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Association between semiologic, autonomic, and electrographic seizure characteristics in children with generalized tonic-clonic seizures

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ABSTRACT

Introduction: Generalized tonic-clonic seizures (GTCS) are associated with elevated electrodermal activity (EDA) and postictal generalized electroencephalographic suppression (PGES), markers that may indicate sudden unexpected death in epilepsy (SUDEP) risk. This study investigated the association of GTCS semiology, EDA, and PGES in children with epilepsy.

Methods: Patients admitted to the Boston Children's Hospital long-term video-EEG monitoring unit wore a sensor that records EDA. We selected patients with at least one GTCS and reviewed video-EEGs for semiology, tonic and clonic phase duration, total clinical seizure duration, electrographic onset, offset, and PGES. We grouped patients into three semiology classes: GTCS 1: bilateral symmetric tonic arm extension, GTCS 2: no specific tonic arm extension or flexion, GTCS 3: unilateral or asymmetrical arm extension, tonic arm flexion or posturing that does not fit into GTCS 1 or 2. We analyzed the correlation between semiology, EDA, and PGES, and measured the area under the curve (AUC) of the ictal EDA (seizure onset to one hour after), subtracting baseline EDA (one-hour seizure-free before seizure onset). Using generalized estimating equation (GEE) and linear regression, we analyzed all seizures and single episodes per patient.

Results: We included 30 patients (median age 13.8 ± 3.6 years, 46.7% females) and 53 seizures. With GEE, GTCS 1 was associated with longer PGES duration compared to GTCS 2 (Estimate (β) = −26.32 s, 95% Confidence Interval (CI): −36.46 to −16.18, $p < 0.001$), and the presence of PGES was associated with greater EDA change (β = 429604 μS, 95% CI: 3550.96 to 855657.04, $p = 0.048$). With single-episode analysis, GTCS 1 had greater EDA change than GTCS 2 ((β = −601339 μS, 95% CI: −1167016.56 to −35661.44, $p = 0.047$). EDA increased with PGES presence (β = 637500 μS, 95% CI: 183571.84 to 1091428.16, $p = 0.01$) and duration (β = 16794 μS, 95% CI: 5729.8 to 27858.2, $p = 0.006$). Patients with GTCS 1 had longer PGES duration compared to GTCS 2 (β = −30.53 s, 95% CI: −44.6 to −16.46, $p < 0.001$) and GTCS 3 (β = −22.07 s, 95% CI: −38.95 to −5.19, $p = 0.016$).

Conclusion: In children with epilepsy, PGES correlates with greater ictal EDA. GTCS 1 correlated with longer PGES duration and may indirectly correlate with greater ictal EDA. Our study suggests potential applications in monitoring and preventing SUDEP in these patients.

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1. Introduction

Epilepsy is one of the most common conditions in children, with a prevalence of 6.3 per 1000 in the United States and a cause of morbidity and mortality [1,2]. Children with epilepsy are at risk of sudden unexpected death in epilepsy (SUDEP), which has an incidence between 1.1 and 4.3 per 10,000 patient years [3–5]. The mechanism of SUDEP is not well understood but likely involves manifestations of severe seizure-induced central and autonomic nervous system dysfunction such as apneas and cardiac arrhythmias [3,6,7].

Risk factors for SUDEP include the presence of other neurological impairments, inadequate supervision or monitoring, uncontrolled seizures, certain anti-seizure medication, and polytherapy [3,6,8–13]. Patients with generalized tonic-clonic seizures (GTCS) are particularly at risk. SUDEP is highest with nocturnal GTCS [6–8] when monitoring is minimal. As such, monitoring and controlling risk factors may help prevent SUDEP [14,15]. It remains challenging to assess, predict, and prevent SUDEP, especially in children, given the low incidence. Nevertheless, recent studies have shown promising data on potential biomarkers such as postictal generalized electroencephalographic suppression (PGES), electrodermal activity (EDA), and specific MRI, cardiac and respiratory features [16].

PGES is characterized by diffuse attenuation of EEG activity, an electrographic phenomenon associated with GTCS of focal and generalized onset in children and adults that may constitute a risk marker for SUDEP [17–19]. EDA, an autonomic response reflecting the sympathetic innervation of the skin, increases peri-ictally with GTCS [20,21], possibly more markedly with SUDEP-associated GTCS [22]. This increase is a measure of seizure-related sympathetic activation, and correlates with the duration of PGES [23,24]. EDA can be measured peripherally using wearable devices such as wristbands and is a reliable method to detect GTCS and evaluate the resulting sympathetic surge and possibly assess SUDEP risk[20,23–25].

Seizure semiology is another potential marker of SUDEP. Studies in adults showed a positive association between GTCS semiology manifesting as decerebrate posturing, with symmetric bilateral arm tonic extension, and PGES duration [26,27]. Other semiologic characteristics, such as those related to the tonic phase of GTCS, may also be related [28,29]. The association of semiology and risk of SUDEP in children is unclear.

In our study, we aimed to evaluate the relationship between semiologic, autonomic, and electrographic features of GTCS in children with epilepsy. Specifically, we evaluated the association of GTCS semiology, duration of tonic and clonic phases, and total duration with EDA surge and PGES duration. Secondarily, we assessed the association between the presence of PGES and its duration with EDA. Thirdly, we evaluated the difference in EDA change and PGES duration during sleep and wakefulness. We hypothesize that specific semiological characteristics of GTCS are associated with greater EDA and longer PGES duration in children with epilepsy.

