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Anxiety is common and independently associated with clinical features of epilepsy

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ABSTRACT

Objective: The objective of this study was to assess for independent association of anxiety symptoms with epilepsy localization and other epilepsy-related and demographic factors in a large tertiary care adult epilepsy population.
Methods: Among 540 adults, anxiety was measured by the Symptom Checklist 90-R (SCL-90R) anxiety subscale, and detailed demographics, epilepsy localization, and depression scores (SCL-90R) were collected. High anxiety was defined by SCL-90R anxiety T-score ≥ 60. Stepwise multiple logistic regression was carried out to assess for independent association of high anxiety scores with demographic and clinical factors.
Results: High anxiety symptoms were present in 46.1% of participants ($N = 250$). Focal or unknown epilepsy type and depression scores were independently associated with high anxiety (adjusted odds ratios (OR): 2.89 (95% confidence interval [CI] = 1.33–6.29, $p = 0.007$) and 2.12 (95% CI = 1.83–2.45, $p < 0.001$), respectively; depression odds per 5-point increase in scale). Among the focal epilepsy subpopulation, mesial temporal sclerosis was also independently associated with high anxiety, with adjusted OR: 2.12 (95% CI = 1.11–4.04, $p = 0.023$). Lower education, non-white race/ethnicity, Spanish native language, prior head trauma, antiseizure drug polytherapy, and left focus or bilateral foci (in focal epilepsy) were associated with high anxiety in simple logistic regression, but these associations were not independent. A total of 46 individuals (18.4% of those with high anxiety) scored high for anxiety but not depression. Only 26% of those with high anxiety symptoms were taking a potentially anxiolytic medication.
Conclusion: Anxiety symptoms, often without concomitant depression, were highly prevalent in this epilepsy sample and independently associated with focal/unknown epilepsy and mesial temporal sclerosis. These results strongly support the value of screening specifically for anxiety in the epilepsy clinic, to direct patients to appropriate treatment.

1. Introduction

In addition to the burden of seizures, psychiatric symptoms, which are associated with poor quality of life, poor seizure outcome, and mortality, are highly prevalent among adults with epilepsy [1–5]. Research in this area has focused more on depression than anxiety, despite a similarly high prevalence of anxiety and depression, and evidence that anxiety is a stronger independent predictor of poor quality of life than depression [1,6–10]. Although the importance of identifying and treating anxiety in epilepsy is now increasingly recognized in the literature, in the clinic, these symptoms are underrecognized and undertreated [6,7,11,12]. Clinicians would benefit from knowledge regarding which patients may be at highest risk for anxiety.

Although some studies have examined the association of anxiety with factors including demographics, epilepsy characteristics, depression, and social factors, further characterization is needed, as only a few consistent associations have been demonstrated across studies [7,13–20]. Factors most consistently associated with anxiety across studies include female gender, depression, and unemployment, but results for other demographic and epilepsy related factors vary substantially across studies, and nearly all of the studies included fewer than 250 individuals and thus had limited power to detect associations [7,13,16,17]. Results of some investigations assessing the relationship between anxiety and epilepsy localization, lateralization, and type have been contradictory, and sample sizes for studies including detailed video-electroencephalography(EEG)-based localization and lateralization data have generally been smaller than those investigating other factors [18,21–24]. To further characterize the relationship between anxiety and epilepsy type,

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seizure focus lateralization/localization, and epilepsy causing lesions, we examined a large tertiary care adult epilepsy sample with detailed characterization of these and other epilepsy factors. Our objectives were to assess the prevalence of high anxiety scores in 540 adults with epilepsy under tertiary care, and to identify demographic and epilepsy-specific factors independently associated with anxiety, including lesions, seizure focus localization, and lateralization among those with focal epilepsy. We also assessed depression symptoms and quality of life.

2. Methods

2.1. Setting, participants, and design

This is a cross-sectional analysis of baseline data from a retrospective cohort study of all patients with epilepsy who were referred and underwent neuropsychological testing at the Columbia Comprehensive Epilepsy Center from 1999 to mid-2013, completed the Symptom Checklist 90-R (SCL 90-R) as a routine component of the clinical neuropsychological evaluation, and had SCL-90R anxiety subscale scores entered into the Neuropsychology Registry. This study includes 540 individuals out of 1094 total in the registry: 375 were excluded because the anxiety subscale scores were not yet routinely entered into the registry at the time of baseline data collection; 171 were excluded due to factors including age < 18 years, SCL-90R scale not completed due to reasons such as poor cognition, or inadequate English or Spanish language skills to complete the English or Spanish version of the instrument, and 8 were excluded due to primary diagnosis of psychogenic seizures. The Columbia Comprehensive Epilepsy Center is an academic medical center in New York, serving a diverse population.

