THE COMORBID ANXIETY AND DEPRESSION DISORDER IN PATIENTS WITH EPILEPSY: DIAGNOSIS, PREVENTION AND TREATMENT

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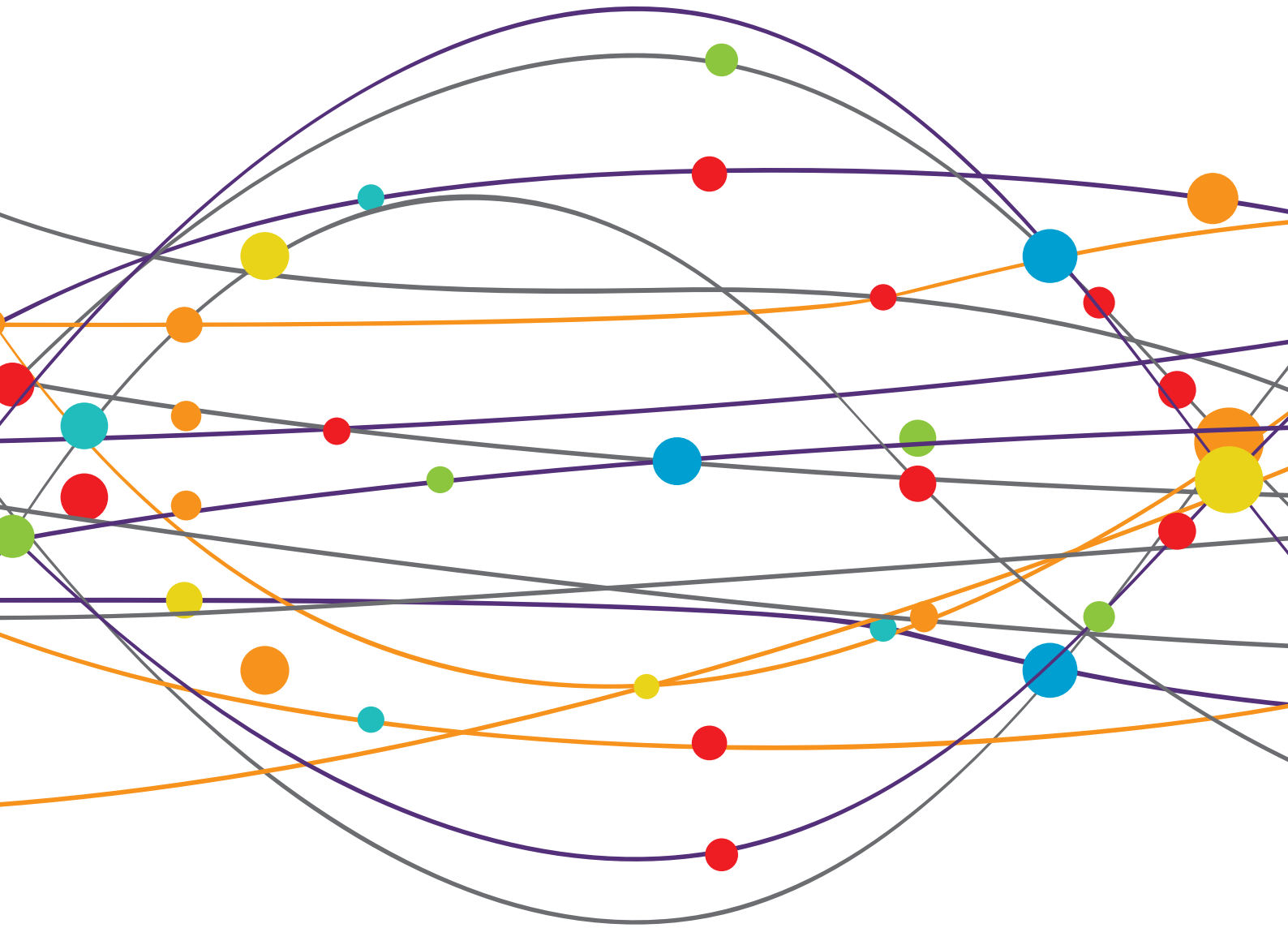

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THE COMORBID ANXIETY AND DEPRESSION DISORDER IN PATIENTS WITH EPILEPSY: DIAGNOSIS, PREVENTION AND TREATMENT

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Editorial: The comorbid anxiety and depression disorder in patients with epilepsy: Diagnosis, prevention and treatment

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epilepsy, anxiety, depression, diagnosis, treatment

Editorial on the Research Topic
The comorbid anxiety and depression disorder in patients with epilepsy: Diagnosis, prevention and treatment

Epilepsy is a common neurological disease, and patients with epilepsy are a huge group. Their quality of life is not only affected by various comorbidities that follow epilepsy, but also the risk of comorbidities such as anxiety and depression is several times higher than that of people without epilepsy, which makes the comorbidity of epilepsy more and more difficult to ignore. In order to further expand the understanding of epilepsy comorbidities and gain a deeper understanding of their pathogenesis, diagnosis, prevention, and treatment, we have collected 14 pieces of literature related to epilepsy comorbidities, hoping to provide more hints for future research in this direction.

People with epilepsy are more likely to feel anxious than the general population or people with other chronic diseases. Rocamora et al. analyzed 493 patients in their hospital who underwent long-term video EEG monitoring and found that anxiety and depression were more prevalent in female patients, Hospital Anxiety and Depression Scale for anxiety (HADS-A), and Beck Depression Inventory (BDI) > 13. The study revealed the factors affecting patients' quality of life in the epilepsy monitoring unit and pointed out that specific treatment methods should be adopted according to the patient's condition in clinical work.

Similarly, Forthoffer et al. argue that newly diagnosed epilepsy patients must be prospectively assessed and screened for anxiety and depression to determine whether anxiety and depression will have an impact on the future course of care.

Rauh et al. searched a series of epilepsy anxiety assessment tools through PubMed to understand how the previous literature assessed the anxiety of epilepsy patients and analyzed what aspects these self-assessment questionnaires covered. Overall, they found

that various questionnaires were used for anxiety assessment of different patients, but there is still a lack of validated assessment tools that can broadly cover epilepsy-related anxiety phenomenology in patients with epilepsy.

However, how to avoid anxiety in patients requires the identification of risk factors for anxiety in patients with epilepsy. Zhong et al. followed up 157 newly diagnosed adult epilepsy patients for 12 months, two important predictors of anxiety disorders were screened from a variety of demographic characteristics such as seizure type, income, and educational background, namely the depression level at baseline and the number of anti-seizure medication (ASM) during follow-up. To a certain extent, it provides a theoretical basis for preventing psychological disorders in patients with epilepsy.