2. Methods

We prospectively enrolled patients admitted for long-term audio–video-EEG monitoring at Boston Children's Hospital between February 2015 and December 2018. Patients wore sensors (E4, Empatica Inc., Milan, Italy) that continuously record EDA signals on their wrist(s) or ankle(s).

2.1. Standard protocol approvals, registrations, and patient consents

The study received approval from the Institutional Review Board at Boston Children's Hospital, and we obtained written informed consent from all patients or their caregivers.

2.2. Patient and seizure selection

Patients were selected for analysis if they met the following criteria: (1) at least one GTCS of focal or generalized onset while undergoing EEG and wristband monitoring and (2) seizure(s) at least 100 min from any other preceding or succeeding seizure to avoid possible contamination of our sensor signals by autonomic impairment caused by other seizures [23]. We excluded patients whose seizures were part of a cluster, patients presenting with status epilepticus, and patients who were off-camera during the seizure. We included a seizure-free baseline portion one hour before seizure onset that is 100 minutes from any preceding seizure for each patient.

2.3. Seizure identification

Patients underwent long-term video-EEG recording using conventional scalp EEG montages according to the 10–20 electrode system. Upon seizure identification, we selected patients with GTCS. Two independent board-certified epileptologists re-reviewed the seizure video-EEGs from these patients to determine seizure electrographic and semiologic characteristics. In cases of discrepancy in opinions, a third round of reviews was completed to find an agreement. All reviewers were blinded to EDA analysis results.

2.4. Seizure characterization

We evaluated the following electrographic and clinical seizure characteristics for each GTCS: electrographic seizure onset and offset, clinical seizure onset and offset, duration of tonic and clonic phases, semiology, sleep/wake status before seizure onset, sleep stage at seizure onset if a patient was asleep and the presence and the duration of PGES. We defined PGES as an immediate postictal generalized lack of EEG activity larger than 10 μV in amplitude, occurring immediately following seizure offset and lasting at least 10 s [19,30].

Seizure semiology was separated into three groups based on the classification for generalized convulsions employed by a previous study [27]. The first class, GTCS 1 describes a GTCS with a bilateral and symmetric tonic extension of the arms, followed by bilateral and symmetric clonic jerking of all limbs. GTCS 2 is characterized by bilateral and symmetric clonic movements of all limbs without tonic extension or flexion of the arms. GTCS 3 describes four-limb clonic convulsions preceded by either tonic arm extension that is unilateral or bilateral but asymmetrical, bilateral tonic arm flexion, or tonic posturing that does not fit in types 1 or 2.

The start of the tonic phase was the time when the tonic posturing remained in a fixed position. The end of the tonic phase is the onset of the clonic phase when clonic jerks start. The end of the clonic phase marks the time when the clonic jerking stops. The total clinical duration of the seizure spans from the start to the end of the video seizure manifestation.

2.5. EDA analysis

We used MATLAB 2017 (MathWorks Inc., Natick, MA) for EDA signal analysis. We calculated the area under the curve (AUC) of the ictal EDA signal, going from electrographic seizure onset to one hour after seizure onset.

To confirm the presence of an EDA surge with seizures, we also measured the AUC of EDA at baseline spanning the period from one hour before seizure onset to seizure onset. By subtracting baseline EDA from ictal EDA, we measured the change in EDA in the setting of a seizure without overestimating seizure-induced changes, especially in patients with higher EDA at baseline or during sleep storms [31]. In patients wearing two wristbands on both the left and right sides of the body, we took an average EDA change of both wristbands.

2.6. Statistical analysis

Statistical analysis was performed on R Studio v.4.0.4 (The R Foundation for Statistical Computing)[4] using generalized estimating equation (GEE) to include repeated seizures per patient and account for within-subject correlation and multiple linear regression model to explore the effects of single episodes per patient. For the latter, we selected the first GTCS that each patient had during the wristband recording. Using each of the two models, we correlated each of AUC-EDA changes and PGES duration with the following variables: semiology class, duration of tonic phase, duration of clonic phase, and total duration of the seizure. As secondary outcomes, we correlated EDA with PGES presence and PGES duration. We accounted for awake and sleep in all analyses. We also ran Wilcoxon rank sum test to compare EDA change and PGES duration between sleep and awake states. A p-value of 0.05 was considered statistically significant.

3. Results

3.1. Demographics

We prospectively enrolled 334 patients admitted for long-term EEG monitoring. Forty patients had at least one GTCS. Thirty-one patients and 55 seizures met our inclusion criteria. An inclusion diagram is available in the supplemental material. We analyzed the AUC of the EDA change. One patient with two seizures had EDA values that were extreme outliers in the residual plots of the statistical analysis, and we, therefore, excluded these values. The final dataset included 30 patients and 53 seizures. We analyzed the EDA of 26 seizures as averaged EDA from two wristbands, and 27 from one wristband (15 seizures in patients initially wearing one wristband and 12 had recordings from one of the sides excluded due to poor signal quality). The patients' median age was 13.7 (±3.6), with 46.7% being female. Patient clinical information is available in Table 1.

Table 1
Patient characteristics.

