Xu et al.'s definition including tonic mouth closure, and was looked for in the present study, we did not however see clear-cut examples of this. It should be noted that (as for electrophysiological criteria), we erred on the side of strictness: any seizure in which the mouth could not be clearly visualized was scored negative for mouth signs. Of the 23 patients with >1 GTCS recorded, 5/23 (22%) presented PGES for some seizures but not others; 14/23 (61%) always showed the same semiological type of GTCS and 9/23 (39%) showed varying types; and 16/23 (70%) always showed the same oral tonicity value. A total of 13/23 patients with multiple seizures showed inhomogeneous semiology for at least one of the following 3 variables: PGES, semiological type and oral tonicity. Such heterogeneity within patients explains the impossibility of univariate analysis per patient, and the study thus focusses on analysis per seizure.

In the immediate post ictal period, patients were nearly all in a comatose state, often with stertorous breathing. However more rarely fairly rapid recovery was seen (n=2), or automatic behavior with altered consciousness (n=1).

GTCS electrophysiological characteristics

Onset of generalization was defined clinically (see Methods) and occurred at a variable time delay after onset of focal seizure (2-124 seconds). Notably, no clear SEEG change corresponding to clinical phase of onset of generalization was generally visible, and it did not appear possible to predict that generalization was taking place from visual inspection of cortical rhythms alone (Figure 1). We also noted that during GTCS, some cortical regions did not display epileptic discharge during the tonic phase; this "sparing" of certain structures could even involve motor system cortex (Figure 1).

Seizure endpoint was defined clinically (last clonic jerk). Unlike onset of generalization, there tended to be clearer electroclinical correlation at seizure offset with the last clonic jerks clearly time-locked with clonic bursts on SEEG.

PGES (as defined in the Methods sections) was observed in 27 seizures (27%) and no PGES occurred in 73 (73%) seizures. PGES duration ranged from 3 to 54 seconds (median 23). PGES occurred abruptly at seizure offset (Figure 2) in 22/27 and in 5/27 seizures PGES was preceded by a period of post-ictal regional suppression (RS) (see below) (Figure 3). End of PGES was characterized by progressive return of electrical activity with variable involvement of electrodes. Contacts exploring the EZ were often slower to recover than other regions.

A total of 47/100 seizures exhibited RS: 5 preceding PGES as described above, and 42/100 exhibiting RS alone with no associated PGES. Of these 42 RS without PGES, 23 involved <50% of electrode contacts and 19 were widespread with >50% of all SEEG contacts showing suppression. This latter pattern could resemble a "subtotal" form of PGES with minimal activity visible in only a few electrode contacts. Duration of RS ranged from 3-63 seconds (median 21). RS, if present, very often involved the same electrode contacts as those involved in the EZ for a given patient, as characterized by overall SEEG analysis: for those with RS alone, localization of RS included EZ in 36/42 seizures (86%) and for the total group of RS +/-subsequent PGES, localization included EZ in 46/47 (98%) seizures.

Surgical outcome

Of the 52 patients, 25/52 (48%) underwent resective surgery and 27/52 (52%) were not operated, of whom 22/27 (81%) because of contraindication: bilaterality, involvement of functional zone (motor, language, visual) or both. Of the other 5/27 non-operated patients, 3 showed improvement (of whom 2 after thermocoagulation performed at the end of the SEEG recording) and 2 declined surgical treatment. No difference in surgical rate was seen in patients with and without at least one seizure with PGES: of 16 patients with PGES, 7 were operated and 9 were not operated; of 36 without PGES, 18 were operated and 18 were not operated (chi square 0.17; p=0.67).

In terms of the surgical results, follow-up data is available for 21/25 operated patients with a mean follow up of 74 months (12-196): 5/21 (23.8%) are Engel class I, 3/21 (14.3%) Engel class II, 5/21 (23.8%%) Engel class III and 8/21 (38.1%) Engel class IV. No difference was seen in surgical outcome between subjects with and without PGES, comparing 7/21 with favorable outcome (Engel classes I or II) with 14/21 who had poorer outcome (Engel classes III or IV) (Chi square 1.05, p=0.31).

