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Childhood trauma in patients with self-reported stress-precipitated seizures

Ikjae Lee [a], Jeffrey R. Strawn [b], Alok K. Dwivedi [c], Michael Walters [a,1], Adrienne Fleck [a], Donna Schwieterman [a], Sheryl R. Haut [d], Emily Polak [d], Michael Privitera [a,*]

[a] Department of Neurology, Neuroscience Institute, University of Cincinnati, 260 Stetson St., Suite 2300, Cincinnati, OH 45267-0525, USA
[b] Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH 45267-0559, USA
[c] Department of Biomedical Sciences, Division of Biostatistics & Epidemiology, Texas Tech University Health Sciences Center, El Paso, TX, USA
[d] Comprehensive Epilepsy Center, Department of Neurology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY 10463, USA

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ABSTRACT

Objective: Stress is the most commonly reported precipitant of epileptic seizures, but the mechanism by which stress precipitates seizures and the risk factors for stress as a seizure precipitant are poorly understood. Previously, we observed higher levels of anxiety symptoms in patients with epilepsy who reported stress as a seizure precipitant. Given that childhood trauma increases the risk of general psychiatric symptom burden, including anxiety symptoms, we sought to examine the relationship between childhood adversity and stress as a seizure precipitant.
Methods: Sequential outpatients (N = 236) evaluated at the Epilepsy Center of the University of Cincinnati Neuroscience Institute who had previously enrolled in an earlier study of stress and seizures were enrolled. Subjects either endorsed stress as a seizure precipitant [Stress (+)] or not [Stress (−)]. The Childhood Trauma Questionnaire Short Form (CTQ-SF), a 28-question scale that evaluates 5 domains of childhood adversity (physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse) was sent via mail and returned on paper or electronically from participants. Total CTQ-SF score and CTQ-SF domain scores were compared between Stress (+) and Stress (−) groups using Wilcoxon rank sum test. Spearman's rank correlation between CTQ-SF scores with depression and anxiety was also determined, and these analyses were followed by a multivariate analysis to identify the association of childhood trauma with other factors including anxiety and depression.
Results: A total of 119 out of 236 CTQ-SFs that were sent out were completed. Response rates were 91/195 for Stress (+) and 28/41 for Stress (−). The Stress (+) group reported higher scores in emotional abuse compared with the Stress (−) group ($p = 0.029$); CTQ-SF total scores were higher in the Stress (+) group compared with the Stress (−) group ($p = 0.08$), and sexual abuse scores were higher in Stress (+) group ($p = 0.07$), but there were no statistically significant differences for other types of trauma. Depression and anxiety scores were higher in the Stress (+) group, but anxiety was the only independent factor associated with the Stress (+) group in the multivariate analysis ($p = 0.0021$).
Conclusion: Patients with epilepsy who report stress as a seizure precipitant are more likely to endorse a history of childhood traumatic experiences, particularly emotional abuse, compared with those who do not perceive stress as a precipitant. Further study is needed to identify how childhood trauma interacts with anxiety in modulating stress response in patients with epilepsy.

1. Introduction

Stress is a commonly reported seizure precipitant in patients with epilepsy [1,2]. *Stress* is a complex phenomenon, but can be defined in terms of its biological, environmental, and psychological aspects, whereby external demands exceed adaptive capacity [3]. Trials of stress reduction in epilepsy have been reported with mixed results, but most of these studies have been uncontrolled [4]. Additionally, stress reduction techniques are associated with decreases in self-reported seizure frequency even in patients who do not endorse stress as a precipitant for their seizures [5]. However, the relationship between stress and seizures is likely moderated by a number of factors. For example, in patients who report stress as a precipitant of their seizures, anxiety symptom severity is also increased [5]. A randomized, controlled trial of integrative, nonpharmacologic adjunctive treatments—which may improve both 'stress' and anxiety—in patients with treatment-resistant

* Corresponding author at: Department of Neurology, 260 Stetson St., Suite 2300, PO Box 670525 Cincinnati, OH 45267-0525, USA. Tel.: +1 513 558 5440.
E-mail address: michael.privitera@uc.edu (M. Privitera).
[1] Current address: Cleveland Clinic Lerner College of Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, USA.

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epilepsy is ongoing to evaluate the role of such treatments in this population [6]. However, the relationship between self-reported stress and seizures, the association with some of the symptoms typically associated with depression or anxiety, and other risk factors associated with stress as a seizure precipitant remain poorly understood.

How might early life stress contribute to the development of epilepsy or precipitation of seizures once epilepsy has been established? Stress has been associated with neurostructural, neurofunctional, neuroendocrine, and immune changes which could influence the development and subsequent course of epilepsy [4,7–9]. Moreover, data from animals further suggest that stress during critical developmental periods contributes to the development of epilepsy and increases vulnerability to seizures through alterations of brain structure, neurophysiology, neurotransmitter, and neuroendocrine mechanisms [10]. Especially, the HPA axis can be hyperactive in adults who experienced profound stress in their youth, which in turn, may lead to the release of more stress hormones when the individual experiences stress in adulthood [11–13]. Early life stress has been examined in adults with depression, anxiety, and posttraumatic stress disorder (PTSD) [14–17]. Kaplan et al. [18] used the CTQ-SF and found that childhood trauma was more prevalent in patients with psychogenic nonepileptic seizures compared with epileptic seizures, but the prevalence of childhood trauma was higher in patients with epilepsy compared with the general population. To our knowledge, characterization of childhood trauma exposure in adults with epilepsy who have identified stress as a seizure precipitant is lacking. With these considerations in mind, this study aimed to increase our understanding of the characteristics of patients with epilepsy who report stress-triggered seizures by exploring early life stress and trauma. We hypothesized that stress-precipitated seizures are associated with increased exposure to traumatic experiences during childhood.