Demographics			
Female ***n*** **(%)**	14 (46.7)		
Age at first seizure **Median (Range)**, years	8.59 (0.25–17.42)		
Age at EEG **Median (Range)**, years	13.78 (8.22–22.17)		
Clinical characteristics	***n*** **(%)**		
Epilepsy Etiology			
Unknown	11 (36.7)		
Structural	15 (50)		
Genetic	1 (3.3)		
Immune	2 (6.7)		
Infectious	1 (3.3)		
History of neurosurgery			
Yes	5 (16.7)		
No	25 (83.3)		
MRI Findings			
Normal	6 (20)		
Abnormal	24 (80)		
Seizure characteristics	**Median (Range)**		
All Seizures frequency per month◇	3.15 (0–375)		
GTCS per patient included in analysis	1 (1–4)		
Electrographic seizure duration, s	92 (30–222)		
Clinical seizure duration, s	82 (29–191)		
Tonic phase duration, s	15 (0–60)		
Clonic phase duration, s	53 (6–85)		
Seizure onset zone	**Left** ***n*** **(%)**	**Right** ***n*** **(%)**	**Bilateral** ***n*** **(%)**
Temporal	5 (9.4)	6 (11.3)	
Frontal		5 (9.4)	1 (1.9)
Parietal	4 (7.5)		
Central	2 (3.8)	3 (5.7)	4 (7.5)
Posterior		1 (1.9)	
Parasagittal		1 (1.9)	
Multilobar^	14 (26.4)		
Generalized	7 (13.2)		
Wristband Location*	***n*** **(%)**		
Left wrist	17 (24.6)		
Right wrist	24 (34.8)		
Left ankle	8 (11.6)		
Right ankle	8 (11.6)		

Seizure Characteristic variables are for all seizures of the patients.
^ Multilobar: Seizures arising from two or more lobes.
* Patients represented in more than one category. Patients may wear one or two wristbands on multiple days of enrollment and on different locations of the body.
◇ Two patients could not provide a numerical frequency and were excluded from this count.

3.2. Analyses of all seizures per patient

3.2.1. Semiologic characteristics and EDA change

Results of all-episode analyses are listed in Table 2. Of 53 seizures, 15 (28%) were GTCS 1, 22 (42%) GTCS 2, and 16 (30%) GTCS 3. GTCS 1 had overall greater ictal EDA change; however, this change was not significant ($p = 0.07$ for GTCS 2 and $p = 0.19$ for GTCS 3, with GTCS 1 as the baseline, adjusting for awake and sleep states). EDA change did not depend on the duration of the tonic phase ($p = 0.71$), clonic phase ($p = 0.85$), and total duration of the seizure ($p = 0.96$).

When seizures were not followed by PGES, EDA change did not differ significantly between the three semiology classes ($p = 0.44$ and $p = 0.49$ for GTCS 2 and GTCS 3, respectively).

Twenty-six seizures (49%) occurred during wakefulness. EDA change did not differ between awake and sleep ($p = 0.10$, Wilcoxon Rank Sum Test W = 443).

3.2.2. PGES and EDA change

The presence of PGES was associated with higher EDA (Estimate (β) = 429604 microSiemens (μS), 95% Confidence Interval (CI): 3550.96 to 855657.04, $p = 0.048$, Fig. 1). Longer PGES duration tended to have higher EDA change, but this was not statistically significant ($p = 0.07$).

3.2.3. Semiologic characteristics and PGES duration

PGES was present after 27 seizures (51%). Eighty-seven percent of GTCS 1, 18% of GTCS 2, and 63% of GTCS 3 had PGES following offset. Taking all seizures, GTCS 1 were associated with longer PGES duration compared to GTCS 2 ($\beta = -26.32$ s, 95% CI: −36.46 to −16.18, $p < 0.001$) but not compared to GTCS 3 ($p = 0.07$), adjusting for awake and sleep states (Fig. 2). PGES duration did not correlate with the duration of the tonic phase ($p = 0.47$), clonic phase ($p = 0.06$), and the total duration of the seizure ($p = 0.51$).

Of seizures followed by PGES, 12 (44%) occurred during wakefulness and 15 (56%) during sleep. Overall, PGES duration did not differ in awake and sleep ($p = 0.83$, Wilcoxon Rank Sum Test $W = 339$).

Table 2
EDA AUC and PGES duration for groupwise comparison including all seizures.