Univariate analysis

Results are summarized in Table 1 listing patient characteristics and Table 2 comparing seizures, in terms of post-ictal suppression pattern. No patient-related factor showed significant association with presence of PGES and/or RS. In order to attempt to investigate possible effects of sampling bias, we analyzed relation between number of lobes explored, bilaterality versus unilaterality of implantation, and presence/absence of PGES and/or RS. No significant difference in occurrence of PGES or RS was seen between unilateral/bilateral explorations, nor according to number of lobes explored (Table 1). PGES occurred in 4/21 unilateral explorations and 11/31 bilateral explorations (Chi square 1.65, p=0.19). Mean

number of explored lobes was 4.8 for patients with PGES in at least one seizure, 4.2 in those with RS but no PGES, and 4.5 in those with no suppression (p= 0.498).

Presence of PGES was correlated with Type 1 tonic posture (bilateral UL extension) (Chi^2 25.3; p <0.001) and oral tonicity (tonic mouth opening and/or vocalization) (Chi^2 8.15; p=0.017). Negative predictive value of Type 1 posture alone was 0.85 (CI95% 0.77-0.91) and of oral tonicity alone 0.91 (CI95% 0.83-0.95). The presence of either one of these features had a negative predictive value of 0.96 (CI95% 0.90-0.99): that is, absence of both signs was associated with very low probability of PGES (Table 3). Other clinical and electrophysiological variables were not correlated with presence of PGES. In particular, no specific region of ictal onset correlated with presence or duration of post-ictal generalized or regional EEG suppression. RS (whether involving < or >50% of electrodes) showed an independent significant association with Type 1 posture (Table 2); however, no association was present between RS and oral tonicity. An association was also seen between RS and right sided laterality of EZ, not present for PGES.

Multivariate analysis

The best mixed model of logistic regression showed a significant effect on the probability of presence of PGES for type 1 tonic posture (p=0.041, OR=8.99 with CI95% 1.09-74.15) and oral tonicity (p=0.029, OR=40.29 with CI95% 1.48-1100.19). This model takes into account the bilaterality of the seizure onset and the total duration of GTCS - although their effect is not significant - as well as the different numbers of seizures per patient.

Discussion

The present study using SEEG to investigate focal to bilateral tonic clonic seizures ("secondarily generalized tonic clonic seizures", GTCS) and PGES showed that (1) post-ictal EEG suppression is characterized by true absence of measurable electrical signal by intracerebral macroelectrodes and not merely markedly reduced amplitude activity; (2) while inevitable sampling issues exist, the presence of suppression across all electrodes in a multi-lobar +/- bilateral distribution makes it likely that true generalized suppression is being recorded; (3) certain semiological features during the tonic phase of GTCS are associated with PGES: bilateral upper limb extension, and oral tonicity (mouth opening +/- vocalization), the absence of which make PGES unlikely; (4) post-ictal regional suppression (RS) may also occur in a regional distribution that often preferentially involves the seizure onset zone as defined by SEEG, and which also showed association with bilateral upper limb extension but not with oral tonicity.

Electroclinical ictal patterns on SEEG

Previous studies reporting PGES and its possible relation with mechanisms underlying SUDEP have been largely based on surface EEG recording[3, 6], in which only activity of sufficient amplitude and within a certain frequency range can be recorded because of the skull barrier, whereby very low amplitude cerebral activity might appear "flat" on surface EEG. For this reason, some overestimation of incidence and duration of PGES reported in studies of scalp EEG might be suspected. Mismatch between scalp and intracranial EEG data when evaluating PGES was previously highlighted in a study using simultaneous scalp and intracranial EEG[7], in which only 7/15 with PGES on scalp EEG also showed true suppression on intracranial recording. It has already been observed from studies using subdural grids that

GTCS are not in fact "generalized", since not all contacts of grids show seizure activity during the period of clinical signs[8]. However, these authors suggested that "epileptiform discharges confined to motor or supplementary areas of the frontal lobe and seizure-induced changes of activity of subcortical structures such as the basal ganglia could suffice to produce clinical signs of general motor involvement"[8]. In fact, the present findings illustrated that even motor system cortex could show absence of epileptic activity during the tonic phase of the seizure (Figure 1), suggesting that cortical activity was not the main determinant of semiological expression during this part of the seizure. Taken together, the present observations reflect the likely driving role of subcortical structures in generalized seizure dynamics and in determination of clinical pattern[15], once the seizure has passed from a focal to a generalized phase.

