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Anxiety is common and independently associated with clinical features of epilepsy

Heidi M. Munger Clary, MD, MPH^a, Beverly M. Snively, PhD^b, and Marla J. Hamberger, PhD^c

^aDepartment of Neurology, Wake Forest School of Medicine, Winston-Salem, North Carolina, U.S.A

^bDepartment of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina, U.S.A

^cDepartment of Neurology, Columbia University Medical Center, New York, New York, U.S.A

Abstract

Objective—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% 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-Caucasian 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

Corresponding Author: Heidi M. Munger Clary, Wake Forest School of Medicine, 1 Medical Center Blvd., Winston-Salem, NC 27157, Phone 336-716-7110, Fax: 336-716-9489, hmungerc@wakehealth.edu.

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temporal sclerosis. These results strongly support the value of screening specifically for anxiety in the epilepsy clinic, to direct patients to appropriate treatment.

Keywords

focal epilepsy; psychiatric comorbidity; depression; mesial temporal sclerosis; anxiety; epilepsy

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 under-recognized 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 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, 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 epilepsy patients 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: Caucasian, 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 1–2. Epilepsy type was classified as generalized, focal, or unknown based primarily on ictal video electroencephalography (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 less than 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 less than 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 only the pre-specified standard predictors and potential confounders (age, sex, race/ethnicity, and education level; selected due to association with

anxiety in other epilepsy studies, the general population, or other medical conditions) [13, 14, 31–33]. Finally, we conducted forward stepwise multiple logistic regression modeling, adjusted for these pre-specified demographics, with independent variables added initially if $p < 0.1$ in the simple logistic regression. In multivariable modeling, $p < 0.05$ was considered significant and variables with $p < 0.1$ were kept in the models; Model B was the final model.

2.6.2 Multivariable modeling in the focal epilepsy subpopulation—To assess whether factors related to seizure localization and lateralization were independently associated with anxiety in the focal epilepsy subpopulation (N=408), a second, similar simple and multivariable logistic regression procedure was conducted, with Model A and Model B generated for the focal epilepsy subpopulation. This modeling incorporated significant focal epilepsy-related variables from a parallel simple regression analysis, including focal epilepsy-specific variables such as focus lateralization and lesions.

2.6.3 Missing data—In each multivariable model, all patients with complete data were included; a single patient with both focal and generalized epilepsy was excluded from analysis related to epilepsy type. To assess for potential impact of missing data on the final results, characteristics of those included in final multivariable models were compared to those excluded due to missingness, using chi square and two-sample t-test.

3. Results

3.1 Characteristics of the study population

Tables 1–3 show characteristics of the high anxiety and lower anxiety groups separately; however, the entire study population (N=540) was characterized by mean age of 39.4 years (standard deviation [SD] 14.0), 55.1% women, 29.7% non-Caucasians or Latino/Hispanic individuals, 25.5% with non-English native language, and mean total education of 14.4 years (SD 3.04). Epilepsy type in the total study population was 10.9% generalized epilepsy, 75.6% focal epilepsy, 13.3% unknown epilepsy type, and one individual (0.2%) with both generalized and focal epilepsy. Among those with focal epilepsy who were subclassifiable (N=387), 87% had temporal lobe epilepsy. Besides mesial temporal sclerosis, the most common epilepsy-associated lesions were tumors (N=27), vascular malformations (N=26), and cortical dysplasia or heterotopia (N=22; total N for lesion status 393). Seizure frequency data was available for 205 individuals; mean seizure frequency was 11.4 per month overall (SD=28.2), including 21.5% with seizure freedom for at least one year (N=44). Demographics and epilepsy characteristics of those with available seizure frequency data were similar to the overall study population.

3.2 Prevalence of anxiety symptoms

The prevalence of high anxiety scores in the entire study population was 46.3%, with 6.1% exhibiting maximal or near-maximal T-scores of 81 or 80.

3.3 Factors associated with anxiety symptoms in the entire study population: bivariable analyses

3.3.1 Demographic and clinical factors—The following factors were associated with high anxiety in the entire population based on chi square analyses as shown in Tables 1–2: lower education ($p=0.041$, $\chi^2=10$), non-Caucasian race/ethnicity ($p=0.009$, $\chi^2=6.9$), Spanish native language ($p=0.005$, $\chi^2=10.4$), unknown or focal epilepsy ($p=0.01$, $\chi^2=9.3$), and history of head trauma ($p=0.003$, $\chi^2=9.0$).