All Episodes (n = 30 patients, 53 seizures)	EDA Change (μS)			PGES Duration (s)		
	Median	Q1	Q3	Median	Q1	Q3
Estimate	7480.79	260.73	51081.7	10.00	0	38
In GTCS 1 (n = 7, 15)	25564.64	3796.67	462687.97	34	31	48.5
In GTCS 2 (n = 16, 22)	1101.53	−284.65	30320.65	0	0	0
In GTCS 3 (n = 7, 16)	6254.9	2661.61	29840.4	24.5	0	39
In Awake (n = 17, 26)	22564.5	550.6	142603.71	0	0	41
In Sleep (n = 13, 27)	3379.6	133.06	34303.87	22	0	33
EDA in patients without PGES (n = 26,18)	1101.53	−198.9	25338.63	n/a	n/a	n/a
EDA in GTCS 1, patients without PGES (n = 2,1)	15303.05	10172.25	20433.84	n/a	n/a	n/a
EDA in GTCS 2, patients without PGES (n = 18, 14)	563.36	−284.65	28951.9	n/a	n/a	n/a
EDA in GTCS 3, patients without PGES (n = 6,3)	2118.91	186.46	4376.43	n/a	n/a	n/a
	Estimate	**95% Confidence Interval**	***P* value**	**Estimate**	**95% Confidence Interval**	***P* value**
GTCS 2	−537,059	−1119559.24 to 45441.24	0.07	−26.32	−36.46 to −16.18	<0.001*
GTCS 3	−353,525	−877564.32 to 170514.32	0.19	−11.47	−24.08 to 1.13	0.07
Duration of Tonic Phase	4141	−17730.64 to 26012.64	0.71	−0.19	−0.72 to 0.33	0.47
Duration of Clonic Phase	609	−5790.4 to 7008.4	0.85	0.28	−0.02 to 0.58	0.06
Total Seizure Duration	−156	−6526 to 6214	0.96	0.064	−0.12 to 0.25	0.51
PGES Duration	5399	−543.72 to 11341.72	0.07	n/a	n/a	n/a
PGES Presence	429,604	3550.96 to 855657.04	0.048*	n/a	n/a	n/a
GTCS 2 in patients without PGES	−225,198	−794766.16 to 344370.16	0.44	n/a	n/a	n/a
GTCS 3 in patients without PGES	120,963	−221115.8 to 463041.8	0.49	n/a	n/a	n/a

Counts displayed as (n = number of patients, number of seizures).
EDA is the EDA change: the difference of EDA AUC between ictal period and baseline.
Abbreviations: EDA: Electrodermal Activity, PGES: postictal generalized EEG suppression, μS: microSiemens, s: seconds.
* Statistically significant.

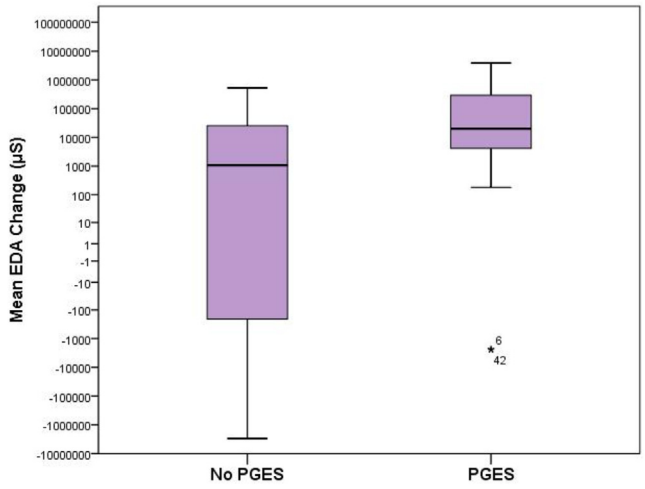

Fig. 1. Log EDA AUC change in presence and absence of PGES taking all seizures per patient. For all-episode analysis, seizures followed by postictal generalized EEG suppression (PGES) had higher EDA changes, compared to seizures without PGES. EDA change is presented in a logarithmic scale.

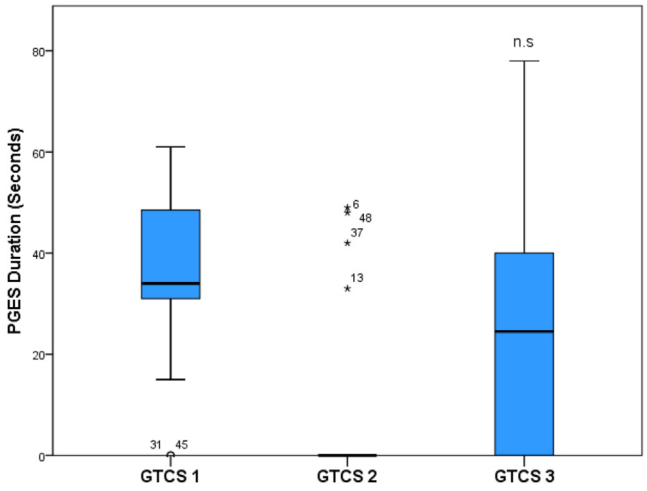

Fig. 2. PGES duration groupwise comparison between GTCS semiology subtypes taking all seizures per patient. For all-episode analysis, seizures belonging to GTCS 1, manifesting as bilateral and symmetric tonic arm extension correlated with a significantly longer postictal generalized EEG suppression (PGES) duration compared to GTCS 2, with no specific tonic arm extension or flexion, but not when compared to GTCS 3 with unilateral or asymmetrical arm extension, tonic arm flexion or posturing that does not fit in the types 1 or 2. n.s; not significant.

3.3. Analysis of one seizure per patient

3.3.1. Semiologic characteristics and EDA change

Results of single-episode analyses are shown in Table 3. We analyzed one seizure per patient for 30 patients, including seven GTCS 1 (23%), 16 (53%) GTCS 2 and seven GTCS 3 (23%). EDA change was higher in GTCS 1 compared to other classes (Fig. 3A). The EDA change in GTCS 1 was greater than GTCS 2 adjusting for awake and sleep (β = −601339 μS, 95% CI: −1167016.56 to −35661.44, p = 0.047), but not compared to GTCS 3 (p = 0.71). The overall fit of the model was R^2 = 0.272 utilizing regression equation (F (3, 26) = 3.23, p = 0.039).