2.2. Clinical and demographic factors

Demographic and epilepsy-related data collected at the time of baseline neuropsychological assessment included age, education level, sex, race/ethnicity, handedness, native language, epilepsy onset age, epilepsy risk factors, seizure frequency, antiseizure drugs, and other medications. Sex and race/ethnicity were determined by investigator assignment, with the following race/ethnicity categories: White, Black, Asian, Hispanic, American Indian or Alaskan Native, Native Hawaiian, or other Pacific Islander. Education was initially classified into 5 categories as listed in Table 1, and then dichotomized for logistic regression modeling after initial bivariable analyses and distribution inspection. The number of antiseizure medications and specific antiseizure drugs prescribed at baseline were recorded, as well as psychotropic medications. We classified the following medications as potential anxiolytics: selective serotonin reuptake inhibitor or serotonin norepinephrine inhibitor [SSRI/SNRI], buspirone, and alprazolam; other benzodiazepines, if scheduled, were categorized by specific drug as an antiseizure drug. Age at baseline, age at epilepsy onset, and number of antiseizure drugs were categorized for chi-square analyses as shown in Tables 1 and 2. Epilepsy type was classified as generalized, focal, or unknown based primarily on ictal video-EEG. Some patients were classified based on interictal EEG findings and the managing epileptologist's clinical impression. For those with unknown epilepsy type, limited EEG data were available, or findings on EEG were inconclusive as to whether the patient had focal or generalized epilepsy. Additional focal epilepsy characteristics were recorded from video-EEG and neuroimaging results, including focus lateralization, focus localization, and presence of lesions including mesial temporal sclerosis, cortical dysplasia, and others. Baseline seizure frequency, defined as typical number of seizures per month over the past year, was collected either at the time of baseline neuropsychological testing, or at a later date (from clinical epilepsy notes if the patient was undergoing an epilepsy surgery workup, prior to surgery). Patients were categorized as seizure-free if they had been seizure-free for at least one year at the time of seizure frequency data collection.

2.3. Anxiety and depression measurement: the SCL-90R

Psychiatric status was measured using the Symptom Checklist-90R (SCL-90R), a 90-question, well-validated, and reliable psychiatric symptom self-report instrument, which has separate subscales for anxiety and depression (with 10 and 13 items, respectively) [25]. Items on the SCL-90R are rated on a 5-point scale by how much distress the symptom has caused in the prior 7 days; the 5 response options include: not at all, a little bit, moderately, quite a bit, and extremely [25]. Examples of items from the anxiety subscale include "feeling fearful" and "nervousness and shakiness inside;" example depression subscale items include "feelings of worthlessness" and "crying easily" [25]. The anxiety and depression subscales have been demonstrated to have good internal consistency, test–retest reliability, factorial invariance, and convergent-discriminant validity; they also perform well as outcome instruments in medication and psychotherapy treatment trials for anxiety and depression [25]. Anxiety and depression T-scores from the respective SCL-90R subscales were calculated using nonpatient norms (outpatients not under care for a psychiatric condition) [25]. High anxiety was defined as anxiety subscale T-score of 60 or higher (corresponding to the 84th percentile of anxiety symptoms in norms) [25]. Lower anxiety was defined as anxiety scale T-score < 60. For the SCL-90R depression subscale, a T-score of 60 similarly corresponds to the 84th percentile of depression symptoms in the normative group; high depression was defined as depression T-score of 60 or more. The range of all possible SCL-90R T-scores for scales and norms used in this study is 34–81 [25].

2.4. Intelligence and quality of life

Intelligence Quotient (IQ) values were Full Scale IQ measured by the Wechsler scales (Wechsler Adult Intelligence Scale III or IV, "WAIS"), unless alternative measures were administered due to conditions rendering the WAIS invalid. In these situations, Full Scale IQ estimates from the Wechsler Test of Adult Reading or Test of Nonverbal Intelligence were used [26–29]. Epilepsy-related quality of life was measured using the Quality of Life in Epilepsy-89 (QOLIE-89) [30].

2.5. Standard protocol approvals, registrations, and patient consents

Data were collected systematically and entered into the Columbia University Neuropsychology Registry by June 10, 2013. Data collection methods were approved by the Columbia University Medical Center Institutional Review Board, with waiver of informed consent. The present analysis, performed in 2016–2017 using de-identified data from the registry, was also approved by the Wake Forest School of Medicine Institutional Review Board.

2.6. Statistical analysis

Analyses were conducted using Stata13.1 (StataCorp). We examined the distribution of data prior to further analyses. Chi-square analysis was used to compare categorical variables between the high anxiety and lower anxiety groups. *t*-Tests for two independent samples were used to compare means of continuous variables between the anxiety groups. A two-tailed p value of <0.05 was considered statistically significant; this was not adjusted for multiple comparisons, as the analyses were done for hypothesis-generation.

2.6.1. Multivariable modeling in the entire study population

Logistic regression modeling was then conducted with anxiety group as the dependent variable, initially as simple logistic regression with each demographic- and epilepsy-related variable as the covariable; these variables were selected for consideration based on the chi-square and *t*-test results described above. This was followed by multiple logistic regression modeling, first with Model A, including