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

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Background and Rationale

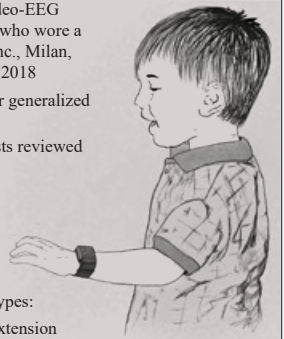
- Patients with **Generalized Tonic-Clonic Seizures (GTCS)** have an increased risk of **Sudden Unexpected Death in Epilepsy (SUDEP)[1]**.
- GTCSs are associated with elevated postictal **Electrodermal Activity (EDA)** and **Postictal Generalized EEG Suppression (PGES)[2].** Thus, EDA and PGES are potential markers for SUDEP risk.
- In adults, GTCS semiology (manifesting as decerebrate posturing with symmetric bilateral arm tonic extension) is positively associated with PGES duration[3]. In children, seizure semiology is another potential SUDEP marker, but has not been sufficiently studied.

Objectives

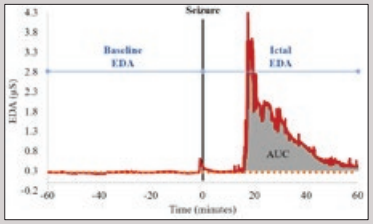
1) Determine the relationship between semiologic, autonomic, and electrographic features of GTCS in children with epilepsy.
2) Determine if PGES presence and duration are associated EDA changes.
3) Determine if EDA changes and PGES duration are different during sleep and wakefulness.

Methods

- Enrolled patients admitted to the long-term video-EEG monitoring unit at Boston Children's Hospital who wore a portable wrist or ankle sensor (E4, Empatica Inc., Milan, Italy) that records EDA from Feb 2015 to Dec 2018
- Included patients w/at least 1 GTCS of focal or generalized onset (n=30 patients)
- Two independent, board-certified epileptologists reviewed video-EEG, collecting the following variables:
  - **Semiologic characteristics**
  - **Duration of tonic and clonic phases**
  - **Total clinical seizure duration**
  - **Electrographic seizure onset and offset**
  - **PGES**
- Grouped patients into 3 GTCS semiology subtypes:
  - **GTCS I:** Bilateral symmetric tonic arm extension
  - **GTCS II:** No specific tonic arm extension or flexion
  - **GTCS III:** Unilateral or asymmetrical arm extension, tonic arm flexion
- Performed GTCS semiology group-wise comparisons between:
  - **Semiology subtypes and EDA change**
  - **Semiology subtypes and PGES duration**
  - **EDA change and PGES duration/presence**



- Analyzed the logarithmic area under the curve (AUC) of ictal EDA with MATLAB.
- Calculated the seizure-induced EDA change by subtracting ictal EDA (60-min segment starting at seizure onset) from baseline EDA (60-min seizure-free segment before seizure onset).



- Using linear regression, we analyzed the first GTCS the patient had during the recording, adjusting for sleep and awake.
- Compared EDA change and PGES duration between awake and sleep amongst all seizures (Wilcoxon Rank Sum Test).

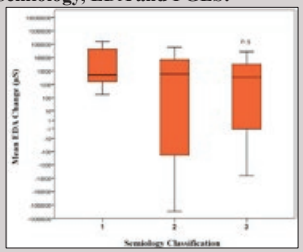
Results

- **Demographics and clinical characteristics:**

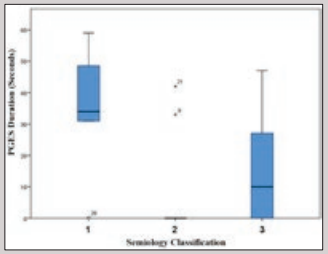
Demographics (n=30 patients)	
Female, **n (%)**	14 (46.7)
Age at first seizure, **Median (Range)**, years	8.59 (0.25-17.42)
Age at EEG, **Median (Range)**, years	13.78 (8.22-22.17)
History of neurosurgery, **n (%)**	
Yes	5 (16.7)
No	25 (83.3)
MRI Findings, **n (%)**	
Normal	6 (20)
Abnormal	24 (80)

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, **sec**	92 (30 – 222)
Clinical seizure duration, **sec**	82 (29 – 191)
Tonic phase duration, **sec**	15 (0 – 60)
Clonic phase duration, **sec**	53 (6 – 85)

