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Age-specific periictal electroclinical features of generalized tonic–clonic seizures and potential risk of sudden unexpected death in epilepsy (SUDEP)

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ABSTRACT

Generalized tonic–clonic seizure (GTCS) is the commonest seizure type associated with sudden unexpected death in epilepsy (SUDEP). This study examined the semiological and electroencephalographic differences (EEG) in the GTCSs of adults as compared with those of children. The rationale lies on epidemiological observations that have noted a tenfold higher incidence of SUDEP in adults. We analyzed the video-EEG data of 105 GTCS events in 61 consecutive patients (12 children, 23 seizure events and 49 adults, 82 seizure events) recruited from the Epilepsy Monitoring Unit. Semiological, EEG, and 3-channel EKG features were studied. Periictal seizure phase durations were analyzed including tonic, clonic, total seizure, postictal EEG suppression (PGES), and recovery phases. Heart rate variability (HRV) measures including RMSSD (root mean square successive difference of RR intervals), SDNN (standard deviation of NN intervals), and SDSD (standard deviation of differences) were analyzed (including low frequency/high frequency power ratios) during preictal baseline and ictal and postictal phases. Generalized estimating equations (GEEs) were used to find associations between electroclinical features. Separate subgroup analyses were carried out on adult and pediatric age groups as well as medication groups (no antiepileptic medication cessation versus unchanged or reduced medication) during admission. Major differences were seen in adult and pediatric seizures with total seizure duration, tonic phase, PGES, and recovery phases being significantly shorter in children ($p < 0.01$). Generalized estimating equation analysis, using tonic phase duration as the dependent variable, found age to correlate significantly ($p < 0.001$), and this remained significant during subgroup analysis (adults and children) such that each 0.12-second increase in tonic phase duration correlated with a 1-second increase in PGES duration. Postictal EEG suppression durations were on average 28 s shorter in children. With cessation of medication, total seizure duration was significantly increased by a mean value of 8 s in children and 11 s in adults ($p < 0.05$). Tonic phase duration also significantly increased with medication cessation, and although PGES durations increased, this was not significant. Root mean square successive difference was negatively correlated with PGES duration (longer PGES durations were associated with decreased vagally mediated heart rate variability; $p < 0.05$) but not with tonic phase duration. This study clearly points out identifiable electroclinical differences between adult and pediatric GTCSs that may be relevant in explaining lower SUDEP risk in children. The findings suggest that some prolonged seizure phases and prolonged PGES duration may be electroclinical markers of SUDEP risk and merit further study.

1. Introduction

The risk of sudden unexpected death in epilepsy (SUDEP) in children is up to tenfold less than that in adults, comparable with general population rates, varying between 1.1 and 3.4/10,000 patient-years [1–3]. Pediatric SUDEP may be phenomenologically different from adult SUDEP [1,4]. Generalized tonic–clonic seizure (GTCS) is the seizure type most strongly associated with SUDEP [5–9]. Carefully analyzed video-EEG studies have shown that typical GTCSs are rare in children under 3 years of age [10,11]. Postictal EEG suppression (PGES) is an EEG phenomenon linked to the tonic phase of GTCSs [12]

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and has been proposed as a risk marker for SUDEP [13], which in the vast majority of cases is an ictal or a postictal phenomenon [9,14]. Other studies have pointed out an association between GTCSs and PGES [15–18] as well as postictal impairment of respiratory function and arousal [15,16,18]. We set out to examine and compare these periictal clinical (semiological) and electroencephalographic differences between adults and children in a population of patients with Treatment-refractory GTCSs, a high-risk group for SUDEP.

2. Methodology

We analyzed the video-EEG data of patients with Treatment-refractory epilepsy from the Epilepsy Monitoring Unit at Rainbow Babies and Children's Hospital and University Hospitals Case Medical Center, Cleveland, USA, monitored during a 9-year period up to January 2012 after obtaining IRB approval. We included all patients >1 month in age who had at least one GTCS event during monitoring. The pediatric group comprised patients ≤16 years of age, whereas older patients were considered adults. Data on age, sex, epilepsy onset, seizure frequency, type of epilepsy, comorbidities, etiology, learning disabilities, MRI findings, localization of the putative epileptogenic zone, current and past antiepileptic drugs (AEDs), and AED status during monitoring (unchanged, reduction, and withdrawal). Electroencephalogram results were recorded on Nihon Kohden EEG acquisition software with a 1000-Hz sampling rate using conventional bipolar and common average referenced 10–20 montages.