While not the main focus of the present study, the surgical outcome results are of interest: firstly, a relatively low rate of surgical intervention (48%) was seen following SEEG in this series. This is in quite marked contrast to our usual surgical rates of 60-88% after SEEG, as reported in previous papers from our group including various epilepsy types[16-20], and was due here to a high rate of surgical contraindication due to bilateral involvement, functional cortical involvement, or both. In addition, long-term surgical results are also rather poor with less than 25% Engel Class I outcome, wherein usual overall seizure freedom rates for our centre are around 60%-80% depending on epilepsy type[16, 19, 21], in keeping with published series from other groups. Indeed, many of the operated cases had resection of only part of the EZ, because of proximity to functional cortex. Taken together, these results suggest that the series presented here, selected because of recorded GTCS during SEEG, showed an over-representation of bilateral epilepsies as well as those involving functional cortex, which may be factors predisposing to secondarily generalization.

Electroclinical correlates of GTCS and post-ictal suppression on SEEG

As well as confirming the previously reported association between bilateral upper limb tonic posture and PGES[6], an interesting observation in the present study was the high degree of correlation between the semiological signs of wide mouth opening and/or vocalization and PGES, collectively termed oral tonicity, in keeping with those of a surface EEG study[12]. Indeed, in the present work, absence of oral tonicity had a strongly negative predictive value for PGES, which was even stronger when combined with bilateral upper limb tonic posture, thus conferring a useful clinical pointer since absence of both signs makes occurrence of PGES unlikely. Mouth opening during GTCS is a common observation that occurs during the tonic phase of the majority of secondarily generalized seizures in humans[22], often associated with involuntary vocalization[9]. In our patients, mouth opening could be symmetric or asymmetric, the latter tending to occur in association with asymmetric facial contraction (the previously described "triangular mouth"[22, 23]), nearly always accompanied by vocalization. In Wada's seminal study of *papio papio* baboons, the maximal stage of kindled seizures ("rapid generalization and bisymmetrical convulsive seizure") involved "sustained screeching vocalization" and corresponded to rapid tonic (rather than spike-wave) discharge within bulbar reticular formation[24]. It could therefore be hypothesized that mouth opening and vocalization during the tonic phase of GTCS reflect the presence of a sufficiently tonic (fast, low voltage) bilateral epileptic discharge involving brainstem at the level of the bulbar nuclei. Since not all seizures with oral tonicity in the present study displayed PGES, it seems likely that other non-seizure related factors, including genetic predisposition as seen in animal models[25], play a role in determining whether PGES occurs[26]. While bilaterality of seizure onset did not *per se* have a significant effect on presence of PGES in the present study, it is of interest that the best multi-variate model showing significant effects of oral tonicity and bilateral UL extension included the condition of bilateral seizure onset.

Hypothetical framework: brainstem spreading depression and laryngospasm?

It has been suggested from animal models that genetic predisposition may render some individuals with epilepsy more susceptible to both PGES and SUDEP because of lower threshold for brainstem spreading depolarization at seizure termination[25]. Spreading depression (SD) refers to a slowly self-propagating wave of depolarization, which can be triggered by seizure activity, with direct current (DC) shift visible on EEG[27]. Genetic animal models of SUDEP investigating the effect of cortical seizures using DC recordings showed a DC shift in brainstem structures associated with seizure termination, autonomic failure and SUDEP[25]. Very large DC shifts are associated with depolarization block, which can underlie spreading depression. This phenomenon can naturally follow a seizure, since depolarization block belongs to the same dynamic repertoire as seizures[28]. Accordingly, *in vitro* models of seizures demonstrate shut-down of synaptic activity and refractoriness after seizure offset [29]. The complete absence of electrical activity observed in the present study suggests that PGES may reflect this process of depolarization block. This provides a potential mechanistic explanation and thus provides a conceptual framework for thinking about the causes of SUDEP in humans[30], since spreading depression within brainstem structures could lead to shutdown of respiratory regulation, apnea, and then asystole, which was observed to be the reproducible sequence of all recorded SUDEP cases in the MORTEMUS study[5]. Our main hypothesis from the present observations is that oral tonicity may represent a clinical marker of bilateral tonic (fast activity) seizure discharge involving brainstem at the level of bulbar nuclei, which could thus trigger SD in susceptible subjects.