Depressive disorders are less common than anxiety, but not uncommon in patients with temporal lobe epilepsy (TLE). Studies have shown that epilepsy and depression have similar networks in neuropsychiatric disorders, which provides a theoretical basis for the high incidence of epilepsy comorbid depression. Therefore, Sun et al. used EEG microstate analysis for the first time to present the temporal fluctuations of the EEG topography in comorbid depression in patients with TLE and found that TLE patients with the depressive disorder had a shorter microstate time course and more high incidence per second, and compared with the normal group, there was no difference in the coverage of microstate A-D between the two groups, which strongly confirmed alterations in a specific subset of the subsecond functional states of the brain. Chang et al. Using resting-state functional magnetic resonance imaging to observe brain functional connectivity (FC) and degree centrality (DC) in TLE with ictal panic (IP). Compared with TLE without IP and healthy people, TLE patients with IP had significantly higher DC values and increased FC. This opens new doors for further exploration of the neuroimaging mechanisms of IP in TLE patients.

In addition, not only does epilepsy comorbidity bring psychological barriers to patients, but uncontrollable seizures in public places may expose patients to social discrimination. Wu et al. investigated epilepsy stigma attitudes in 310 Chinese native-speakers by using the Simplified Chinese Mandarin version of the Stigma Scale of Epilepsy and subsequently verified the scale's accuracy. To some extent, the degree of disease stigma is quantified, and it provides direction for the development of effective public interventions in the future. Seizures can also be psychologically traumatic for the patient. Using a scale to assess traumatic experienced seizures in patients with pharmacoresistant focal epilepsy, Mariotti et al. found that seizures are the source of the development of postepileptic seizure-posttraumatic stress disorder (PS-PTSD) and noted that early identification and treatment could improve patients' quality of life.

Children with epilepsy are a particularly distinct group of patients with epilepsy. The disease itself will harm children's psychology and adversely affect the quality of life of their families. Operto et al. surveyed 103 children with different forms of epilepsy and 93 in a control group and found that compared with their peers, children with epilepsy were more likely to have emotional and behavioral problems, and the stress of parents in the epilepsy group was significantly higher than that in the control group. Therefore, it is essential to identify emotional and behavioral problems in children with epilepsy early and support their parents accordingly. This is similar to the study by Wei et al. who pointed out that the incidence of depression among primary caregivers of children with epilepsy was close to 70%, and the degree of depression in caregivers was positively correlated with the severity of epilepsy in children; the study by Zhang et al. found that the caregivers' anxiety status, sleep quality, family role dimension, family general function dimension, and the number of co-caregivers were predictors of depression status in caregivers. João et al. assessed anxiety and depression in adults with epilepsy and their caregivers, and although epilepsy patients were more likely than their caregivers to experience depression and suicidal ideation, the proportion and intensity of clinical anxiety symptoms were similar. All three studies point to concern not only for the psychological problems of people with epilepsy but also for their caregivers.

Due to the coronavirus disease 2019 (COVID-19) pandemic, all patients' medical examinations have been delayed, which may worsen patients' diseases. Therefore, Niimi et al. speculated that psychological differences might exist between patients with epilepsy who underwent epilepsy surgery before and during the COVID-19 pandemic, and used the Zung Self-Rating Depression Scale (SDS) to evaluate the difference in depression between the two groups of patients. The results showed that the SDS score was higher in the pre-pandemic group than in the within-pandemic group, indicating that patients with less positive outlooks may be less likely to seek medical attention during periods of societal or personal stress.

Due to the high cost of surgery, some patients still prefer drug therapy. Levetiracetam is considered one of the first-choice drugs for patients with brain tumor-related epilepsy, but side effects come with it. Dono et al. retrospectively analyzed 28 patients with brain tumors and found that prophylactic use of levetiracetam had a higher incidence and severity of psychiatric symptoms than controls. Accurate epileptological evaluations in patients with brain tumors are mandatory to select who would benefit most from ASM.

Author contributions

ZX, XT, XW, YC, QX, and GA organized this Research Topic and wrote the editorial. All authors have approved the final version of the editorial.

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We thank the authors for contributing their valuable work to this Research Topic and the reviewers for their constructive comments. We are also grateful to the editorial board for approving this topic and we hope this issue will advance the state of research on the comorbidities of epilepsy.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Patients With Epilepsy Who Underwent Epilepsy Surgery During the COVID-19 Pandemic Showed Less Depressive Tendencies

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Introduction: Our hypothesis in this study was that differences might exist between patients with epilepsy (PWE) who underwent epilepsy surgery before and within the period of the coronavirus disease 2019 (COVID-19) pandemic. The purpose of this study was to compare results of the Zung Self-Rating Depression Scale (SDS) between PWE who underwent epilepsy surgery before and during the pandemic period.

Methods: Participants were PWE who underwent open cranial epilepsy surgery between February 2019 and February 2021 in our hospital. Patients who underwent surgery in the first half of this period, between February 2019 and January 2020, were defined as the pre-pandemic period group (pre-Group) and those treated in the second half, between February 2020 and February 2021, were categorized as the pandemic period group (within-Group). All patients completed the SDS before surgery, and scores were compared between groups.

Results: SDS score was significantly higher in the pre-Group than in the within-Group ($p = 0.037$). Other factors, including age ($p = 0.51$), sex ($p = 0.558$), epilepsy duration from onset to SDS score evaluation ($p = 0.190$), seizure frequency ($p = 0.794$), number of anti-seizure medications ($p = 0.787$), and intelligence quotient ($p = 0.871$) did not differ significantly between groups.

Conclusion: SDS score was higher in the pre-pandemic group than in the within-pandemic group, which may indicate that PWE with less-positive outlooks may be less likely to seek medical attention during stressful periods.

Keywords: Zung self-rating depression scale, pandemic, epilepsy surgery, COVID-19, SARS-CoV-2

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HIGHLIGHTS

- PWE who underwent surgery during the pandemic period showed less depressive symptoms.
- PWE with depressive tendencies might be at risk during stressful periods.
- Technology might offer hope for PWE showing depressive tendencies.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in 2019, and has shown three peaks in Japan since the beginning of 2020.