2.1. Clinical analysis

Generalized tonic–clonic seizures were defined as seizures resulting in tonic and clonic motor phenomena, regardless of sequence, involving all four limbs and with complete loss of consciousness. Seizure type, lateralizing signs, clinical onset, and duration of tonic and clonic phases of each seizure were studied. Where there was more than one tonic or clonic phase, the sum of both phases was used in statistical analysis. Onset of the tonic phase was defined as the point where there was clear bilateral tonicity and included the "vibratory" or "jittery" phase described by Gastaut (8-Hz EMG artifact) [19]. The onset of the clonic phase was defined as the end of the "vibratory period" (where EMG artifact slowed to 4 Hz). Seizure end was defined as cessation of all clinical manifestations and/or EEG paroxysmal activities.

2.2. Electrophysiological analysis

Electroencephalogram recordings of GTCSs were analyzed. Postictal EEG suppression was defined as the immediate postictal (within 30 s), generalized absence of EEG activity >10 μV in amplitude, allowing for muscle, movement, breathing, and electrode artifacts [13,15–18]. We extended EEG analysis to the "recovery phase", defined as the period beginning from the end of continuous PGES until normal background resumed. Three channel electrocardiographic recordings were considered in automatic R-wave detection and results of detection visually validated. Afterward, heart rate variability (HRV) measures including RMSSD (root mean square successive difference of RR intervals), SDNN (standard deviation of RR intervals), SDSD (standard deviation of differences) [20], and standard Poincare′ parameters [21] were computed (short-term variability SD1, long-term variability SD2, and the short-term to long-term ratio SD1/SD2) and analyzed during the preictal baseline and ictal and postictal (to 5 min) phases using an in-house validated and automated MATLAB™ HRV program.

3. Statistical analysis

All data were analyzed using STATA 10 for Windows. *T*-test mean values and analogous two-sample *t*-test were used to report means, which correspond to nonparametric tests but are more robust to normality violations. Generalized estimating equation (GEE) model analysis using linear regression models was used to find associations between electroclinical features. Generalized estimating equation models were employed to account for correlation between more than one seizure event in a single subject.

4. Results

A total of 105 seizure events fulfilled the study criteria (12 children with 23 seizure events and 49 adults with 82 seizure events). Clinical characteristics of subjects and seizures are presented in Table 1. Mean ages (with standard deviations) were 11.1 ± 3.4 years for the pediatric population and 35.1 ± 12.2 years for the adult population. All study children were ≥5 years old at the time of assessment. No gender differences were found.

4.1. Periictal seizure phases

Adult and pediatric seizures were different. Postictal EEG suppression was present in 13/23 (57%) GTCS events in 5/12 (42%) pediatric patients, whereas it was present in 77/82 (94%) seizure events in 44/49 (90%) adult patients. Using the independent sample Mann–Whitney *U* test, total seizure, tonic phase, PGES, and recovery phase durations were all found to be significantly shorter in children (Fig. 1, Table 2). In terms of means, PGES duration was 8 times longer in adults and recovery duration twice as long. A periictal seizure phase versus time plot was constructed to compare groups. In adults, the PGES and recovery phases contributed to almost three quarters of the periictal period (Fig. 2).

Table 1
Patient characteristics.

	Children (seizures; N = 12)	Adults (seizures; N = 49)
Mean age with standard deviation at assessment	11.1 ± 3.4 years	35.1 ± 12.2
Etiology		
Unknown/cryptogenic	6 (50%)	30 (62%)
Remote stroke	1 (8.33%)	1 (2%)
Meningoencephalitis	1 (8.33%)	2 (4%)
Cortical dysplasia	1 (8.33%)	0
Posterior leukomalacia	1 (8.33%)	0
Gliosis caused by previous abscess	1 (8.33%)	3 (6%)
Mesial temporal sclerosis	0	7 (14%)
Encephalomalacia (unexplained)	0	2 (4%)
Post traumatic brain injury	0	1 (2%)
Low grade glioma	0	1 (2%)
Cavernoma	0	1 (2%)
Genetic generalized	1 (8.33%)	1 (2%)
Ictal localization		
Left temporal lobe	1 (8.33%)	16 (32%)
Right temporal lobe	1 (8.33%)	4 (8%)
Bitemporal lobe	0	11 (23%)
Left frontal lobe	1 (8.33%)	6 (13%)
Right frontal lobe	0	4 (8%)
Left parietal	1 (8.33%)	0
Right occipital	0	2 (4%)
Right hemisphere	0	1 (2%)
Genetic generalized	6 (50%)	4 (8%)
Multifocal	1 (8.33%)	1 (2%)
Left insular	1 (8.33%)	0
Number of antiepileptic medications at the time of seizure [23 seizure events (children) and 82 seizure events (adults)]		
One or none	4 (18%)	18 (22%)
Two	12 (52%)	44 (54%)
Three	6 (26%)	17 (21%)
Four	1 (4%)	3 (3%)