3.3.2 Antiseizure drugs—High anxiety individuals were taking more antiseizure drugs than individuals with lower anxiety (mean 1.89 (SD 0.79) vs. 1.69 (SD 0.77) respectively, $p=0.03$; $N=293$, two sample t-test). The most commonly prescribed antiseizure drugs were lamotrigine and levetiracetam (42.3% and 36.2% respectively; $N=124$ and 106), followed by zonisamide, carbamazepine, and oxcarbazepine (16.0%, 15.7%, and 11.6% respectively; $N=47$, 46, and 34). There was no association between any individual antiseizure drug and anxiety group (chi square test done for each drug, results not shown).

3.3.3 Depression—In the entire study population, 297 (55%) had SCL-90R depression T-scores ≥ 60 . High anxiety was associated with high depression ($p<0.001$, chi-square). Mean depression T-score among those in the high anxiety group was 67.0 (SD 9.1), compared to 54.3 (SD 9.8) for the lower anxiety group ($p<0.001$, two sample t-test). More than a third of subjects reported both high anxiety and high depression (37.8%, $N=204$). Although high anxiety and high depression were associated, 139 individuals (26% of total study population) were classified as having high depression or high anxiety, but not both (93 with high depressive symptoms and 46 with high anxiety symptoms). Thus, 18.4% of those with high anxiety did not report high depression (46 of 250).

3.3.4 Psychotropic medications—With data available for 442 individuals, 354 (80.1%) were not prescribed any type of psychotropic medication at baseline. Of the 20% ($N=88$) who were, 15.8% ($N=70$) were taking a potential anxiolytic (selective serotonin reuptake inhibitor or serotonin norepinephrine inhibitor [SSRI/SNRI], buspirone, or alprazolam). Among the high anxiety group, 26% (49 of 185) were prescribed these anxiolytic medications. In the overall study population, anxiety levels were significantly higher among those prescribed a potential therapy for anxiety compared to those not taking one of these medications (mean SCL-90R anxiety T-score 64.3 (SD10.8) vs. 56.2(SD 56.2), $p=0.001$, two sample t-test). Among those with lower anxiety scores, 8.5% (21 of 247) were prescribed a potential anxiolytic.

3.3.5 Quality of life—High anxiety was associated with poor overall quality of life (high anxiety mean QOLIE-89: 40.8 (SD 10.5), lower anxiety mean QOLIE: 51.9 (SD 10.2); higher scores indicate better quality of life ($p<0.001$, two sample t-test), and with poor quality of life on all subscales of the QOLIE-89 (all $p \leq 0.001$, two sample t-test).

3.4 Multiple logistic regression: entire study population

Simple logistic regression demonstrated bivariable associations of high anxiety with lower education, non-Caucasian race/ethnicity, native Spanish language, focal or unknown

epilepsy, history of head trauma, depression, and more prescribed antiseizure drugs, consistent with the chi square analyses presented in Tables 1–2. The unadjusted odds of high anxiety for native Spanish language, history of head trauma, and number of prescribed antiseizure drugs were 2.15, 1.99 and 1.25, respectively (CI 1.34–3.44, 1.27–3.14, 1.00–1.56; $p=0.001$, 0.003, 0.048, respectively). Table 4 shows the other unadjusted results and the results of multivariable model A (includes only the pre-specified standard predictors/potential confounders: age, sex, race/ethnicity, and education). In the final multivariable model (Model B), only depression and epilepsy type were independently associated with anxiety status, adjusted for the pre-specified variables from Model A (Table 4). The adjusted odds ratio (OR) of high anxiety vs. lower anxiety was 2.12 for 5-point increments in the SCL-90R depression scale (95% confidence interval [CI] 1.84–2.45, Table 4). Those with focal or unknown epilepsy had nearly three-fold higher adjusted odds of high anxiety symptoms (vs. lower anxiety) compared to those with generalized epilepsy (OR 2.89, CI 1.33–6.29, Table 4). Although seizure free status was included in the early multivariable modeling based on simple logistic regression results (OR 1.82 for lack of seizure freedom, CI 0.90–3.69, $p=0.096$; $N=205$), high anxiety was not independently associated with lack of seizure freedom, and seizure freedom did not meet criteria for inclusion in the final multivariable model (Model B).