Longer tonic phase tends to present with lower EDA; however, the effect of duration of the tonic phase duration on EDA was not significant (p = 0.25). No relationship was found between mean EDA and duration of the clonic phase (p = 0.93), or the total duration of the clinical seizure (p = 0.63) adjusting for awake and sleep.

In the absence of PGES, no significant correlation was found for EDA change in the three semiology classes (p = 0.99 for GTCS 2, and p = 0.65 for GTCS 3).

Seventeen patients (57%) had their seizure during the awake state. EDA change did not differ between awake and sleep (p = 0.213, Wilcoxon Rank Sum Test W = 141).

Table 3
EDA AUC changes and PGES Duration taking one seizure per patient in different seizure types.

Single Episodes (n = 30)	EDA Change (μS)			PGES Duration (s)		
	Median	Q1	Q3	Median	Q1	Q3
Overall Estimate	4210.53	181.76	97036.03	0	0	31.75
In GTCS 1 (n = 7)	5041.45	1773.15	462687.97	34	31	48.5
In GTCS 2 (n = 16)	13196.93	−181.69	62818.42	0	0	0
In GTCS 3 (n = 7)	3379.6	−974.87	34241.3	10	0	27
In Awake (n = 17)	25439.5	180.11	152090.	0	0	10
In Sleep (n = 13)	994.43	186.71	43043.1	22	0	32
EDA in patients without PGES (n = 18)	1101.53	−198.86	29052.78	n/a	n/a	n/a
EDA in GTCS 1, patients without PGES (n = 1)	5041.45	n/a	n/a	n/a	n/a	n/a
EDA in GTCS 2, patients without PGES (n = 14)	1101.53	−198.86	30320.65	n/a	n/a	n/a
EDA in GTCS 3, patients without PGES (n = 3)	507.66	−3032.47	12973.58	n/a	n/a	n/a
	Estimate	**95% Confidence Interval**	***P* value**	**Estimate**	**95% Confidence Interval**	***P* value**
GTCS 2	−601,339	−1167016.56 to −35661.44	0.047*	−30.53	−44.6 to −16.46	<0.001*
GTCS 3	−129,965	−808160.28 to 548230.28	0.71	−822.07	−38.95 to −5.19	0.016*
Duration of Tonic Phase	12,781	−8735.88 to 34297.88	0.25	−0.013	−0.67 to 0.64	0.97
Duration of Clonic Phase	534.6	−12215.79 to 13284.99	0.93	0.32	−0.03 to 0.68	0.09
Total Seizure Duration	1852	−5511.72 to 9215.72	0.63	0.09	−0.13 to 0.3	0.43
PGES Duration	16,794	5729.8 to 27858.2	0.006*	n/a	n/a	n/a
PGES Presence	637,500	183571.84 to 1091428.16	0.01*	n/a	n/a	n/a
GTCS 2 in patients without PGES	11,097	−1429403.04 to 1451597.04	0.99	n/a	n/a	n/a
GTCS 3 in patients without PGES	368,449	−1207685 to 1,944,583	0.65	n/a	n/a	n/a

EDA is the EDA change: the difference of EDA AUC between ictal period and baseline.
Abbreviations: EDA: Electrodermal Activity, PGES: postictal generalized EEG suppression, μS: microsiemens, s: seconds.
* Statistically significant.

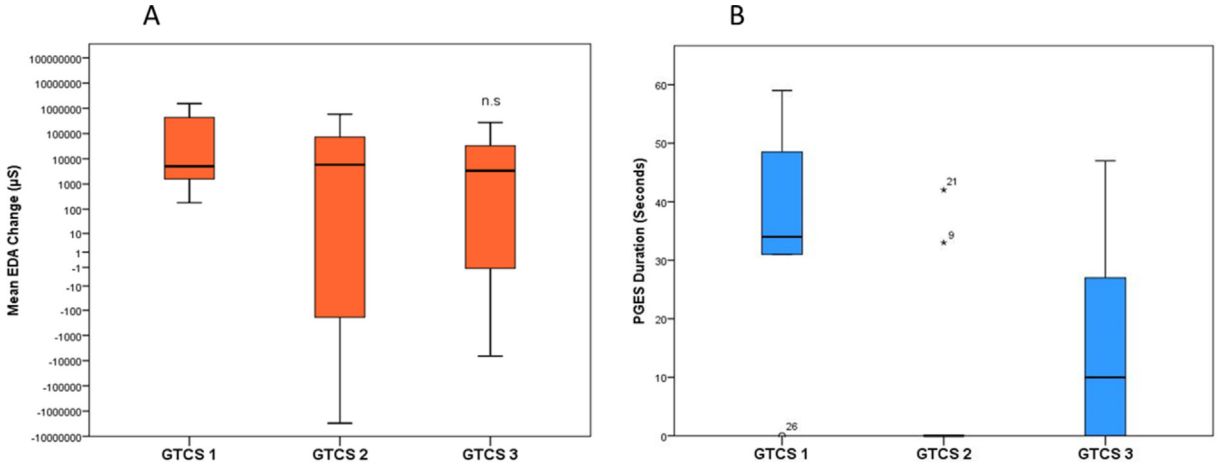

Fig. 3. Taking a single seizure per patient; (A) Log EDA AUC change groupwise comparison between GTCS semiology subtypes, (B) PGES duration groupwise comparison between GTCS semiology subtypes for single-episode analysis, (A) patients with GTCS1, manifesting as bilateral and symmetric tonic arm extension correlated with a significantly greater EDA change from baseline compared to GTCS 2, with no specific tonic arm extension or flexion, but not GTCS 3 with unilateral or asymmetrical arm extension, tonic arm flexion or posturing that does not fit in the types 1 or 2. (B) Patients with GTCS 1 had a significantly longer postictal generalized EEG suppression (PGES) duration compared to GTCS 2 and GTCS 3. EDA change presented in logarithmic scale. n.s; not significant.