2. Methods

2.1. Study population

The same cohort of subjects from the prior study "Characteristics of People with Stress Precipitated Seizures" was approached and asked to complete the CTQ-SF [4]. The study population was recruited from the Epilepsy Center of the University of Cincinnati Neuroscience Institute with outpatient clinics that include 6 epilepsy specialists at two sites, with a focus on the treatment of medication-resistant epilepsy. This population is anticipated to have a very low incidence of psychogenic seizures since patients with questionable spells were referred to the Epilepsy Monitoring Unit. A total of 252 patients were identified who had previously answered a question "Do you believe that stress, especially emotional stress, makes a seizure more likely?" and were subsequently categorized as Stress (+) if they answered yes, Stress (−) if they answered no. Those who answered "unknown" to this question were excluded from analysis ($n = 16$). Written consent in the prior study allowed us to reapproach subjects for future study. The CTQ-SF was mailed with instructions and consent form. Each individual was asked to complete the questionnaire and return it via mail or complete the form online through a secure website. Informed consent and study protocol were approved by the University of Cincinnati Institutional Review Board.

2.2. Childhood Trauma Questionnaire Short Form (CTQ-SF)

The CTQ-SF is a well-validated 28-item self-report inventory that identifies 5 types of trauma: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect [19]. There are 5 questions for each type of trauma with an additional 3 questions to assess minimization/denial. Elements of the questionnaire are included in the appendix. Each item is answered with a 5-point Likert scale that includes never true, rarely true, sometimes true, often true, and very often true. Item scores are summed to produce scaled scores that quantify the severity of maltreatment. Cutoff scores (provided with the questionnaire) for detecting the presence or absence of abuse/neglect were used in addition to score analysis as a continuous variable. Minimization/denial scores are converted to 1 for very often true and 0 for the rest.

2.3. Mood assessment instruments

Standard clinical practice in our clinics is to administer the Neurological Disorders Depression Inventory (NDDI-E) and Generalized Anxiety Disorders-7 (GAD-7) instruments to screen for anxiety and depression in all patients at each visit. The NDDI-E, a 6-item self-rating instrument is specifically designed to evaluate depression in patients with epilepsy [20], while the GAD-7 is a 7-item self-rating instrument that measures generalized anxiety [21]. The NDDI-E score is determined by assigning scores of 1 to 4 to the categorical responses: "Never", "Rarely", "Sometimes", and "Always or Often", respectively. These scores from each of the six questions are then summed with a score of 15 or more having a sensitivity of 81% and a specificity of 90% [20]. The GAD-7 score is determined by assigning scores of 0, 1, 2, and 3, to the categorical responses: "not at all", "several days", "more than half the days", and "nearly every day", respectively. These scores—from each of the 7 questions—are then summed, with a score of 10 having a sensitivity of 89% and a specificity of 82% for GAD as well as a high sensitivity and specificity for other anxiety disorders (e.g., panic disorder, social anxiety disorder) [22].

2.4. Statistical plan

Our primary aim was to determine the association of a continuous score of CTQ domains with Stress (+) and if that association is independent from other variables (i.e., NDDI-E, GAD-7, or any other baseline characteristics). The demographic and baseline characteristics were compared between survey responders and nonresponders and between Stress (+) and Stress (−) groups among responders. Unpaired t-test was used for comparing normal quantitative variables while Wilcoxon rank sum test was used for comparing nonnormal quantitative variables. Fisher's exact test was used for comparing categorical variables between groups. We first computed each domain score (emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect) and total score of CTQ-SF. Then we determined associations of continuous scores of CTQ total and domain scores with Stress (+) using nonparametric Wilcoxon rank sum test. In addition, we also explored the association of categorized CTQ domains with Stress (+) using Fisher's exact test. The Spearman's rank correlations between CTQ-SF scores and anxiety and CTQ-SF scores and depression were determined for the entire cohort and separately for Stress (+) and Stress (−) groups. Univariate and multivariable logistic regression analyses were performed to determine the association of all variables including CTQ scores, NDDI-E, GAD-7, and other baseline characteristics with Stress (+). The results of logistic regression analyses are presented as odds ratio (OR) with 95% confidence intervals (CI). Results were considered significant at the $p < 0.05$ level, and SAS 9.3 was used for analyses. We did not adjust the p-value for multiple analysis since the comparison of categorized CTQ-SF domains and the correlation analysis were completely exploratory. Quantitative data were described using either mean and standard deviation (SD) or median and interquartile range (IQR). Fewer than 20% of the missing data in any domain were replaced using the mean of the remaining responses of items in a particular domain.

3. Results

A total of 119 out of 236 CTQ-SFs that were sent out were completed. Response rates were 91/195 (47%) for the Stress (+) and 28/41 (68%) for the Stress (−) patients. There was no significant difference in