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Autonomic changes following generalized tonic clonic seizures: An analysis of adult and pediatric patients with epilepsy

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ABSTRACT

Objective: Sudden unexpected death in epilepsy (SUDEP) is the most common cause of mortality directly related to epilepsy. Its incidence is higher in adult patients and its pathophysiology remains poorly understood, but likely involves autonomic dysregulation following generalized tonic clonic seizures (GTCS). In the current study, we aimed to analyze post-ictal autonomic changes following GTCS in adult and pediatric patients.

Methods: Patients admitted to the epilepsy monitoring unit were prospectively recruited, and wore an electrodermal activity (EDA) wrist sensor that continuously measured sympathetic activity while being monitored with EEG and EKG electrodes. Peri-ictal EDA parameters were assessed as a measure of sympathetic activity. Peri-ictal parasympathetic activity was determined through the high frequency component (HF) analysis of heart rate variability (HRV). The duration of post-ictal generalized EEG suppression (PGES) was also documented.

Results: Twenty patients with GTCS were included in the study on whom 30 GTCS were recorded. PGES duration strongly correlated with age ($r = 0.62$, $p = 0.004$) and measures of the EDA response. After controlling for PGES duration, we found pediatric patients had greater sympathetic activation measured as log rising portion of the area under the curve of the EDA response ($\beta = +0.67$, $p = 0.034$) and a higher degree of vagal suppression measured as maximal percentage change of HF power ($\beta = -12.65$, $p = 0.0036$).

Conclusion: Sympathetic activity can be measured in the peri-ictal period, and directly correlates with PGES duration. Age is a significant determinant of the sympathetic and parasympathetic response following a GTCS; given the same PGES duration, pediatric patients demonstrate stronger sympathetic activation and higher vagal suppression. However, the increase in PGES duration with age and the associated autonomic dysregulation may provide clues as to why there is a variable vulnerability to SUDEP across age groups.

Abbreviations: AUC, area under the curve; EDA, electrodermal activity; GTCS, generalized tonic clonic seizure; HRV, heart rate variability; PGES, post-ictal generalized EEG suppression; SUDEP, sudden unexpected death in epilepsy.

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1. Introduction

Patients with epilepsy are at risk of premature death. Sudden unexpected death in epilepsy (SUDEP) is the most common cause of mortality directly related to epilepsy (Surges et al., 2009). It exceeds the expected sudden death rate in the general population by 24 times, and patients between the ages of 15–44 are at highest risk (Ficker et al., 1998). Its incidence in pediatric patients seems to be lower than in adults (Donner et al., 2001; Nickels et al., 2012). The exact pathophysiology of SUDEP remains unclear, but likely involves a cascade of events often following generalized tonic-clonic seizures (GTCS) with prominent autonomic dysregulation (Ryvlin et al., 2013b; Massey et al., 2014). Following GTCS there can be a period of post-ictal generalized electroencephalographic suppression (PGES), which has been noted in all monitored (but unwitnessed) cases of SUDEP (Ryvlin et al., 2013a).

Peri-ictal parasympathetic activity analysis is possible through the high frequency power of heart rate variability (HRV) which correlates with vagal tone (Malik, 1996). However, adequate measures of the sympathetic response have been lacking. Sweat causes changes in skin conductance referred to as electrodermal activity (EDA), which is considered a measure of sympathetic activity (Critchley, 2002). In a previous study using EDA sensors in patients with epilepsy aged 3–20 years, we were able to successfully show prominent sympathetic activation after different seizure types, especially after seizures with long duration of PGES (Poh et al., 2012).

The goal of the current study is to evaluate autonomic responses following GTCS in a cohort with a wide age range, and to determine whether differences in autonomic responses between pediatric and adult patients exist.

2. Materials and methods

2.1. Patient cohort

Pediatric and adult epilepsy patients admitted to the epilepsy monitoring units at Boston Children's Hospital and Brigham and Women's Hospital, respectively, were recruited over a 2 year period (2011–2013). The study was approved by the local institutional review boards. Patients or their legal guardians provided informed consent.

During the hospital admission, a wrist-worn EDA sensor was placed on the ventral aspect of the left forearm (Q-Sensor, Affectiva Inc., Waltham, MA, USA). The sensors consist of Ag/AgCl disk electrodes, which provide continuous reliable measurements of EDA by applying direct current and measuring conductance from the skin (Poh et al., 2010a, 2010b).