Previously, as pandemics in the 20th century, we experienced the Spanish flu, acquired immunodeficiency syndrome (AIDS) and highly pathogenic avian influenza viruses (1–4). However, in the 21st century, the frequency of epidemics seems to have increased markedly (5–9). Regardless of the cause, the possibility of pandemics occurring more frequently in the near future must naturally be considered.

Patients with epilepsy (PWE) are known to have been suffering during the calamity of COVID-19 due to anxiety and depression (10). In particular, PWE with surgically remediable epilepsy are known to be vulnerable to psychiatric disturbance before and after surgery, even when societal calamities are not present. Since the adequate treatment of psychiatric comorbidities increases the likelihood of seizure freedom and optimizes the psychosocial benefits afforded by epilepsy surgery (11), provision of psychological care to PWE must be a priority. At the same time, continuity of treatment for PWE is also necessary. The idea of continuing business functions in society has already been described in 2012 by the International Organization for Standardization (ISO) as ISO22301 (https://www.iso.org/standard/75106.html). This ISO standard describes how to continually manage business in an organization to protect against the occurrence of disruptive incidents. These underlying principles are also applicable to healthcare businesses and our hospital follows this standard.

We have already described a retrospective study showing the importance of local interdisciplinary care for PWE (12). We have also shown that SARS-CoV-2 did not influence the volume of epilepsy surgeries in our facility (13). From these efforts, approaches to the calamity from the healthcare perspective might improve such negative situations for PWE. However, in the real world, worsening of seizure frequency and postponement of medical examinations are commonplace experiences for many PWE during the COVID-19 pandemic (14). If many PWE postponed adequate medical treatments during the pandemic, psychological differences might exist between PWE who did not postpone treatments and underwent epilepsy surgery during the pandemic and PWE who underwent epilepsy surgery before the pandemic.

Our hypothesis for the present study was thus that psychological differences might exist between PWE who underwent epilepsy surgery before and during the COVID-19 pandemic. The purpose of this study was to compare results from a depression scale among PWE who underwent epilepsy surgery before and during the COVID-19 pandemic.

METHODS

Study Design and Ethics Approval

The ethics committee at Seirei Hamamatsu General Hospital, Japan, approved the protocol for this retrospective study (approval no. 3578), which was performed in accordance with the principles of the Declaration of Helsinki. Subjects in this study were identified from a review of the electronic medical records for patients who had undergone epilepsy surgery between February 2019 and February 2021 in the Comprehensive Epilepsy Center at Seirei Hamamatsu General Hospital.

Clinical Information

We collected information from patients who underwent epilepsy surgery between February 2019 and February 2021, as the first half of this period between February 2019 and January 2020 was pre-pandemic and the second half between February 2020 and February 2021 was just within the pandemic period in Japan. Patient age was recorded at the time of depression scale evaluation.

Data were obtained from all 32 patients who underwent open cranial epilepsy surgery for medically intractable epilepsy between February 2019 and February 2021 in our hospital. Among this population, inclusion criteria were: (1) age $\geq$18 years at evaluation, as the depression scale used was the Zung Self-Rating Depression Scale [SDS], which is adapted for individuals $\geq$18 years old (15); and (2) full intelligence quotient (IQ) $\geq$60. Among this population, exclusion criteria were: (1) patients who had undergone vagus nerve stimulation (VNS) therapy; and (2) patients who exhibited psychogenic non-epileptic seizures (PNES) (16) or other non-stereotypical activities.

As intellectual disorder and depression are sometime difficult to differentiate, such as in depressive cognitive disorders (17), patients with more than moderate intellectual disorder were allowed to enroll in this study. As VNS therapy has antidepressant effects (18), patients with VNS devices were excluded. All patients underwent long-term video electroencephalography and stereotypical epileptic seizures were captured. Based on the stereotypical seizure semiology, PWE who had experienced non-stereotypical activities were excluded because these non-stereotypical activities were regarded as possible PNES or non-epileptic events.

Depression Scale as the Primary Outcome Measurement

The SDS test is a 20-item self-reported questionnaire in common use as a screening tool, covering affective, psychological, and somatic symptoms associated with depression. The questionnaire takes 5–10 min to complete, and items are framed in terms of positive and negative statements. The total score is derived as the sum of scores for the individual item scores, ranging from 20 to 80. Patients who undergo epilepsy surgery in our institution undergo SDS before the surgery. We divided the enrolled patients into two groups: those who underwent surgery in the first half of the period, categorized as during the pre-pandemic period group between February 2019 and January 2020 (pre-Group); and those who underwent surgery in the second half of the period, categorized as during the pandemic period between February 2020 and February 2021 (within-Group). We compared SDS scores between these two groups.

Seizure Frequency, Duration From Epileptic Seizure Onset to SDS Score Evaluation, and Anti-seizure Medications as Secondary Outcome Measurements

We also compared seizure frequency, duration from onset to SDS score evaluation, and number of anti-seizure medications (ASMs) between the pre-Group and within-Group. Seizure

TABLE 1 | Clinical information and SDS scores.

	Pre-group ($n = 10$)	Within-group ($n = 9$)	p-value
Sex (female), *n*	3 (30%)	4 (44%)	0.558
Age at evaluation (years)	mean 30.7, SD 14.2, median 27	mean 34.7, SD 11.5, median 37	0.51
Type of epilepsy	7 TLE, 2 FLE, 1 OLE	7 TLE, 2 FLE	na
IQ	mean 85.8, SD 20.7, median 89.5	mean 84.3, SD 18.1, median 86	0.871
SDS score	mean 39.9, SD 6.4, median 41.5	mean 33.2, SD 6.45, median 32	0.037*
Seizure frequency	mean 2.6, SD 0.84, median 3.0	mean 2.67, SD 1.12, median 3	0.794
Duration from onset to SDS evaluation (m)	mean 115.5, SD 113.2, median 72	mean 193.3, SD 155.7, median 144	0.19
No. of ASMs	mean 2, SD 0.94, median 2	mean 1.89, SD 0.928, median 2	0.787

SD, standard deviation; SDS, self-rating depression scale; TLE, temporal lobe epilepsy; FLE, frontal lobe epilepsy; OLE, occipital lobe epilepsy; IQ, intelligence quotient; ASM, anti-seizure medication; m, months. Seizure frequency was classified as: (1) daily; (2) weekly; (3) monthly; or (4) yearly. *significant difference, $p < 0.05$.*

TABLE 2 | Use of ASMs.