Recent animal studies have analyzed seizure-induced apnea during GTCS[31-33]. Both obstructive apnea caused by laryngospasm (tonic adduction of the vocal cords) and central apnea may occur during GTCS, but notably obstructive rather than central apnea was

associated with EEG flattening and cardiac arrhythmia[33]. This marked effect of laryngospasm occurred in a context of attempted respiration against a closed glottis, provoking an intense autonomic response. The proposed model suggests that seizure activity propagates to medullary regions where it impacts on medullary nuclei, respiratory centers and laryngeal motor neurons, with obstructive apnea occurring due to tonic closure of vocal cords. While in the present series we do not have data on cardio-respiratory function, this model could also fit with our clinical observations of oral tonicity, since involuntary tonic vocalization during GTCS is considered due to forced expiration against closed vocal cords[9, 34], which might immediately precede apnea if vocal cord adduction persisted. Future animal studies could further explore the relation between tonic bulbar-level seizure discharge, laryngeal function and PGES. Finally, a recent clinical MRI study highlighted the presence of brainstem atrophy in subjects who subsequently presented SUDEP, compared to a control population[35], suggesting vulnerability to autonomic dysfunction at this anatomical level. Thus, various multi-modal evidences appear to be converging upon a putative role for brainstem structures in some epilepsies, suggesting a pathophysiological framework for the observed association between PGES and SUDEP.

Key points

- Stereo-EEG reveals true absence of signal during post-ictal EEG suppression
- PGES is associated with ictal mouth opening +/- vocalization (“oral tonicity”)
- Absence of both oral tonicity and upper limb extension indicates low risk of PGES
- Bilateral tonic discharge in bulbar structures could explain link between oral tonicity, PGES and eventual risk of SUDEP

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Conflict of interest

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

Ethical statement

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

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Table 1 Description of patient characteristics (n=52)

PATIENTS		**n or mean (95% CI)**
Number of patients		52
	With at least 2 seizures (max. 6)	23
	With inhomogenous seizures regarding PGES	5
	With inhomogenous seizures regarding PGES, type or oral tonicity	13
Sex		
	F	25
	M	27
Age at epilepsy onset		
	Child <5 years	15
	Child 5-17 years	28
	Adult >=18 years	9
Epilepsy duration in yrs : mean (95% CI)		19.2 (16.6-22.0)
Epileptogenic zone as defined by SEEG		
	Central region	4
	Premotor	5
	Prefrontal	3
	Mesial temporal	9
	Lateral temporal	2
	Temporal "plus"	16
	Posterior cortex	8

	Multifocal	5
SEEG exploration		
	Bilateral	31
	Unilateral	21
Number of explored lobes		4.4 (4.1-4.8)

Table 2. Comparison of seizures (n=100) with regards to pattern of post-ictal suppression on SEEG: post-ictal generalised suppression (PGES), post-ictal regional suppression (RS) or no suppression

					p value (univariate descriptive analysis)			
SEIZURES		**PGES**	**RS without PGES**	**no suppression**	**PGES / RS without PGES / no suppression**	**PGES Yes / No**	**RS (without PGES) vs no suppression**	**RS vs PGES**
Number of seizures (n = 100)		27	42	31				
GTCS from sleep		16	22	14	0.562	0.510	0.709	0.755
Type GTCS					**< 0.001 *** **	**0.003 ****	**0.006****	**0.033***
	1	18	17	3				
	2	1	0	2				
	3	8	25	24				
	4	0	0	2				
Oral tonicity		24	27	17	**0.017 ***	**0.013 ***	0.566	**0.047***
Type of oral tonicity					**0.017 ***	**0.020 ***	0.082	0.072
	Mouth opening alone	7	9	1				
	Both mouth opening + vocalization	17	18	16				
	Neither	3	15	14				
Type GTCS 1 or oral tonicity		26	30	18	**0.004****	**0.005****	0.347	**0.024***
Seizure onset condition					0.975	1.000	1.000	1.000
	Spontaneous	24	38	28				
	Stimulation	3	4	3				
Epileptogenic zone as defined by SEEG					0.341	0.143	0.679	0.064
Seizure onset laterality					**0.013 ***	0.268	**0.005****	**0.021***
	Right	15	20	11				
	Left	7	21	11				
	Bilateral	5	1	9				
GTCS total duration		47.2 (41.2-53.2)	51.9 (46.1-57.6)	56.4 (46.7-66.1)	0.415	0.221	0.558	0.313
RS duration		16.9 (13.3-20.5)	25.5 (21.0-30.0)	-	0.114	0.116		