3.5 Focal epilepsy subpopulation

3.5.1 Bivariable analyses in focal epilepsy—Among the focal epilepsy subpopulation ($N=408$), mesial temporal sclerosis and left (compared to right) hemisphere lateralization were both associated with high anxiety ($p=0.023$, $\chi^2=5.2$ and $p=0.049$, $\chi^2=3.9$, respectively, Table 3). Results of chi square and two sample t-tests for the demographic and clinical factors shown in Tables 1–2 were similar to the overall population results in Tables 1–2. Among the 336 individuals with temporal lobe epilepsy (TLE), the associations were also similar. There was no association between anxiety status and more specific localization within the temporal lobe (mesial/lateral or anterior/posterior), though data this detailed was available in only approximately one-third of those with TLE.

3.5.2 Multiple logistic regression: focal epilepsy—Multiple logistic regression among those with focal epilepsy demonstrated similar findings to the overall study population in Model A (for race/ethnicity, sex, age, and education), and a nearly identical, independent association of depression with high anxiety in the final multivariable model (OR 2.08, CI=1.73–2.51, Model B, Table 5). Mesial temporal sclerosis was independently associated with high anxiety (OR 2.12, CI=1.11–4.04, Table 5). Presence of left or bilateral independent foci did not demonstrate a statistically significant association with high anxiety symptoms in multivariable modeling, but prespecified criteria for inclusion in the final Model B were met due to $p<0.1$ (OR 1.86 compared to right hemisphere focus, CI=0.96–3.60, Table 5).

3.6 Missing values

Of variables included in the final multiple logistic regression models (Model B, Tables 4–5), only race/ethnicity and mesial temporal sclerosis had more than minimal missing data (13%, 468/540 and 23%, 316/408 respectively). We ran additional multiple logistic regression

models, dropping the race/ethnicity and mesial temporal sclerosis variables: the results for variables remaining in the models were unchanged from the results in Tables 4–5. We also assessed the characteristics of those included in final multivariable models and compared those with complete data to those with missing data (eTables 1–2). Subjects with unknown epilepsy type were more likely to have missing data (eTable 1), and among those with focal epilepsy, lower education was associated with missing data (eTable 2). Missing data was unlikely if mesial temporal sclerosis was present (eTable 2). Other characteristics were similar among those with complete vs. missing data.

4. Discussion

This large, exploratory study of 540 adults assessed the association of high anxiety symptoms with a detailed set of epilepsy and demographic characteristics, and it is the first to our knowledge demonstrating an independent association of mesial temporal sclerosis with anxiety symptoms in focal epilepsy. As demonstrated in prior studies, we found an independent association of depression with high anxiety scores [13, 16, 17]. We also demonstrated an independent association of high anxiety symptoms with focal or unknown epilepsy type (vs. generalized); this is consistent with multivariable analyses by Kimiskidis et al. who found symptomatic focal epilepsy to be independently associated with anxiety measured by the State-Trait Anxiety Inventory, and smaller studies comparing generalized and focal epilepsies [14, 21, 22]. Those with focal or unknown epilepsy in our study had nearly three-fold odds of high anxiety compared to those with generalized epilepsy, adjusted for potential demographic confounders. Although this association could be confounded by other factors not included in the models, such as anxiogenic properties of some antiseizure drugs, the lack of association of high anxiety scores with individual antiseizure medications in our bivariable analyses renders this unlikely. Among those with focal epilepsy, presence of mesial temporal sclerosis was independently associated with high anxiety symptoms, consistent with bivariable analyses reported in smaller studies and with findings reported previously for depression [21, 22, 34]. Considering the role of the amygdala and other components of the limbic system in anxiety symptoms, the predominance of temporal lobe epilepsy in our focal epilepsy subpopulation (87% with focal epilepsy had temporal lobe epilepsy, see Table 3), and the fact that mesial temporal sclerosis is a lesion directly within the limbic system, our findings may reflect a common pathologic localization for anxiety and the seizure focus and potentially provide clues to a common underlying pathophysiology. Regardless of theoretical considerations on why an association may exist, our results suggest that patients with focal or unknown epilepsy and patients with mesial temporal sclerosis may be at increased risk for anxiety.