	Pre-group							Within-group				
Anti seizure medications	LCM	LEV	PER	CBZ	CLB	TPM	LTG	LCM	LEV	PER	CBZ	CLB
No. of PWE	7	5	4	1	1	1	1	6	5	4	1	1

LCM, Lacosamide; LEV, Levetiracetam; PER, Perampanel; CBZ, Carbamazepine; CLB, Clobazam; TPM, Topiramate; LTG, Lamotrigine.

frequency was classified as: (1) daily; (2) weekly; (3) monthly; or (4) yearly. These secondary outcomes were chosen as factors potentially related to anxiety or depressive disorders (19).

Statistical Analyses

The Mann-Whitney *U*-test and Student's *t*-test were used in this study, as appropriate. Statistical significance was set at the level of $p < 0.05$. Analyses were conducted using Sigma plot (Systat Software, San Jose, CA, USA).

RESULTS

Clinical information and results of the SDS are shown in **Table 1**.

Seven female PWE and 12 male PWE (mean age at evaluation, 32.6 years; median age, 35.0 years; range, 18–59 years; standard deviation, 12.8 years; confidence interval of the mean, 6.16 years) fulfilled the inclusion criteria. None of the patients exhibited PNES. **Table 2** shows the ASMs used by the patients.

Primary Outcome Measurement

SDS scale score was significantly higher in the pre-Group than in the within-Group ($p = 0.037$). No other factors, including age ($p = 0.51$), sex ($p = 0.558$), or IQ ($p = 0.871$), showed significant differences between groups (**Table 1**).

Secondary Outcome Measurements

Epilepsy duration from onset to SDS score evaluation ($p = 0.190$), seizure frequency ($p = 0.794$), and number of ASMs ($p = 0.787$) all showed no significance differences between groups (**Table 1**).

DISCUSSION

SDS scale score was significantly higher in the pre-Group than in the within-Group. Even though scores were not within the diagnostic range for depression, the pre-Group was relatively closer to the range for depressive symptoms than the within-Group. This might be because PWE with a more positive outlook were less likely to put off epilepsy surgery even during the pandemic period.

Rayner and Wilson (11) reported that a less compromised psychiatric profile may contribute to better outcomes of epilepsy surgery. Even though we did not provide special treatments for psychiatric comorbidities for enrolled PWE, the fact that PWE with a less negative outlook underwent epilepsy surgery during the pandemic in this study might partially support this theory by Rayner and Wilson. Given the disaster-preparedness measures taken by our facility, the continuity plan might have worked. As Japan experiences relatively frequent disasters, such as earthquakes, typhoons, and floods, many facilities in Japan might prepare for such disruptive events. The other effort was that as our local interdisciplinary system for epilepsy treatment became established (13), the flow cycle for PWE among local general physicians and our epilepsy center was able to be maintained. Based on these approaches to the calamity that might be decreasing psychological stresses among surgical candidates, thereby improving such negative situations for PWE, epileptologists might not hesitate to perform epilepsy surgery even during a pandemic.

Conversely, about 30% of PWE are considered to have depressive symptoms (20). Many of these patients might be more strongly influenced by psychological factors than by the epilepsy itself (21). From our results and those of previous reports, the possibility should be considered that some PWE might neglect

beneficial advanced medical care such as epilepsy surgery under disruptive situations.

As interventions in medical treatments, including for epilepsy, have a certain order of priority (22), some PWE might be classified as having non-urgent disorders (23), despite they might have severe conditions such as COVID-19-related status epilepticus (24). However, using advanced technologies such as telemetry (10, 25), home-video recordings (26) and tele-neuropsychology tests (27) should be implemented to maximize efficient provision of appropriate medical interventions.

A key limitation of this study was the small number of PWE in each group. However, the suggestion that some PWE might be neglected under various circumstances is important and worth exploring further in future work.

SDS scores obtained from multiple centers before and during the pandemic and other societal circumstances should be analyzed in future investigations.

CONCLUSION

SDS score was higher in the pre-pandemic group than in the within-pandemic group, which may indicate that PWE with less-positive outlooks may be less likely to seek medical attention during periods of societal or personal stress.

DATA AVAILABILITY STATEMENT

The original contributions generated for this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The ethics committee of Seirei Hamamatsu General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KN, AF, HE, KS, and TO: acquisition of data. AF, TO, and HE: analysis and interpretation of data. AF: epilepsy surgery. All authors contributed to the article and approved the submitted version.

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Past Trauma Is Associated With a Higher Risk of Experiencing an Epileptic Seizure as Traumatic in Patients With Pharmacoresistant Focal Epilepsy

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Objective: The present study aimed to evaluate the prevalence of traumatic experienced seizures (TES) and of postepileptic seizure PTSD (PS-PTSD) in patients with pharmacoresistant focal epilepsy and to explore the determining factors of TES.

Methods: We conducted an observational study enrolling 107 adult refractory epilepsy patients. We used the DSM-5 criteria of traumatic events and PTSD to define TES and PS-PTSD. We assessed all traumatic life events unrelated to epilepsy, general and specific psychiatric comorbidities, and quality of life.

Results: Nearly half ($n = 48$) of the 107 participants reported at least one TES (44.85%). Among these, one-third ($n = 16$) developed PS-PTSD. The TES group was more likely to experience traumatic events unrelated to epilepsy ($p < 0.001$), to have generalized anxiety disorder ($p = 0.019$), and to have specific psychiatric comorbidities [e.g., interictal dysphoric disorder ($p = 0.024$) or anticipatory anxiety of seizures ($p = 0.005$)]. They reported a severe impact of epilepsy on their life ($p = 0.01$). The determining factors of TES according to the multifactorial model were the experience of trauma ($p = 0.008$), a history of at least one psychiatric disorder ($p = 0.03$), and a strong tendency toward dissociation ($p = 0.03$).

Significance: Epileptic seizures may be a traumatic experience in some patients who suffer from pharmacoresistant epilepsy and may be the source of the development of PS-PTSD. Previous trauma unrelated to epilepsy and psychiatric history are determining factors of TES. These clinical entities should be explored systematically.

Keywords: drug-resistant focal epilepsy, trauma, traumatic experienced seizure, psychiatric comorbidities, postepileptic seizure posttraumatic stress disorder, posttraumatic stress disorder

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INTRODUCTION

Epilepsy is defined as a chronic brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition (1). Epilepsy is present in ∼1% of the population, accounting for a total of 70 million people worldwide, approximately one-third of whom have refractory epilepsy (2). Psychiatric disorders have been identified in 25–50% of patients with epilepsy, with a higher prevalence among patients with poorly controlled seizures (3).