3.3.2. PGES and EDA change

PGES was associated with a higher EDA (β = 637500 μS, 95% CI: 183571.84 to 1091428.16, p = 0.01, Fig. 4A), with an overall model fit of R^2 = 0.32 and with a regression equation (F (2, 27) = 6.27, p = 0.006). EDA increased with increasing PGES duration, adjusting for sleep and awake states (β = 16794 μS, 95% CI: 5729.8 to 27858.2, p = 0.006, Fig. 4B). The overall fit of the model was R^2 = 0.34 and with a regression equation (F (2, 27) = 6.99, p = 0.004).

3.3.3. Semiologic characteristics and PGES duration

PGES occurred in 12 patients (40%), 88%, 12%, and 57% of seizures belonging to GTCS 1, 2, and 3, respectively had PGES. Including all 30 patients, patients with GTCS 1 events had longer PGES duration compared to patients with GTCS 2 (β = −30.53 s, 95% CI: −44.6 to −16.46, p < 0.001) and GTCS 3 (β = −22.07 s, 95% CI: −38.95 to −5.19, p = 0.016) events adjusting for awake and sleep states (Fig. 3B). The overall fit of the model was R^2 = 0.44 and with a regression equation (F (3, 26) = 6.82, p = 0.002). There was no association between PGES duration and duration of tonic phase (p = 0.97), clonic phase (p = 0.09), or total seizure duration (p = 0.43).

Of the 12 seizures followed by PGES, five (42%) occurred out of wakefulness and seven (58%) out of sleep. PGES duration did not differ in awake and sleep (p = 0.277, Wilcoxon Rank Sum Test W = 87) in all patients.

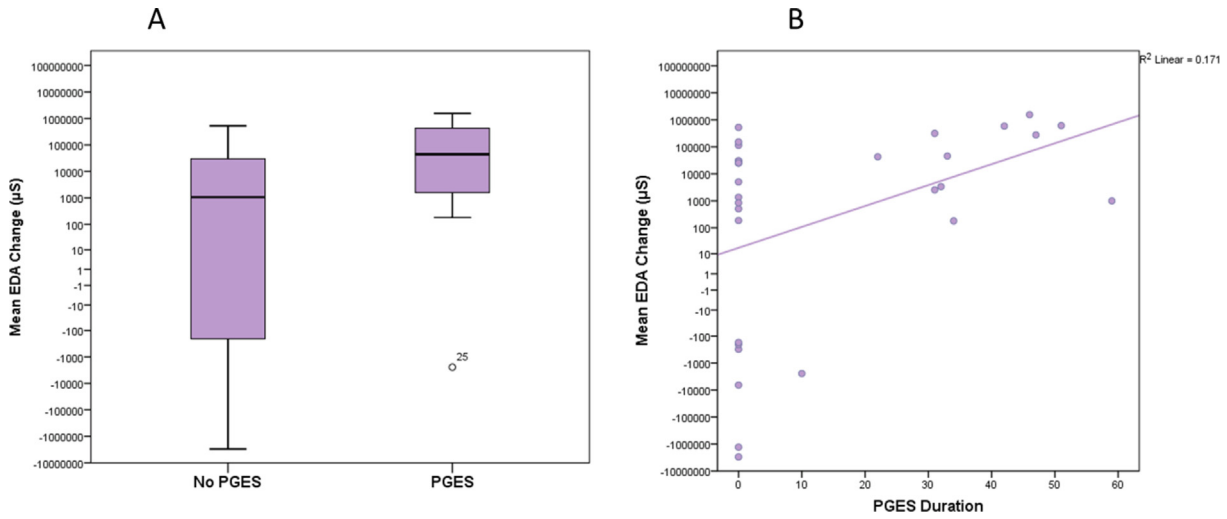

Fig. 4. Taking a single seizure per patient; (A) Log EDA AUC change in presence and absence of PGES, (B) Log EDA AUC change for single-episode analysis, (A) patients with postictal generalized EEG suppression (PGES) had greater EDA changes, compared to patients without PGES. (B) patients with longer PGES had greater EDA changes.

4. Discussion

4.1. Summary

Our study expands the literature on the association of PGES with seizure semiology from adult studies to children while exploring the association of EDA with PGES and semiology in children with epilepsy. We established a relationship between specific semiologic, autonomic and electrographic characteristics of GTCS in children with epilepsy. Seizures manifesting with semiological features suggestive of decerebrate posturing or bilateral tonic arm extension (GTCS 1) were associated with longer PGES duration. Furthermore, the presence of PGES, irrespective of its duration, was associated with a higher ictal EDA. Additionally, when analyzing single episodes per patient, GTCS 1 was associated with greater EDA change. Here, the duration of PGES also correlated with greater EDA change. In the absence of PGES, EDA change was not significantly different between semiology groups. The clinical seizure duration, other semiologic characteristics, namely duration of tonic and clonic phases and, sleep and wakefulness, did not correlate with PGES or EDA.