EEG recordings were conducted using the conventional (10–20) system at a sampling frequency of 256 Hz (Natus Medical Corp, San Carlos, CA). For analysis, only patients with a GTCS while wearing the sensor were included in the study. Both focal and generalized onset seizures were included. The previously reported cohort of 6 patients (aged 11–19) with GTCS was also included in the present analysis (Poh et al., 2012), one of the patients was later on excluded due to a seizure lasting >10 min. In the prior study, the 5 patients had worn an older prototype of the wrist-worn sensor.

2.2. EEG/EDA/HRV

The EEG recordings were reviewed by a board-certified electroencephalographer (RS) blinded to the patients' clinical and autonomic data. The duration of PGES was defined as the immediate postictal suppression of EEG activity to <10 μV excluding artifacts (Lhatoo et al., 2010).

EDA (as a measure of sympathetic activity) and HRV (as a measure of parasympathetic activity through its high frequency component) was analyzed by a computerized algorithm and analysis was performed by a research team member blinded to clinical and EEG seizure data (MZP) (Poh et al., 2012). The raw EDA signal was low-pass filtered (Hamming window, length = 1025 samples, 3 Hz) to reduce artifacts. To establish a pre-ictal EDA baseline, the mean EDA was computed from the 60 min epoch immediately preceding the first definite ictal EEG change which was considered the EEG seizure onset. An EDA response was defined as an increase greater than 2 standard deviations above the pre-ictal baseline, and the response end time was established as the time the response fell below 90% of the EDA peak amplitude. Our primary measure of interest was the area under the rising portion of the EDA curve (μSiemens × Seconds), since it was previously shown to have the highest correlation with PGES (Poh et al., 2012). EDA measures also included the peak of EDA amplitude (μSiemens) and area under the EDA response curve (AUC: μSiemens × Seconds) (Supplementary material Figure 1). Area calculations were then natural-log transformed.

Time-frequency mapping of HRV was performed to assess post-ictal parasympathetic changes. All EKG recordings were analyzed using custom written software in MATLAB (MathWorks Inc., Natick, MA). After filtering using a 12-tap low-pass filter (35 Hz) with equal ripple in the pass and stop bands, the peri-ictal EKG (30 min prior and 30 min after the seizure) was segmented. The interbeat interval (R–R interval) time series was extracted from the EKG recordings and analyzed using the smoothed pseudo-Wigner-Ville time-frequency distribution. The parasympathetic-mediated HF spectral component was extracted from the smoothed pseudoWigner-Ville distribution by integrating the spectral powers between 0.15 and 0.4 Hz.

2.3. Statistical analysis

To analyze the correlation between individual seizures and autonomic measures, linear correlation using the Pearson correlation coefficient was used to assess the relationship between PGES and EDA measures (response amplitude, log AUC, log area under rising portion of EDA curve) and HF-HRV (change in pre vs. post-ictal HF and maximal pre vs. post-ictal change in HF) variables for all GTCS.

To analyze the effect of age, individual patients were then divided into adult (≥18 years) and pediatric groups. For this analysis, only the first GTCS in each patient was included. The Wilcoxon rank-sum test was used to compare PGES duration, EDA measures, and HF-HRV measures between groups. The false discovery rate correction for multiple comparisons was used to determine statistical significance (Benjamini and Hochberg, 1995) when comparing variables for the adult vs. pediatric samples.

To determine whether EDA responses differed between age groups regardless of the PGES duration we divided the cohort into patients with a PGES duration of <20 s and ≥20 s. A PGES cut-off of >20 s was used, as this threshold was associated with a higher odds ratio for SUDEP in a previous study (Lhatoo et al., 2010).

A multiple linear regression analysis was then performed with log area under the rising portion of the EDA curve, and maximal percentage change in HF as outcomes and age (adult vs. pediatrics) and PGES duration (<20 or ≥20 s) as predictors. All statistical analyses were performed using the JMP software (JMP pro 11.0, SAS). A p-value <0.05 was considered statistically significant.

3. Results

A total of 276 patients were recruited for the study, 33 of whom had at least 1 GTCS during their monitoring admission. Eighteen