Although history of head trauma, lower education (less than college degree), non-Caucasian race/ethnicity, Spanish native language, and left or bilateral independent seizure lateralization were associated with high anxiety in bivariable analyses, multivariable analysis demonstrated these associations were not independent. The lack of independent association of seizure lateralization with anxiety symptoms in our large sample likely suggests that if an association exists, its magnitude is small, which is not inconsistent with the overall contradictory findings in the literature assessing focus lateralization and anxiety [18, 22, 23]. Strengths of our study include the assessment of epilepsy risk factors including head trauma,

and the diverse study population which allowed assessment of native language. Future study of sociodemographic factors including education, race/ethnicity, and native language is important to characterize potential health disparities in epilepsy linked to these factors and explore whether these contribute to anxiety symptoms. History of head trauma could potentially be an indicator of adverse social factors or brain pathophysiology that may contribute to anxiety.

We found an alarmingly high prevalence of significant anxiety symptoms; nearly half (46%; 250/540) of patients' anxiety scores were at least as high as the most anxious 16% of norms. Despite this high prevalence of significant anxiety symptoms, only one quarter of patients with high anxiety scores were taking a psychotropic drug with anxiolytic properties (specifically SSRI/SNRI, buspirone, or alprazolam), and these individuals still had high anxiety scores. This finding may reflect under-recognition and under-treatment of anxiety symptoms. Although some in the study population may have been receiving other treatments for anxiety that were not recorded (such as cognitive behavioral therapy or other counseling/psychotherapy services), those reporting high anxiety symptoms did not have adequate symptom relief at the time of assessment and, thus, were likely under-treated. Based on clinical protocols, it is likely that epileptologists were notified of symptoms identified due to the SCL-90R administration, but data on how the symptoms were managed after the assessment were not available in the registry study.

Considering that 8.5% of those with lower anxiety scores were taking a potential anxiolytic, our results may underestimate the true prevalence of high anxiety symptoms; additionally, an unknown number of individuals may have been receiving successful non-pharmacologic treatment. Considering the significant consequences of anxiety in epilepsy demonstrated by recent studies, including increased mortality due to suicide, poor quality of life, increased medical costs, increased cognitive complaints and antiseizure drug side effects, recognizing these symptoms in clinical care is imperative [2, 5, 35–39]. Fortunately, the current AAN quality measurement set introduced a measure to screen for psychiatric or behavioral health disorders [11]. However, it provides no guidance on which symptom types to screen, and most of literature to date on psychiatric comorbidity in epilepsy focuses on depression rather than anxiety. Furthermore, a recent survey of epileptologists indicated they are less likely to screen for anxiety than depression, and a recent meta-analysis suggested that anxiety is under-recognized when clinician assessment is unstructured [10, 12]. Although depression and anxiety were associated, there was not a full overlap of these symptoms; that is, nearly 20% of those with high anxiety did not report high depression in our study. Therefore, these patients are likely to be missed by screening protocols focusing on depression alone.

Although the prevalence of high anxiety scores may have been reduced by ongoing anxiolytic treatment among some individuals, the prevalence of high anxiety symptoms we report is indeed more elevated than in most prior studies [10, 13, 15–17, 39]. The prevalence of high anxiety scores in our sample may be higher than would be seen in the overall epilepsy population, given the tertiary care setting of our study, and that these patients had undergone neuropsychological evaluation (thus they likely had more severe epilepsy and potentially higher rates of anxiety). However, recent studies showed no difference in prevalence of anxiety symptoms based on epilepsy severity [10, 40]. Our analysis also failed

to find an independent association of anxiety with seizure frequency or number of antiseizure drugs, though a limitation of our analysis is the smaller sample size available for these variables (N=205 and 440 for these variables, Table2). This difference may be due to bias in the patient population studied (as noted above) or other factors, including use of the SCL-90R instrument, which might better detect subclinical or subtle symptoms.

4.1 Limitations

A weakness of this study is use of a self-report instrument without specific validation using a structured psychiatric interview. We were unable to conduct such interviews because of the retrospective nature of the analysis, with some data dating back more than a decade. The SCL-90R has not been specifically validated in epilepsy, although there is prior research using this measure in epilepsy [41]. This instrument was used for our study because it was administered uniformly to epilepsy patients who received neuropsychological testing throughout the study period to assess overall psychiatric distress; this practice and portions of our dataset predate the existence of instruments now commonly used in epilepsy, such as the Generalized Anxiety Disorder-7 (GAD-7) and Neurological Disorders Depression Inventory-Epilepsy (NDDI-E) [42, 43]. An overall limitation of the SCL-90R for use in epilepsy is that some items overlap with symptoms of epilepsy, and it is possible that items such as “feeling fearful” in the anxiety subscale may reflect focal epilepsy symptoms rather than anxiety, and thus may contribute to the demonstrated association of anxiety symptoms with epilepsy type. Future work is needed to develop an anxiety measure specifically for individuals with epilepsy, similar to the NDDI-E for depression.