The association between epilepsy and negative life events is multidirectional and complex. Early-life stress might promote epileptogenesis during brain development with a vulnerability to limbic epilepsy (4, 5). People with posttraumatic stress disorder (PTSD) have a higher risk of developing epilepsy in the future (6). Moreover, self-reported stress is the most common seizure precipitant (7). Therefore, acute stress due to traumatic events could trigger an epileptic seizure (8). People who live in war zones (9) or in disaster-prone countries (10) are more likely to experience a seizure. PTSD is a mental health condition that is known to affect people who have experienced or witnessed a traumatic event (11). Illnesses can also be forms of trauma. Several studies have proven that acute diseases could be considered traumatic for patients, such as acute coronary syndrome (12), stroke (13, 14), asthma (15), or first-episode psychosis (16).

Two studies have evaluated whether an epileptic seizure could be perceived as a traumatic event and reported different findings. Chung and Allen (17) investigated the incidence of PTSD following epileptic seizure and called it postepileptic seizure PTSD (PS-PTSD). Their results indicated that 51% of 71 patients with all types of epilepsy met the diagnostic criteria for full-PTSD in reference to their "most traumatic seizure" according to the Posttraumatic Diagnostic Scale (PDS-5). Labudda et al. (18) used a modified version of the PDS-5 and conducted interviews to assess patients who fulfilled the criteria for PS-PTSD and asked about their worst seizure. Only 5% of the 120 patients in the sample fulfilled all criteria for PTSD.

Patients with pharmacoresistant focal epilepsy (PRFE) have more psychiatric comorbidities compared to patients with controlled epilepsy, and these associated psychiatric factors cause poorer life quality (19). Therefore, focusing on these comorbid factors, especially on traumatic dimension, could be an important resource to take actions to improve the life quality of the patients with PRFE for whom the antiepileptic treatment is limited.

Our study aimed to measure the prevalence of traumatic experience of an epileptic seizure (TES) and of PS-PTSD in patients with focal refractory epilepsy and to explore the determining factors (epileptic and psychiatric) linked to TES.

MATERIALS AND METHODS

This prospective study was conducted between November 2018 and February 2020 in the Epileptology Department of our University Hospital. We enrolled consecutive adult patients hospitalized for presurgical work-up with a confirmed diagnosis of pharmacoresistant focal epilepsy (according to the ILAE) few months before possible intracranial exploration. All patients provided written consent. We collected data based on our clinical systematic evaluation. Sociodemographic data were collected, including age, sex, marital status, education, and employment status.

Seizure Data

We identified the age at epilepsy onset and the type of seizures (focal and/or focal to bilateral tonic–clonic seizures). Localization and lateralization of seizure foci were based on the recorded seizures during long-term video-EEG monitoring and images in all patients and additional video-SEEG (stereo-electroencephalography) for some patients. MRIs for epileptogenic lesions were sought. Data assessing ongoing antiepileptic treatment were collected. The impact of epilepsy on life and quality of life was evaluated by the Quality of Life in Epilepsy Inventory (QOLIE-31) (20), composed of seven multi-item subscales evaluating emotional well-being, social function, energy, cognitive function, seizure worry, medication effects, and overall quality of life, and by a question in which the impact of epilepsy on daily life was evaluated by the patients as absent, mildly, moderately, and severely. The most impacted life areas were also investigated, e.g., family, sentimental, working, and leisure.

Trauma Data

Traumatic Experienced Seizure (TES)

The risk or fear of death or serious injury during a seizure was examined based on the definition of trauma provided by the DSM-5 (21). If this risk or fear was present, we confirmed TES and further questions were asked, such as the number of traumatic seizures experienced and which seizure was the most traumatic one (e.g., the first one, the last one, and the most serious one in terms of severity of the circumstances or the consequences). The temporal relationship between the onset of epilepsy and the first traumatic seizure was also explored.

Postepileptic Seizure Posttraumatic Stress Disorder

The patients who experienced TES constituted the TES group, while all other patients composed the non-TES group. In the TES group, the PCL-5 (PTSD Checklist Scale for DSM-5) (22) was used to evaluate the severity of symptoms associated with this seizure as a traumatic event. The PCL-5 is a 20-item questionnaire corresponding to the DSM-5 symptom criteria for PTSD. The self-report rating scale is 0–4 for each symptom: "Not at all," "A little bit," "Moderately," "Quite a bit," and "Extremely." It combines four subcategories intrusion (item B, questions 1–5) avoidance behavior (item C), cognition and mood alteration (item D), and hypervigilance (item E). A provisional PTSD diagnosis can be made by treating each item rated as 2 = "Moderately" or higher as a symptom endorsed, then following the *DSM-5* (23) diagnostic rule that requires at least one B item (questions 1–5), one C item (questions 6–7), two D items (questions 8–14), and two E items (questions 15–20). Following this method, we identified a positive provisional PTSD group and a negative provisional PTSD group.

History of Trauma, Independent of a Seizure

The experience of traumas other than epilepsy was evaluated using the Traumatic Life Event Questionnaire (TLEQ) (24). The frequency and type of trauma and the age of occurrence were evaluated. Traumas during childhood were assessed using the TLEQ and the Childhood Trauma Questionnaire (CTQ) (23). These scales enabled the establishment of three types of trauma: sexual, physical, and psychological trauma, as well as the occurrence, the age at the first experience, and the time between the first traumatic event and the appearance of epilepsy. The PTSD part of Mini International Neuropsychiatric Interview (MINI) was used to diagnose an actual PTSD. We also investigated a past PTSD, which refers to a total remission of the PTSD symptoms at least for 1 month.

Dissociation

Dissociation was assessed through the Dissociative Experiences Scale (DES) (25), a 28-item self-report tool that rates the severity and frequency of dissociative experiences, which explores three subcategories of dissociative symptoms: depersonalization, amnesia, and absorption.

Psychiatric Assessment

Non-specific Psychiatric Disorders

Psychiatric comorbidities were assessed through the semi-structured interview MINI (26). Depression and generalized anxiety disorder (GAD) were evaluated by two specific validated scales for patients with epilepsy: the Neurological Disorders Depression Inventory for Epilepsy (NDDIE) (27) and the GAD-7 (28), respectively. Data about ongoing psychotropic treatment were collected, as were comorbidities induced by these treatments.