4.2. PGES and GTCS semiology in children are related

Compared to adults, children have shorter seizure duration, tonic phases, and PGES. The mean PGES duration in adults is approximately 39 s, and the risk of SUDEP increases significantly when the duration exceeds 50 s [17,19]. PGES duration is on average 28 s shorter in children [17]. An increase in age correlates with an increase in tonic phase duration, which in turn correlates with an increase in PGES duration [17]. In adults, the presence of a tonic phase is associated with PGES, and the latter is remarkably longer with decerebrate posturing [26]. Compared to our cohort, adults seem to have more GTCS with symmetrical tonic arm extension [26,27].

In adults, the presence of PGES, but not its duration, correlated with bilateral and symmetric tonic arm extension, but not with other semiologies and phase durations [27]. In children, the presence of PGES was associated with a decerebrate tonic posturing and shorter clonic phase [30]. A study involving both adults and children showed that for each 0.12-second increase in tonic phase duration, there was a one-second increase in PGES. Inversely, an increase in the clonic phase duration correlated with a decreased PGES duration [17]. In our study, longer PGES was associated with bilateral symmetric arm extension; however, we did not find a relationship between the durations of tonic and clonic phases and PGES duration. Similar to other studies [26], we did not find a correlation between the total seizure duration and PGES duration.

Some studies report that PGES may occur more frequently post-seizures out of sleep [27,30], while others did not find a significant difference in PGES presence or duration between awake and sleep [23,26] as seen in our study.

4.3. PGES and EDA in children are related

Sympathetic activation is the most common seizure-activated autonomic response, especially with GTCS [32]. This activation can be measured by EDA and may provide information for SUDEP risk evaluation [23,24]. EDA increases peri-ictaly with GTCS [20,21], and even more profoundly with terminal events [22]. In our study, the occurrence and duration of PGES correlated with higher EDA, similar to findings of other studies in adults and children [23,24].

4.4. EDA and seizure semiology in children are related

Specifically, in the single episode analysis, GTCS 1 was associated with a greater EDA change. However, in the absence of PGES, EDA change did not differ significantly between semiology classes. Research on EDA and its relation to the semiologic characteristics of GTCS is lacking. In our study, EDA did not correlate with the total duration of the seizures or the duration of its phases. Ictal EDA monitoring may have potential, albeit not independently, in SUDEP risk assessment in children with epilepsy.

4.5. Individual differences in EDA exist among patients

In addition to group differences, our findings show individual differences in EDA changes. Autonomic responses and the resulting electrodermal response may vary with age, sex, ethnicity, activity, and emotions such as anxiety and fear [33]. EDA may peak interictally, especially in slow-wave sleep [31,34]. We did not find a significant difference in EDA change between sleep and awake; nevertheless, we had interesting findings on an individual patient level. In our study, we had six seizures out of slow-wave sleep from

five patients. The two patients with the lowest EDA change values had seizures out of stage 3 sleep. The first patient had an elevated EDA throughout the baseline period, possibly representing an EDA storm. His EDA drops at seizure onset, likely at arousal, then increases again, with a lower peak than that found pre-ictally. In the second patient, the EDA drops halfway through the baseline period and peaks again after seizure onset. His ictal peak is remarkably smaller than the baseline peak. In both patients, the assumingly storm-related EDA elevations were more durable than ictal elevation.

In addition to individual differences in baseline EDA, variations in EDA response to seizures exist in our cohort as well. Three other patients had seizures out of stage 3 sleep; one with ictal EDA that rises to a level comparable to baseline EDA but over a shorter period, and two other patients (3 seizures) had a higher ictal EDA than baseline. The patient with the highest positive EDA change in both of our models had a somewhat average baseline EDA but had the highest ictal EDA. The patient was awake at baseline, with a few short and small EDA peaks. After seizure onset, EDA peaks dramatically and remains elevated for over 20 min. Understanding and accounting for individual differences may open opportunities for a potential diagnostic and predictive biomarker.

4.6. Adults and children have different seizure profiles

Adults and children have different seizure profiles, and seizure monitoring tools and risk assessment measures cannot be generalized to all age groups. In children under the age of 10, epilepsy of generalized or unknown onset is the most common. In older children and adults, focal epilepsy becomes the most common, and seizure semiology starts to resemble that of adults, possibly reflecting cortical maturation [35]. Differences may be attributed to maturation of the nervous system. Decerebrate posturing may be related to seizure-induced brainstem dysfunction and cortical disconnection, resulting in a possibly fatal cardiorespiratory compromise. PGES may reflect this neuropathophysiological phenomenon [26,36,37]. The shorter tonic phase in children may be related to immature neuronal networks, which may also explain why PGES and decerebrate posturing is less common here. The lower incidence of SUDEP in children compared to adults may be related to these differences. Similarly, autonomic regulation differs between the two groups. Seizures often arise or spread to brain areas involved in autonomic control, resulting in prominent autonomic dysfunction, which may contribute to the mechanism of SUDEP. Differences in seizure-activated autonomic responses exist between children and adults. Likely due to their developing autonomic network, children are susceptible to intense autonomic responses [38]. Children have higher peri-ictal EDA indicating higher sympathetic activation [24]. This is presumably due to excessive loss of inhibitory control in the immature autonomic network resulting from cortical and brainstem dysfunction that manifests as PGES and decerebrate posturing.