Other limitations include missing values for some variables, which may have reduced our power to identify other associations with anxiety symptoms and may have created bias, though it is reassuring that our final multivariable modeling results did not change when we dropped variables with more than minimal missingness. It is not surprising that those with unknown epilepsy, focal epilepsy without mesial temporal sclerosis and focal epilepsy with lower education were more likely to have missing data (eTables 1-2), as these individuals often had less extensive prior workup, and thus epilepsy was less fully characterized at baseline data collection. Also, the generalized epilepsy and extratemporal focal epilepsy subgroups were relatively small (<60), which may have limited ability to fully characterize these groups. This study does not include controls with a distinct neurological or medical diagnosis, thus it is uncertain whether high anxiety scores are more common in epilepsy than other conditions based on our results. Factors recently shown to be associated with anxiety in epilepsy such as sleep quality and physical activity, as well as social factors including employment were not available in the registry for our analyses [7, 13, 19, 20]. Finally, the cross-sectional study design precludes any consideration of the factors assessed as true risk factors for anxiety in epilepsy. Future prospective, longitudinal investigation is needed to identify factors associated with subsequent development of anxiety symptoms in epilepsy and to confirm the findings of our study.

5. Conclusions

Overall, our results reveal a very high prevalence of significant anxiety symptoms among a large group of adults with epilepsy, particularly among those with focal or unknown epilepsy, mesial temporal sclerosis, and high depressive symptoms. Because many patients with high anxiety symptoms did not report high levels of depressive symptoms, routine screening for both anxiety and depression is important in the epilepsy clinic, particularly among those who do not have generalized epilepsy. While there is increasing recognition that psychiatric symptoms, including anxiety, are common and have a significant impact on patients with epilepsy, future work should address how best to screen and manage these symptoms in the clinic.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- High anxiety symptoms were seen in 46% of this adult tertiary care epilepsy sample.
- Focal or unknown epilepsy type was independently associated with high anxiety.
- Mesial temporal sclerosis was independently associated with high anxiety symptoms.
- Depression was independently associated with high anxiety symptoms.
- Nearly 20% of those with high anxiety scores did not have high depression symptoms.

Table 1

Demographic characteristics by anxiety status (N=540)

	<i>Mean SCL-90R anxiety T-score(SD)</i>	Lower anxiety^a N=290	High anxiety^b N=250	<i>p</i>^c (χ^2)
Overall	57.8 (12.1)	53.7%	46.3%	
Age				0.16 ($\chi^2=5.2$)
18-29 years (N=163)	55.9 (13.0)	58.9%	41.1%	
30-39 years (N=121)	56.9 (11.7)	57.0%	43.0%	
40-49 years (N=116)	60.6 (11.7)	46.6%	53.5%	
50+ years (N=140)	58.7 (11.2)	50.7%	49.3%	
Education N=537				0.041 ($\chi^2=10$)
Less than high school (N=64)	56.8 (12.9)	53.1%	46.9%	
Completed high school (N=121)	59.4 (11.3)	51.2%	48.8%	
Some college (N=101)	59.3 (12.4)	41.6%	58.4%	
College degree (N=138)	56.7 (11.9)	59.4%	40.6%	
Beyond college degree (N=113)	56.8 (12.2)	60.2%	39.8%	0.090 ($\chi^2=2.9$)
Sex N=539				
F (N=297)	57.2 (11.5)	56.9%	43.1%	
M (N=242)	58.6 (12.8)	49.6%	50.4%	0.059 ($\chi^2=7.4$)
Race/ethnicity N=468				
Caucasian (N=331)	57.3 (11.6)	57.1%	42.9%	
Black (N=27)	59.6 (12.0)	48.2%	51.9%	
Asian (N=23)	56.1 (13.8)	47.8%	52.2%	
Hispanic/Latino (N=87)	60.7 (12.7)	41.4%	58.6%	0.009^d ($\chi^2=6.9$)
<i>All non-Caucasian (N=137)</i>	<i>59.7 (12.8)</i>	<i>43.8%</i>	<i>56.2%</i>	
Native language N=538				0.005 ($\chi^2=10.4$)
English only (N=401)	57.4 (11.9)	56.9%	43.1%	
Spanish/Spanish bilingual(N=87)	60.8 (12.8)	37.9%	62.1%	
Other(with English bilingual) (N=50)	56.4 (11.8)	56.0%	44.0%	