Specific Interictal Psychiatric Disorders Associated With Epilepsy—With No Temporal Link to Seizures

We evaluated *interictal dysphoric disorder* according to Blumer's criteria, defined as the occurrence of at least three episodes lasting from a few hours to a few days, grouped together at least three of the following eight criteria: depressed mood, asthenia, atypical pain, insomnia, fear and anxiety, irritability, euphoric mood, and instability of mood (29). Anticipatory anxiety of a seizure, defined as the fear of having an epileptic seizure, was assessed. We also explored avoidance behavior linked to the fear of seizures.

Peri-Ictal Disorders—With a Temporal Link to Seizures

For the three major dimensions of psychiatric comorbidities (depression, anxiety, and psychosis), we assessed the presence of preictal disorder, ictal disorder, and postictal disorder.

Psychological Dimensions

Alexithymia was assessed through the use of the Toronto Alexithymia Scale (TAS-20) (30), which is a self-report tool with three subscales: feelings' description and identification difficulties and thoughts turned to the outside.

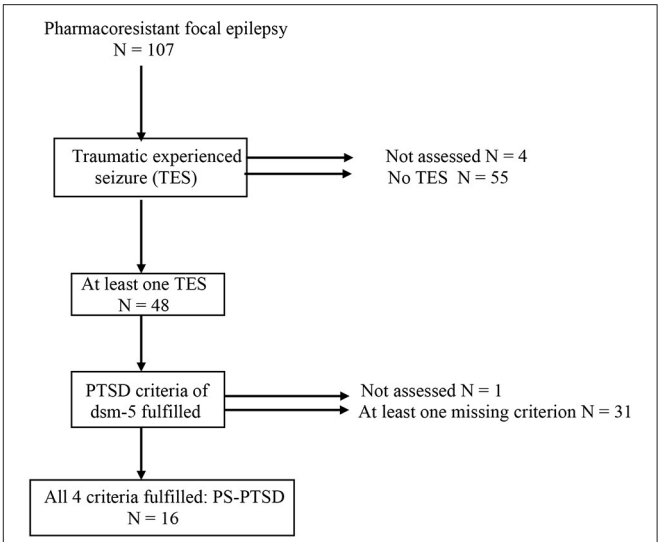

FIGURE 1 | Representation of patients with/without TES and with/without PS-PTSD.

Statistical Analyses

To evaluate differences between participants who experienced or did not experience TES, the Chi-square test and Fisher's exact test were used to analyze categorical variables. We used Student's *t*-test for normally distributed continuous variables with enough patients (>30) and the Mann–Whitney *U*-test for other continuous variables. Missing data were excluded from the respective analyses. A two-tailed *p*-value of <0.05 was considered statistically significant. Since these analyses were exploratory, the Bonferroni correction was not necessary (31, 32).

We also performed a multivariate logistic regression analysis, which models the probability of a TES. The variables included were the duration of epilepsy, the existence of interictal anticipatory anxiety, previous trauma, a history of at least one psychiatric disorder, current anxious disorder, and the total DES score. Missing values were processed by multiple account assignment (MAA).

RESULTS

Study Population

Assessments were completed by 107 patients (age 33.2 years, 18–66): 48 had a TES and 16 had PS-PTSD (**Figure 1**). The female-to-male ratio was 1.14. The mean age at onset of epilepsy was 17.55 years, with an average duration of evolution of 15.6 years. A majority of participants (55.14%) reported at least one traumatic experience unrelated to epilepsy in their lifetime. In 27.1% of the cases, this trauma preceded the onset of epilepsy. A majority of patients (59.81%) had an ongoing psychiatric disorder. Only 16.82% of our patients reported having mood disorders at the time of evaluation, whereas 31.77% of our population reported current anxiety disorders. Thirty-eight patients suffered from anticipatory anxiety of seizures, while 41.1% avoided at least one situation in their daily life (**Supplementary Table 1**).

Figure 1 presents the repartition of patients.

TABLE 1 | Demographics and epileptic features of patients with/without traumatic experienced seizure (TES).

	At least one traumatic experienced seizure (*N* = 48)	No traumatic experienced seizure (*N* = 55)	*p*
DEMOGRAPHIC FACTORS			
Sex ratio M/F, *n*	0.92	0.77	0.66*
Age at enrollment, years (SD)	31.45 (10.25)	34.43 (13.01)	0.20****
Learning disabilities, *n* (%)	13 (27.08)	16 (29.09)	0.82*
Marital status (single), *n* (%)	26 (54.16)	27 (49.09)	0.6*
Education level since primary school, years (SD)	12.87 (2.54)	12.2 (2.71)	0.15***
Professional activity, *n* (%)	18 (37.5)	25 (45.45)	0.41*
EPILEPTIC FEATURES			
History			
Neurological history—head injury, *n* (%)	5 (10.41)	15 (27.27)	0.03*
Age at the onset of epilepsy, years (SD)	19.54 (11.52)	16.2 (12.01)	0.15****
Duration of epilepsy, years (SD)	11.72 (8.81)	17.98 (11.30)	0.002****
Type, frequency and localization			
Focal seizure (focal), *n* (%)	43 (89.58)	51 (92.72)	0.73**
Focal to bilateral tonic–clonic seizures, *n* (%)	28 (58.33)	22 (40)	0.06*
Focal seizures frequency per month, *n* (SD)	44.57 (139.7)	13.47 (20.92)	0.47***
Focal to bilateral tonic–clonic seizures—per month, *n* (SD)	8.28 (22.08)	0.78 (1.02)	0.28***
Left-sided focus of epilepsy, *n* (%)	24 (57.14)	27 (52.94)	0.68*
Right-sided focus of epilepsy, *n* (%)	16 (38.09)	19 (37.25)	0.93*
Bilateral focus of epilepsy, *n* (%)	2 (4.76)	5 (9.8)	0.45**
Temporal lobe epilepsy, *n* (%)	30 (71.42)	39 (75)	0.69*
Frontal lobe epilepsy, *n* (%)	7 (16.66)	11 (21.15)	0.58*
Insular epilepsy, *n* (%)	3 (7.14)	7 (13.46)	0.5**
Posterior lobe epilepsy, *n* (%)	5 (11.9)	9 (17.3)	0.46*
Severity			
Loss of consciousness during a seizure, *n* (%)	24 (50)	35 (64.81)	0.13*
Urine or feces loss during a seizure, *n* (%)	10 (20.83)	10 (18.51)	0.76*
Fall during a seizure, *n* (%)	24 (50)	18 (33.33)	0.08*
Injuries during a seizure, *n* (%)	20 (41.66)	20 (37.03)	0.63*
IMPACT OF EPILEPSY ON LIFE			
Subjective impact			
Impact on daily life evaluated as severe, *n* (%)	10 (32.25)	4 (9.30)	0.01*
Family life affected by epilepsy, *n* (%)	7 (22.58)	5 (11.62)	0.20*
Sentimental life affected by epilepsy, *n* (%)	6 (19.35)	7 (16.27)	0.73*
Working life affected by epilepsy, *n* (%)	24 (77.41)	30 (69.76)	0.46*
Leisure affected by epilepsy, *n* (%)	22 (70.96)	18 (41.86)	0.013*
Quality of life (QOLIE 31)			
Worry about seizures, score (SD)	42.01 (28.41)	52.24 (25.01)	0.055***
General quality of life, score (SD)	51.36 (20.25)	57.34 (19.64)	0.16***
Emotional wellness, score (SD)	60.09 (23.03)	66.23 (21.65)	0.22***
Vitality and energy feeling, score (SD)	46.66 (17.91)	47.49 (19.91)	0.57***
Memory, cognitive disorders, score (SD)	40.965 (19.85)	46.89 (25.35)	0.12***
Side effects from treatments, score (SD)	44.92 (24.74)	53.45 (26.50)	0.069***
Social functioning, score (SD)	51.08 (25.65)	63.13 (23.38)	0.012***