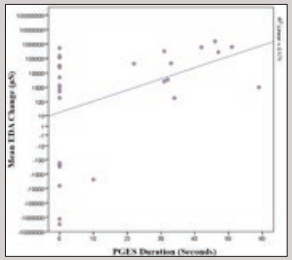
- **Semiology, EDA and PGES:**



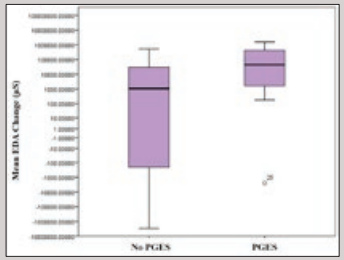
- **GTCS 1 patients showed greater EDA change than GTCS 2** ($p = 0.047$) but not compared to GTCS 3 ($p = 0.71$)
- $R^2 = 0.272$ with regression equation (F (3, 26) = 3.23, $p = 0.039$).
- No association between mean EDA change, clonic phase (p = 0.93), or clinical seizure durations (p = 0.63)
- EDA change did not differ between awake and sleep ($p = 0.213$, W= 141)



- **GTCS 1 patients had longer PGES duration as compared to GTCS 2** ($p < 0.001$) and GTCS 3 ($p = 0.016$)
- $R^2 = 0.44$ with regression equation (F (3, 26) = 6.82, $p = 0.002$)
- No association between PGES, tonic phase ($p = 0.97$), clonic phase ($p = 0.09$), or total seizure durations ($p = 0.43$)
- PGES duration did not differ in awake and sleep ($p = 0.277$, W= 87)



- **EDA change increased with increasing PGES duration** ($p = 0.006$)
- $R^2 = 0.34$ with regression equation (F (2, 27) = 6.99, $p = 0.004$)



- **PGES presence correlated with a higher EDA change** ($p = 0.01$)
- $R^2 = 0.32$ with regression equation (F (2, 27) = 6.27, $p = 0.006$)

Results

First GTCS Patient Had During Recording (n=30 patients)

	EDA Change			PGES Duration		
	Median	Q1	Q3	Median	Q1	Q3
Overall Estimate	4210.53	181.76	97036.03	0	0	31.75
GTCS 1 (n=7)	5041.45	1773.15	462687.97	34	31	48.5
GTCS 2 (n=16)	13196.93	-181.69	62818.42	0	0	0
GTCS 3 (n=7)	3379.6	-974.87	34241.3	10	0	27
Awake (n=17)	25439.5	180.11	152090.	0	0	10
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 β, μS	**95% Confidence Interval**	**P-value**	**Estimate**	**95% Confidence Interval**	**P-value**
GTCS 2	-601339	-1167016.56 to -35661.44	0.047*	-30.53	-44.6 to -16.46	<0.001*
GTCS 3	-129965	-808160.28 to 548230.28	0.71	-22.07	-38.95 to -5.19	0.016*
Tonic Phase Duration	12781	-8735.88 to 34297.88	0.25	-0.013	-0.67 to 0.64	0.97
Clonic Phase Duration	534.6	-12215.79 to 13284.99	0.935	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	16794	5729.8 to 27858.2	0.006*	n/a	n/a	n/a
PGES Presence	637500	183571.84 to 1091428.16	0.01*	n/a	n/a	n/a
GTCS 2 in patients without PGES	11097	-1429403.04 to 1451597.04	0.99	n/a	n/a	n/a
GTCS 3 in patients without PGES	368449	-1207685 to 1944583	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, *statistically significant. EDA (microsiemens, μS); Durations: Seconds

Conclusion

- In children with epilepsy, GTCS I subtype semiology presenting with bilateral and symmetrical tonic arm extension correlated with longer PGES duration and may indirectly correlate with greater ictal EDA.
- Our study suggests potential applications of GTCS subtype, PGES duration, and EDA AUC in pediatric seizures, and potentially SUDEP risk assessment.
- Further research is needed to validate our findings.

References and Disclosures

1. Devinsky O. Sudden, unexpected death in epilepsy. N Engl J Med 2011;365:1801–11. **2.** Ryvlin P, Rheims S, Lhatoo SD. Risks and predictive biomarkers of sudden unexpected death in epilepsy patient. Curr Opin Neurol 2019;32:205–12. **3.** Vilella L, Lacuey N, Hampson JP, Zhu L, Omidi S, Ochoa-Urrea M, et al. Association of peri-ictal brainstem posturing with seizure severity and breathing compromise in patients with generalized convulsive seizures. Neurology 2021;96:e352–65.

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. Marta Amengual-Gual was supported by Fundación Alfonso Martín Escudero. Other authors report no disclosures.