^a SCL-90R T-score less than 60,^b SCL-90R T-score 60 or greater,^c chi-square test,^d non-Caucasian vs. Caucasian

Table 2

Epilepsy-related and cognitive characteristics by anxiety status (N=540)

	<i>Mean SCL-90R anxiety T-score(SD)</i>	Lower anxiety^a N=290	High anxiety^b N=250	<i>p^c (χ² or t)</i>
Overall	57.8 (12.1)	53.7%	46.3%	
IQ: mean full scale(SD) N=465		97.6 (16.1)	95.4 (16.6)	0.14 (t=1.5)
Age of epilepsy onset N=532				0.48 (X ² =2.5)
Prior to 10years (N=127)	57.0 (11.7)	57.5%	42.5%	
10-19 years (N=168)	57.1 (12.5)	53.0%	47.0%	
20-29 years (N= 96)	57.6 (12.3)	58.3%	41.7%	
30+ years (N=141)	59.0 (11.5)	49.7%	50.4%	0.65 (X ² =0.85)
Handedness N=539				
Right (N=467)	57.9 (12.2)	54.4%	45.6%	
Left (N=56)	57.6 (10.9)	48.2%	51.8%	
Ambidextrous or switched late (N=16)	57.9 (13.9)	50.0%	50.0%	0.01 (X ² =9.3)
Epilepsy Type N=540				
Generalized (N=59)	55.1 (12.1)	71.2%	28.8%	
Focal (N=408)	58.0 (12.1)	52.5%	47.6%	
Unknown (N=72)	59.4 (11.5)	45.8%	54.2%	0.92 (t=0.11)
Seizure frequency: mean per month(SD) N=205		11.5 (31.8)	11.1 (22.5)	
Seizure free N=205				
Yes (N=44)	56.5 (12.2)	68.2%	31.8%	
No (N=161)	57.4 (12.0)	54.0%	46.0%	0.10 (X ² =4.5)
Number of antiseizure drugs N=440				
0-1 (N=190)	57.2 (12.6)	57.5%	40.5%	
2 (N=187)	57.0 (11.8)	53.5%	46.5%	
3 or more (N=63)	60.7 (12.5)	44.4%	55.6%	0.98 (X ² =0.98)
Family history of epilepsy N=395				
Yes (N=24)	59.1 (14.1)	54.2%	45.8%	
No (N=371)	57.8 (12.0)	53.9%	46.1%	
History of febrile seizures N=395				0.40 (X ² =0.71)
Yes (N=34)	59.4 (11.4)	47.1%	53.0%	
No (N=361)	57.7 (12.2)	54.6%	45.4%	
History of head trauma N=395				0.003 (X ² =9.0)
Yes (N=104)	60.6 (13.1)	41.4%	58.7%	
No (N=291)	56.9 (11.6)	58.4%	41.6%	

^aSCL-90R T-score less than 60,^bSCL-90R T-score 60 or greater,^ctwo-sample t-test for continuous variables, chi-square for categorical variables

Table 3

Focal epilepsy characteristics by anxiety status (N=408)

	<i>Mean SCL-90R anxiety T-score</i>	Lower anxiety^a N=214	High anxiety^b N=194	<i>p^c (χ^2)</i>
Overall	58.0 (12.1)	52.5%	47.6%	
Lateralization N=388				0.13 ^f ($\chi^2=4.0$)
Right (N=121)	56.9 (12.5)	60.3%	39.7%	
Left (N=196)	58.3 (12.2)	49.0%	51.0%	
Bilateral (N=71)	57.9 (11.4)	50.7%	49.3%	
Localization N=387				g 0.11 ($\chi^2=2.6$)
Temporal (N=336)	58.3 (11.9)	50.6%	49.4%	
Extratemporal (N=51)	56.5 (14.1)	62.8%	37.3%	
Frontal (N=35)	56.7 (14.2)	62.9%	37.1%	
other (N=16)	56.0 (14.4)	62.9%	37.5%	
Lesion on MRI N=339				0.18 ($\chi^2=3.4$)
yes (non-MTS ^d e (N=108)	57.3 (13.0)	57.4%	42.6%	
MTS only (N=82)	57.8 (12.3)	43.9%	56.1%	
No (N=149)	58.4 (12.1)	53.0%	47.0%	
Cortical dysplasia N=340				0.27 ($\chi^2=1.2$)
Yes (N=26)	55.5 (13.6)	61.5%	38.5%	
No (N=314)	58.3 (12.3)	50.3%	49.7%	
Mesial temporal sclerosis? N=316				0.02 ($\chi^2=5.2$)
Yes (N=96)	59.0 (12.0)	40.6%	59.4%	
No (N=220)	57.8 (12.2)	54.5%	45.5%	