**Chi 2; **Fisher exact test; ***Mann–Whitney U-test; ****Student's t-test.*
SD, standard deviation; QOLIE, quality of life in epilepsy inventory.

Traumatic Experience of Seizures

Of the 107 participants, 48 (44.85%) experienced at least one TES, for an average of 2.79 TESs in a lifetime. Among these 48 patients, 29.16% assessed their first seizure as a TES and 41.66% considered their most serious seizure (in term of circumstances or consequence) as a TES. The average duration between the onset of epilepsy and a TES was 5.29 years (**Supplementary Table 1**). Of these 48 patients, 16 met all 4 criteria of PTSD diagnosis and were constituted PS-PTSD group.

Profile of Patients in the TES Group? Comparative Univariate Analyses

Demographic Data

There was no difference between the two groups in sociodemographic or educational data.

Characteristics of Epilepsy

The mean age at epilepsy onset as well as the frequency, lateralization, and localization of seizures did not differ significantly between the two groups. However, TES patients tended to have more frequent focal to bilateral tonic–clonic seizures ($p = 0.06$) and more frequent falls ($p = 0.08$). We observed a longer duration of epilepsy among patients without TES (17.98 vs. 11.72, $p = 0.002$). Patients without TES were more likely to experience head injury (27.27 vs. 10.41%, $p = 0.03$).

Impact of Epilepsy on Quality of Life

Patients in the TES group reported more severe impact of epilepsy than other patients (32.25 vs. 9.3%, $p = 0.01$). The various aspects of daily life were equally impacted between groups, except for leisure, which was more disrupted in the TES group ($p = 0.013$). On the QOLIE 31, the social function was lower in the TES group ($p = 0.012$). The TES group had overall poorer quality of life, but not significant on the following dimensions: worry about seizures ($p = 0.055$), side effects from

TABLE 2 | Psychiatric features of patients with/without traumatic experienced seizure (TES).

	At least one traumatic seizure (*N* = 48)	No traumatic seizure (*N* = 55)	*p*
Personal psychiatric history			
Psychiatric follow-up, *n* (%)	22 (45.83)	23 (41.81)	0.68*
Hospitalization for psychiatric care, *n* (%)	8 (16.66)	4 (7.27)	0.13*
Personal history of suicide attempt, *n* (%)	7 (14.58)	5 (9.09)	0.38*
Number of past psychiatric comorbidities, mean (SD)	1.58 (1.11)	0.87 (1.07)	<0.001***
Current psychiatric comorbidities			
At least one current pathology (MINI), *n* (%)	33 (68.75)	29 (52.72)	0.09*
Number of current psychiatric comorbidities, mean (SD)	1 (0.93)	0.74 (0.83)	0.12***
Number of Current psychotropic treatment, mean (SD)	0.375 (0.78)	0.09 (0.28)	0.04***
Antidepressants, *n* (%)	7 (14.58)	3 (5.45)	0.18**
Antipsychotics, *n* (%)	5 (10.41)	1 (1.81)	0.09**
Anxiolytics, *n* (%)	6 (12.5)	1 (1.81)	0.04**
Mood disorders			
Current depressive disorder (MINI), *n* (%)	8 (16.66)	4 (7.27)	0.13*
Depression according NDDIE score ≥16, *n* (%)	11 (26.19)	6 (11.76)	0.07*
Specific mood disorder linked with epilepsy			
Interictal dysphoric disorder, *n* (%)	16 (33.33)	8 (14.54)	0.024*
Pre-ictal mood disorder, *n* (%)	7 (14.58)	0 (0)	0.003**
Ictal mood disorder, *n* (%)	3 (6.25)	0 (0)	0.09**
Post-ictal mood disorder, *n* (%)	10 (20.83)	6 (10.9)	0.16*
Anxiety disorder			
At least one current anxiety disorder (MINI), *n* (%)	23 (47.91)	11 (20.0)	0.002*
Panic disorder, *n* (%)	3 (6.25)	5 (9.09)	0.72**
Agoraphobia, *n* (%)	7 (14.58)	2 (3.63)	0.07**
Generalized anxiety disorder, *n* (%)	10 (20.83)	3 (5.45)	0.019*
Social phobia, *n* (%)	6 (12.5)	2 (3.63)	0.14**
GAD according GAD-7 score ≥8, *n* (%)	14 (33.33)	9 (17.64)	0.08*
Specific anxiety disorders linked with epilepsy			
Pre-ictal anxiety, *n* (%)	21 (43.75)	14 (25.45)	0.050*
Interictal/anticipatory anxiety of a seizure, *n* (%)	21 (70)	16 (37.2)	0.005*
Ictal anxiety, *n* (%)	22 (45.83)	12 (21.81)	0.009*
Post-ictal anxiety, *n* (%)	10 (20.83)	5 (9.09)	0.09*
Behavior of limitation or avoidance, *n* (%)	26 (54.16)	16 (29.09)	0.009*
Obsessive-Compulsive			
Obsessive-compulsive disorder, *n* (%)	3 (6.25)	1 (1.81)	0.33**
Psychotic disorders			
Psychotic disorder (MINI), *n* (%)	4 (8.33)	6 (10.90)	0.74**
Post-ictal psychosis, lifetime, *n* (%)	1 (2.08)	0 (0)	0.46**
Addictive disorders			
Alcohol addiction (MINI), *n* (%)	0 (0)	3 (5.45)	0.24**
Cannabis addiction (MINI), *n* (%)	2 (4.16)	3 (5.45)	1**
Alexithymia			
Alexithymia (according TAS score >61), *n* (%)	14 (33.33)	2 (4.76)	<0.001*
Feelings' description difficulties mean score (SD)	13.97 (4.36)	12.11 (3.45)	0.035****
Feelings' identification difficulties mean score (SD)	18.8 (6.93)	16 (5.23)	0.041****
Thoughts turned to the outside mean score (SD)	20.59 (4.46)	20.47 (3.49)	0.89****