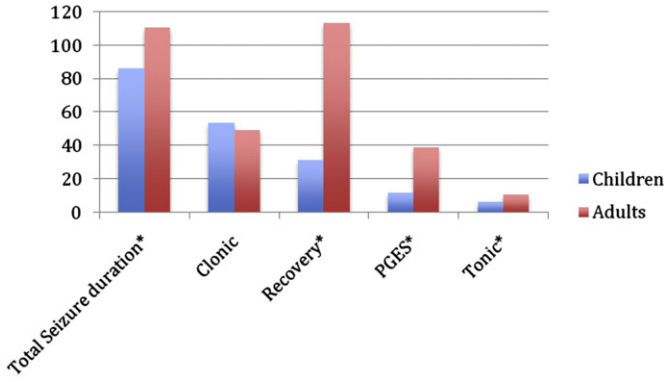

Fig. 1. Comparison of durations in seizure phases, postictal generalized EEG suppression (PGES), and the recovery phase in children and adults. y axis = time in seconds. * significant difference ($p < 0.001$). PGES = postictal generalized EEG suppression.

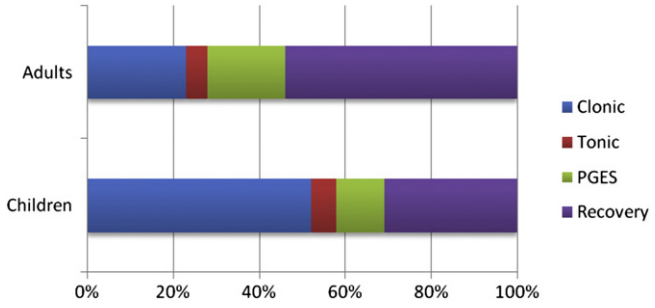

Fig. 2. Periictal seizure phases showing differences between children and adults. PGES = postictal generalized EEG suppression.

4.2. Primary versus secondary GTCSs

Since 50% of the children had genetic generalized epilepsy, while only 8% of the adults had this diagnosis, we looked at phase durations in the primary GTCSs of genetic generalized epilepsies and the secondary GTCSs of focal epilepsies to clarify whether seizure types were significantly different. We found that (Table 3) total seizure duration, tonic, PGES, and recovery phases were significantly longer in secondary GTCSs as compared with primary GTCSs.

4.3. Tonic phase duration

Using GEE models looking at parametric estimates and tonic phase duration as the dependent variable, we found age to be significantly associated (B = 0.122, 95% CI: 0.075–0.196; $p < 0.0001$) (Table 4a). In subgroup (adult or child) analysis, this remained significant such that each year, an increase in age increased tonic phase duration by 0.12 s on average. Similarly, PGES duration was significantly increased in direct proportion to tonic phase duration (B = 0.030, 95% CI: 0.002–0.058; $p < 0.05$). Each second of PGES correlated with a 0.12-second increase in tonic phase duration. Antiepileptic drug cessation significantly prolonged the tonic phase ($p < 0.05$) by an average of 1.7 s. In subanalysis, this did not hold true in children ($p = 0.207$).

4.4. PGES duration

With GEE analysis using PGES duration as the dependent variable, children had PGES phases that were on average 28 s shorter. Each year of increase in age at the time of study was associated with a 0.6-second increase in PGES duration. Clonic phase duration was significantly and inversely proportional to PGES duration. Recovery phase duration and decreased HRV were significantly and directly proportional to PGES duration (Table 4b). In subgroup analysis (adult or child), only recovery phase duration remained a significant association in children. Conversely, when recovery phase duration (Table 4c) was taken as the dependent variable, PGES duration increase was the only significant association.