^aSCL-90R T-score less than 60,^bSCL-90R T-score 60 or greater,^cchi-square test;^dmesial temporal sclerosis;^ethis group includes patients with dual pathology;^f**p 0.05** ($\chi^2=3.9$)for comparison of right and left only;^gtemporal vs extratemporal

Table 4

Multiple logistic regression modeling results: Odds of high anxiety in entire study population

Variable	Unadjusted results: Simple logistic regression			Multivariable MODEL A: Prespecified demographics ^a			Multivariable MODEL B: Final multiple logistic regression ^{b,c}		
	Odds Ratio ^d	95% Confidence Interval	p	Odds Ratio	95% Confidence Interval	p	Adjusted Odds Ratio ^e	95% Confidence Interval	p
Age (per 10 years)	1.07	0.96-1.22	0.22	1.10	0.96-1.26	0.16	1.01	0.86-1.20	0.90
Gender (male)	1.34	0.95-1.89	0.09	1.50	1.03-2.18	0.03	1.53	0.96-2.45	0.08
Race (non-Caucasian)	1.71	1.14-2.55	0.009	1.61	1.06-2.45	0.03	1.46	0.87-2.47	0.15
Education (less than a college degree)	1.59	1.13-2.24	0.008	1.52	1.04-2.23	0.03	1.26	0.79-2.02	0.34
Depression (per 5 point increase in SCL-90R depression subscale)	2.02	1.78-2.29	<0.001				2.12	1.83-2.45	<0.001
Focal/unknown epilepsy (vs. generalized)	2.33	1.29-4.21	0.005				2.89	1.33-6.29	0.007

^aN=463, overall p=0.002, pseudo R²(goodness of fit measure)=0.03;^bN=463, overall p<0.001, pseudo R²(goodness of fit measure)=0.31;^c other variables tested but not included in final multivariable model B due to lack of statistical significance: native Spanish language, history of head trauma, number of prescribed antiepileptic drugs.^d odds of SCL-90R anxiety subscale T score >60;^e adjusted odds of SCL-90R anxiety subscale T score >60

Table 5

Multiple logistic regression modeling results: Odds of high anxiety in focal epilepsy subpopulation

Variable	Unadjusted results: Simple logistic regression			Multivariable MODEL A: Prespecified demographics ^a			Multivariable MODEL B: Final multiple logistic regression ^b		
	Odds Ratio ^c	95% Confidence Interval	p	Odds Ratio	95% Confidence Interval	p	Adjusted Odds Ratio ^d	95% Confidence Interval	p
Age (per 10 years)	1.06	0.92-1.22	0.43	1.10	0.94-1.28	0.26	1.03	0.82-1.23	0.82
Gender (male)	1.24	0.84-1.84	0.28	1.26	0.82-1.91	0.29	1.16	0.63-2.12	0.64
Race (non- Caucasian)	1.62	1.04-2.53	0.03	1.54	0.97-2.44	0.07	1.21	0.63-2.33	0.56
Education (less than a college degree)	1.67	1.13-2.48	0.01	1.50	0.98-2.30	0.06	1.38	0.76-2.53	0.29
Depression (per 5 point increase in SCL-90R depression subscale)	1.95	1.70-2.24	<0.001				2.08	1.73-2.51	<0.001
Mesial temporal sclerosis	1.75	1.08-2.85	0.02				2.12	1.11-4.04	0.02
Left hemisphere or bilateral focus (vs. right hemisphere focus)	1.56	1.01-2.41	0.05				1.86	0.96-3.60	0.07

^aN=360, overall p=0.04, pseudo R²(goodness of fit measure)=0.02;^bN=276, overall p<0.001, pseudo R²(goodness of fit measure)=0.31;^c odds of SCL-90R anxiety subscale T score >60;^d adjusted odds of SCL-90R anxiety subscale T score >60