Table 3. Clinical predictive value for PGES

	Sensitivity	**Specificity**	**PPV**	**NPV**
Type 1	0.67 (0.57-0.75)	0.73 (0.63-0.80)	0.47 (0.38-0.57)	**0.85** (0.77-0.91)
Oral tonicity	0.89 (0.81-0.94)	0.40 (0.31-0.50)	0.35 (0.27-0.45)	**0.91** (0.83-0.95)
Type 1 or oral tonicity	0.96 (0.91-0.99)	0.34 (0.26-0.44)	0.35 (0.26-0.45)	**0.96** (0.90-0.99)

Figure Legends

Figure 1 showing partial sparing of motor cortex during tonic-clonic phase of secondary generalization. Blue colored boxes highlight supplementary motor areas (SA), frontal and rolandic operculum (OF and OR). On the schematic representation of SEEG exploration in this patient in a lateral view of all depth electrodes superimposed on a three-dimensional reconstruction of the neocortical surface, regions involved in the generation of the ictal discharge (epileptogenic zone) are colored in yellow and motor areas spared by the discharge are colored in purple.

Fig.2. A. Example of post-ictal generalized EEG suppression (PGES) as seen on SEEG (trace parameters indicated bottom left). Abrupt cessation of electrical activity (clonic bursts) corresponds with the clinical end of the GTCS (last clonic jerk) and is immediately followed by generalized SEEG flattening (PGES) visible in all implanted electrodes. Baseline shift is visible in some channels just before flattening. After 25 seconds of no visible signal, minimal electrical activity is detectable on internal contacts of GPH'. For the purposes of this study the end of PGES was defined strictly as the reappearance of any activity, although it can be seen that the SEEG remains generally very suppressed throughout. (C) time-frequency representation from SEEG trace with magnified view of mesial channel of GPH' showing total absence of activity during PGES.

Fig. 2. B. Schematic representation of SEEG exploration with a lateral view of all depth electrodes superimposed on a three-dimensional reconstruction of the neocortical surface over the main explored hemisphere. Each depth electrode recorded from specific regions as follows (internal/ external contacts): A (amygdala/anterior middle temporal gyrus), TB (basal

temporal areas), TP (temporal pole), H (insula / anterior part of the superior temporal gyrus), GPH (parahippocampal gyrus/), GL (gyrus lingual/lateral occipital gyri), Cu (cuneus/dorsolateral occipital cortex), FCA (anterior calcarine fissure), GC (posterior cingulate gyrus/supramarginal gyrus), OP (parietal operculum, BA 40), OR (rolandic operculum), PA (precuneus/ superior parietal lobule), PP (pre-cuneus), PFG(inferior parietal lobule), SA (supplementary motor area/frontal eye field), LES (exploring the lesion). Regions involved in the generation of the ictal discharge are colored in yellow.

Fig.3. A. Example of post-ictal regional EEG flattening (RS) on SEEG involving premotor regions first on the left (SA') and then on the right hemisphere (SA and PM). This region participates in the epileptogenic zone (EZ). After 35 seconds of regional flattening, generalized flattening is then observed during 15 seconds and then slight electrical activity re-emerges in OR', although as in Figure 2 it can be seen that activity in all contacts remains very suppressed; for the purposes of this study we chose a strict definition of PGES and defined it as shown.

Fig. 3.B. Time-frequency representation of magnified view of SA' contacts shows a total absence of activity during RS.

Fig.3. C. Schematic representation of SEEG exploration in this patient with a lateral view of all depth electrodes superimposed on a three-dimensional reconstruction of the neocortical surface over the main explored hemisphere. Each depth electrode recorded from specific regions as follows (internal/ external contacts): OF (frontal operculum, BA 44), OR (rolandic operculum), PA (precuneus/ superior parietal lobule), SA (supplementary motor area/frontal eye field), CR (BA 32/ BA 9/46V), PA (precuneus/superior parietal lobule), PM (pre-SMA/BA 9), CC (BA 24/BA8V). Regions involved in the generation of the ictal discharge are colored in purple.

Supplementary figure

Semiological characteristics: (A) an example of type 1 posture, bilateral upper limb extension at the end of the tonic phase; (B) two examples of oral tonicity, the tonic mouth opening being respectively symmetric for the patient on the left and asymmetric on the right.