4.5. Medication effects

Medication profiles in terms of AED numbers in both groups were similar (Table 1). With medication as the dependent variable using GEE, no differences in tonic, clonic, PGES, or recovery phases between medication groups were seen. However, in subanalysis, total seizure duration with cessation of medication was significantly increased by a mean value of 8 s in children and 11 s ($p < 0.05$) in adults. Medication cessation significantly increased PGES duration in adults ($p < 0.0001$) but not in children ($p = 0.385$). Similar significances were not seen when clonic phase duration was the dependent variable. The differences in subjects on different classes of AEDs were not analyzed because the numbers were too small for any meaningful analysis.

4.6. Heart rate variability

Generalized estimating equation models looking at RMSSD (to 5 min postictally), SDSD, and SDNN with seizure phase, PGES, and recovery durations did not show any significant results except for RMSSD (at 2 min) which had a negative correlation with PGES duration (longer PGES durations were associated with decreased vagally mediated heart rate variability; $p < 0.05$) when tonic phase and PGES duration were dependent variables (Table 4).

5. Discussion

Sudden unexpected death in epilepsy is rare in children. One study, assuming a pediatric epilepsy prevalence of 0.59% over a 10-year period, estimated an incidence of 27/138,620 person-years of epilepsy (2 per 10,000 person-years). In comparison with predominantly adult SUDEP estimates of 1 to 2 per 1000 person-years [22,23], this represents a 10-fold lower rate of SUDEP in children [1]. Whether this is due to age-related syndromic, etiologic, electroclinical, or other factors is not clear.

Table 2
Comparison of mean durations of seizure phases (in seconds), postictal generalized EEG suppression (PGES), and the recovery phase in children and adults.

Phase (in seconds)	Children (N = 23)	Adults (N = 82)	Significance
Total seizure duration	86.2 ± 48.5	110.5 ± 53.6	0.001*
Tonic	6.5 ± 2.2	10.5 ± 3.6	0.00*
Clonic	53.5 ± 33.6	49.2 ± 26.8	0.464
PGES	11.7 ± 14.4	38.8 ± 24.4	0.00*
Recovery	31.5 ± 42.1	113.7 ± 77.3	0.00*

PGES = postictal generalized EEG suppression.
* Significant finding at $p < 0.05$.

Table 3
Comparison of mean durations of seizure phases (in seconds), postictal generalized EEG suppression, and recovery phases in the primary GTCSs of genetic generalized epilepsies and secondary GTCSs of focal epilepsies.

Phase (in seconds)	Primary GTCSs (N = 19)	Secondary GTCSs (N = 86)	Significance
Total seizure duration	76.2 ± 37.94	111.62 ± 54.2	0.008*
Tonic	7.42 ± 2.73	10.08 ± 3.78	0.005*
Clonic	53.16 ± 37.56	49.48 ± 26.02	0.611
PGES	16.26 ± 21.72	36.51 ± 24.55	0.001*
Recovery	19.63 ± 58.01	32.29 ± 43.48	0.028*

PGES = postictal generalized EEG suppression.
GTCSs = generalized tonic–clonic seizures.
* Significant finding at $p < 0.05$.

Table 4
Estimated generalized linear models using generalized estimating equations and different dependent variables.