4.7. Assessment of SUDEP risk and the role of EDA monitoring

Semiology and PGES are important factors in SUDEP risk assessment [17–19,26,27]. These require means of monitoring, including video and EEG, often in a hospital setting. While PGES has long been associated and may invariably occur with SUDEP [7,19], it is noteworthy that some studies report that the PGES may occur inconsistently in patients and therefore, alone, may not be very reliable in predicting SUDEP [39]. Frequent GTCS remain the main and most consistently reported risk factor for SUDEP [13]. Hence, patients with epilepsy may benefit from additional monitoring, including GTCS detection and prediction algorithms such as those present in seizure detection devices. EDA can be measured continuously outside the hospital setting, using non-invasive and less stigmatizing wearable devices, such as wristbands, making them well-tolerated and accepted by users [20,40,41]. EDA monitoring provides helpful information on GTCS-related sympathetic changes relevant to SUDEP risk assessment and has shown utility seizure detection and prediction, especially when combined with other physiologic modalities [25,42–45]. EDA monitoring may be a supplementary and necessary tool for evaluating seizure and SUDEP risk circumstances, particularly when other methods are not available.

4.8. Challenges

We need to interpret our findings in the setting of data collection. Our cohort comprised of children with epilepsy admitted for long-term EEG monitoring, primarily for pre-surgical evaluation. Hence, they may not represent all the population of children with epilepsy and their behavior outside the hospital setting. Many epilepsy and non-epilepsy-related differences exist even within a pediatric population [35,46] and may interfere with the consistency of outcomes. However, given our relatively small sample size, we could not control for factors that may confound our results such as age, gender, epilepsy duration, syndrome, etiology, MRI findings, seizure onset, and epileptogenic zone. Anti-seizure medications and other treatments may also contribute to differences in groups. Recordings were taken at different times of the day and at different emotional states and activity levels, which may generate different EDA responses. Unlike other studies, we accounted for sleep and awake in all our analyses. We also subtracted the ictal EDA from a baseline to avoid overestimating ictal EDA. Yet, we cannot completely rule out the EDA contaminants related to stress [33], circadian fluctuation [25], or sleep storms [31] that may lead to higher surges. In our study, patients wore the wristband on either wrist or ankle left or right side. EDA measured from different sites, and sides of the body may generate different results [47,48]. Data quality may also be a limitation. As we did not include real SUDEP cases, our interpretation of our findings remains hypothetical, and larger validation studies, that include assessment of peri-ictal cardiorespiratory status and more granular semiology characterization, are warranted.

5. Conclusion

GTCS manifesting as decerebrate posturing or bilateral tonic arm extension were associated with longer PGES duration, and the presence and a longer PGES duration are associated with a higher ictal EDA. GTCS with decerebrate posturing were associated with greater EDA change. In the absence of PGES, EDA change in this semiology group was not significantly greater. Other clinical semiologic characteristics did not correlate with PGES or EDA. In children with epilepsy, GTCS semiology correlated with longer PGES duration and may indirectly correlate with greater ictal EDA. Our study suggests potential applications in monitoring and preventing SUDEP risk in these patients, providing potentially novel biomarkers on a group and individual level.

6. Data Availability

Anonymized data used in this study are available based on reasonable request.

7. Project Funding

This study was funded by the Epilepsy Research Fund.

8. Disclosures

Tobias Loddenkemper serves on the Council of the American Clinical Neurophysiology Society, on the American Board of Clinical Neurophysiology, as founder and consortium PI of the pediatric status epilepticus research group (pSERG), as an Associate Editor for Wyllie's Treatment of Epilepsy 6th edition and 7th editions, and as a member of the NORSE Institute, PACS1 Foundation, and CCEMRC. He served as Associate Editor of Seizure and served on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring in the past. He is part of patent applications to detect and predict clinical outcomes and to manage, diagnose, and treat neurological conditions, epilepsy, and seizures. Dr. Loddenkemper is co-inventor of the TriVox Health technology, and Dr. Loddenkemper and Boston Children's Hospital might receive financial benefits from this technology in the form of compensation in the future. He received research support from the Epilepsy Research Fund, NIH, the Epilepsy Foundation of America, the Epilepsy Therapy Project, the Pediatric Epilepsy Research Foundation, and received research grants from Lundbeck, Eisai, Upsher-Smith, Mallinckrodt, Sunovion, Sage, Empatica, and Pfizer, including past device donations from various companies, including Empatica, SmartWatch, and Neuro-electrics. In the past, he served as a consultant for Zogenix, Upsher Smith, Amzell, Engage, Elsevier, UCB, Grand Rounds, Advance Medical, and Sunovion. He performs video electroencephalogram long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies at Boston Children's Hospital and affiliated hospitals and bills for these procedures, and he evaluates pediatric neurology patients and bills for clinical care. He has received speaker honorariums from national societies, including the AAN, AES, and ACNS, and grand rounds at various academic centers.

His wife, Dr. Karen Stannard, is a pediatric neurologist, and she performs video electroencephalogram long-term and ICU monitoring, electroencephalograms, and other electrophysiological studies and bills for these procedures, and she evaluates pediatric neurology patients and bills for clinical care.

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Other authors report no disclosures.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2021.108228.

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