Total sample (N = 105 seizure events)	Estimated B-value estimate	Standard error of interval	95% Wald confidence	p value
a) Tonic phase duration in seconds as the dependent variable				
PGES duration	0.030	0.0143	0.002 to 0.058	0.034*
Clonic phase duration	0.003	0.024	−0.36 to 0.043	0.864
Total seizure duration	0.006	0.0046	−0.03 to 0.16	0.167
Effect of medication	−1.704	0.7578	2.565 to 8.644	0.025*
Recovery phase	−0.004	0.0081	−0.020 to 0.012	0.625
RMSSD	0.000	0.0001	0.000 to 0.000	0.159
Intercept	5.605	1.5507	2.565 to 8.644	0.000*
b) Postictal generalized EEG suppression duration in seconds as the dependent variable				
Tonic phase duration	1.477	0.908	−0.301 to 3.26	0.104
Clonic phase duration	−0.155	0.0586	−0.270 to −0.041	0.008*
Total seizure duration	−0.016	0.0243	−0.063 to 0.032	0.516
Effect of medication reduction	11.689	6.281	−0.62 to 2400	0.063
Recovery phase	0.228	0.0300	0.169 to 0.287	0.000*
RMSSD	0.002	0.0007	0.000 to 0.003	0.009*
Intercept	45.472	12.037	2.1.88 to 69.07	0.000*
c) Recovery phase as the dependent variable				
Tonic phase duration	−3.07	1.631	−3.504 to 2.889	0.851
Clonic phase duration	0.214	0.2523	−.0281 to 0.708	0.397
Total seizure duration	−0.123	0.1789	−0.474 to 0.228	0.492
Effect of medication reduction	13.9	13.878	−13.3 to 41.1	0.317
RMSSD	2.581	0.2421	2.107 to 3.056	0.000*
PGES	0.003	0.0016	−1.983 to 0.006	0.051
Intercept	−53.292	25.824	−103.9 to −2.678	.039*

PGES = postictal generalized EEG suppression.
Effect of medication = no or some reduction versus no medication.
RMSSD = root mean square successive difference of RR intervals.
* Significant finding at $p < 0.05$.

Generalized tonic–clonic seizures are the commonest seizure type associated with SUDEP. Semiological analyses in pediatric seizures indicate differences from adult seizures [10,11,24] that may be relevant in agonal SUDEP phenomenology. One analysis of 109 seizure events in 77 infants did not find a single typical GTCS [11]. Another study of 296 seizure events in 76 children up to the age of three years similarly reported complete absence of GTCSs [10], suggesting that this is a rare seizure type in children. Few studies have compared electroclinical seizure phases [13], and none have done so comparing adults and pediatric GTCSs. In our study, only 23 children in >500 patients monitored over 9 years had true GTCSs, and none were under the age of 5 years. On the other hand, Dravet's syndrome is a pediatric epilepsy syndrome strongly associated with SUDEP. In an analysis of 623 patients with Dravet's syndrome, 59 deaths were examined (a proportional mortality rate of >10%), of which 53% were sudden death cases [25]. Generalized tonic–clonic seizures are frequently observed in patients with Dravet's syndrome [26,27] in contrast to those without [10,11] and may at least, in part, explain the relatively lower incidence of SUDEP in children without Dravet's syndrome as compared with children and adults with Dravet's syndrome. These observations are of interest because of the consistently strong association between GTCSs and SUDEP in case–control and epidemiological studies in both adults and children [5–9].

In our study, we found several age-related electroclinical differences in GTCSs. Total seizure and tonic phase durations were significantly longer in adults, and AED cessation during monitoring further prolonged these in this higher SUDEP-risk population. Children appear to have a shorter tonic phase that is relatively unaffected by the absence of medication. Why childhood GTCSs are semiologically different from adult GTCSs is unclear. This has been attributed to relative immaturity and lack of organization of developing brains, characterized by variable neuronal excitability, imperfect myelination, and incomplete interhemispheric connections [10,11,28]. Partial seizures in humans are attributed to forebrain seizure circuitry [29] although some phases of GTCSs may be driven by brainstem seizure circuitry [30,31]. In animals, GTCSs can be induced by electrical stimulation of the brainstem reticular core, despite the removal of the forebrain. Although there is no described mechanism to connect brainstem-driven GTCS phenomena in humans with postictal autonomic and cardiorespiratory compromise, it is tempting to speculate that in adults, prolonged tonic phases may conceivably drive pontomedullary autonomic network dysfunction and increase SUDEP risk. The shorter tonic phase in children may reflect immature, poorly established subcortical seizure networks and lesser postictal autonomic dysregulation.

The directly proportional relationship between tonic phase duration (when tonic phase was the dependent variable) and PGES duration seen in our study confirms the findings of one recent report [12]; the chronology of these phenomena seems to suggest that prolonged tonic phases are reflected in greater disturbances of cortical function in our patients, regardless of age. The recovery phase was not similarly affected, suggesting that the tonic phase's main effect is on the early postictal period when the patient is presumed most vulnerable to SUDEP. Prolonged PGES has been shown to indicate increased SUDEP risk in refractory epilepsy in one study [13] where it was significantly longer in the GTCSs of patients with SUDEP. With PGES durations of >50 s, SUDEP odds were significantly increased, with a quadrupled risk with PGES >80 s. Another study which examined the EEG records of 17 SUDEP cases and matched controls questioned this association although this may be explained by methodological differences [18]. Patients undergoing presurgical evaluations for temporal lobectomy were predominantly those with temporal lobe epilepsy. The matched surviving controls are likely to have become seizure-free with surgery and the risk of SUDEP artificially removed but, in essence, are potentially biologically indistinct from cases. Postictal EEG suppression also appears to inversely correlate with clonic phase duration, regardless of tonic phase and total seizure duration. This effect is difficult to explain unless seizures with long clonic phases result in less obtundation. It may be relevant that in clinical practice, generalized clonic seizures (without a tonic component) sometimes occur without loss of consciousness. Overall, PGES was three times longer in adults.

Postictal EEG suppression occurs in between 8% of pediatric patients with seizure [32] to 65% or more of adult patients with GTCSs [13] and has been reported in several monitored SUDEP/near SUDEP cases [13,33–37] where some authors have used the term “cerebral shutdown” [35]. The increased incidence and duration of PGES in adults are

noteworthy as they are a higher risk population than children. Several studies highlight the possible significance of PGES. In one study of 48 patients, those with PGES were significantly more likely to be motionless postictally and to have simple resuscitative interventions [15]. These observations are indirectly corroborated in another study that analyzed 21 GTCS events with no periictal interventions and 84 with interventions. Earlier interventions were associated with briefer hypoxia and shorter PGES duration [16]. Another study compared secondary GTCSs with and without PGES and found that oxygen desaturation duration and extent as well as peak end-tidal CO_2 elevation were more marked in patients with PGES [17]. Thus, PGES appears to indicate a greater degree of postictal obtundation and vulnerability to respiratory compromise. The high incidence of PGES in our patients possibly reflects a high rate of medication cessation during monitoring. Postictal EEG suppression duration appears to directly correlate with recovery phase duration suggesting a continuum of recovery processes in the postictal period.

In common with at least one more study [18], we found no correlation between HRV measures and electroclinical seizure variables, with one exception. Root mean square successive difference measures at 2 min postictally were negatively correlated to PGES suggesting that PGES may be associated with the reduced vagal tone observed in some patients [38].

The effect of AED cessation during monitoring (usually done to induce seizures as part of presurgical assessment) is interesting as this artificially amplifies the refractoriness of a patient's epilepsy or creates a situation akin to noncompliance, another risk factor for SUDEP [14]. Total seizure durations were significantly increased by a mean value of 8 s and 11 s, respectively, in children and adults, and both PGES and tonic phase durations significantly increased in adults when medication was stopped. This indirectly appears to corroborate literature suggesting greater SUDEP risk in patients with refractory epilepsy and, in particular, those who are noncompliant with medication, where seizure frequency and severity can be expected to be worse than on treatment.

Our study has limitations. Patient records were retrospectively analyzed with its attendant biases. A much smaller number of pediatric GTCSs reflect the relative rarity of this seizure type in this age group and limit statistical power. The medication tapering protocols and total duration of hospital stay is, in general, shorter in children. Antiepileptic drugs have different half-lives which may influence the seizure duration, but our AED groups are too small to look for these differences. We also considered the adult population to be >16 years of age rather than the ≥20-year figure used in some SUDEP studies for pragmatic reasons. All 4 patients in the 16- to 20-year bracket were aged 19 years and, in biological terms, were more suited to be analyzed as adults. Additionally, we did not have respiratory measurements to determine the presence and influence of hypoxia, bradypnea, and apnea, phenomena that are potential SUDEP mechanisms and that are known to occur in pediatric seizures [39].

Since there is no forward surveillance of patients, the true incidence of SUDEP in both groups cannot be known, and, hence, there is no gold standard for validation of the observed results. However, our data clearly point out identifiable electroclinical differences between the adult and pediatric population which may at least, in part, explain differences in SUDEP incidence. It also highlights the importance of careful characterization of seizure semiology and EEG, particularly PGES. There is a gathering body of evidence that PGES is an important postictal phenomenon; its pathophysiology requires further, careful elucidation. Overall, however, prolonged PGES may be best seen as a potential risk "marker" of SUDEP rather than a risk "factor"; the latter implies a causal role which is as yet uncharacterized and unproven.

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.

Disclosure

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

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