**Chi 2; **Fisher exact test; ***Mann–Whitney U-test; ****Student's t-test.*
SD, standard deviation; GAD, generalized anxiety disorder; NDDI-E, neurological disorders depression inventory for epilepsy; TAS, Toronto alexithymia scale; MINI, mini international neuropsychiatric interview.

epileptic illness, and side effects from treatments ($p = 0.069$). Data concerning patients profile are presented in **Table 1**.

Psychiatric Disorders

Patients in the TES group were more likely to have psychiatric disorders than non-TES patients (68.75 vs. 52.72%, respectively, $p = 0.003$) and used to take more psychotropic drugs than other patients ($p = 0.04$).

Mood Disorders. According to the MINI or the NDDIE, there was no difference between the two groups in terms of general mood disorders. Regarding specific mood disorders linked with epilepsy, interictal dysphoric disorders were more often found among TES patients (33.33 vs. 14.54%, $p = 0.024$) as well as preictal mood disorders (14.58 vs. 0%, $p = 0.003$).

Anxiety Disorders. Current anxiety disorders were more frequent in patients in the TES group (47.91 vs. 20%, $p = 0.002$). Specifically, it concerned current GAD (20.83 vs. 5.45%, $p = 0.019$) according to MINI, but the two groups did not differ in terms of GAD according to a positive score on the GAD-7 scale ($p = 0.08$). People in the TES group were more likely to present anxious disorders related to epilepsy, such as anticipatory anxiety (70 vs. 37.2%, $p = 0.005$), ictal anxiety—twice as likely to occur in patients in the TES group ($p = 0.009$)—and avoidance behaviors related to anxiety ($p = 0.009$). See **Table 2**.

Addictive and Psychotic Disorders

No significant differences were found.

Alexithymia

Patients in the TES group were more likely to develop alexithymia: 33.33 vs. 4.76%, respectively ($p < 0.001$).

TABLE 3 | Traumatic characteristics of patients with/without traumatic experienced seizure (TES).

	At least one traumatic seizure (*N* = 48)	No traumatic seizure (*N* = 55)	*p*
Trauma data			
Previous trauma, *n* (%)	39 (81.25)	26 (47.27)	**<0.001***
Number of previous trauma, mean (SD)	1.70 (1.41)	0.70 (0.88)	**<0.001*****
Age at first trauma, years (SD)	17.37 (10.81)	15.22 (9.64)	0.71***
Onset of trauma before epilepsy, *n* (%)	18 (37.5)	11 (20)	**0.048***
One trauma, *n* (%)	14 (29.16)	12 (21.81)	0.39*
Several trauma, *n* (%)	25 (52.08)	14 (25.45)	**0.005***
Trauma during adulthood			
Sexual, *n* (%)	0 (0)	1 (1.81)	0.34**
Physical, *n* (%)	8 (16.66)	3 (5.45)	0.06*
Psychological/emotional, *n* (%)	19 (39.58)	6 (10.9)	**<0.001***
Trauma during childhood			
Sexual, *n* (%)	7 (14.58)	5 (9.09)	0.38*
Physical, *n* (%)	14 (29.16)	7 (12.72)	**0.038***
Psychological/emotional, *n* (%)	23 (47.91)	16 (29.09)	**0.049***
PTSD unrelated to epilepsy			
Past PTSD, *n* (%)	10 (20.83)	4 (7.27)	**0.045***
Actual PTSD, *n* (%)	4 (8.33)	1 (1.81)	0.18**
Post Seizure PTSD (PS-PTSD)			
At least one criteria significant of PS-PTSD (PCL 5) n (%)	38 (79.16)	-	**-**
All 4 criteria fulfilled: PS-PTSD n (%)	16 (33.33)	-	**-**
Total mean score of PCL-5 (SD)	18.44 (15.30)	-	**-**
Dissociation tendency(DES)			
Total mean score (SD)	13.29 (8.06)	7.18 (7.70)	**<0.001*****
Depersonalization, mean score (SD)	13.84 (9.38)	7.02 (7.38)	**0.001*****
Amnesia, mean score (SD)	9.15 (7.97)	4.98 (5.88)	**0.01*****
Absorption, mean score (SD)	20.13 (13.88)	10.58 (11.68)	**0.002*****

**Chi 2; **Fisher exact test; ***Mann–Whitney U-test; ****Student's t-test.*
SD, standard deviation; PTSD, post-traumatic stress disorder; DES, dissociative experiences scale; PCL-5, post-traumatic stress disorder checklist for DSM-5.
Bold values correspond to significant results.

History of Trauma

The majority (81.25%) of the TES group experienced a previous trauma (vs. 47.27% in the non-TES group, $p < 0.001$), with a higher average number of traumatic experiences (1.7 vs. 0.7, $p < 0.001$) and a higher proportion of patients who experienced several traumatic events (52.08% vs. 25.45%, $p = 0.005$). The TES group was more likely to experience trauma before the onset of epilepsy (37.5 vs. 20%, $p = 0.048$) and to have a history of PTSD unrelated to epilepsy (20.83 vs. 7.27%, $p = 0.045$)

Thirty-eight patients in the TES group (79.16%) presented at least one PTSD symptoms related to a TES, and 16 patients had the four criteria. The average total score for dissociation was significantly higher among patients in the TES group ($p < 0.001$). See **Table 3**.

TABLE 4 | Multivariate logistic regression analysis modeling the probability of a traumatic experienced seizure (TES).

	Multivariate (CI 95%) OR[a]	Multivariate *p*-value[a]
Duration of epilepsy, years[b]	0.944 (0.886–1.006)	0.08
Interictal anticipatory anxiety of a seizure	3.111 (0.687–14.083)	0.14
Existence of previous trauma	4.823 (1.53–15.211)	**0.008**
At least one history of psychiatric disorder	5.565 (1.178–26.285)	**0.03**
At least one current anxious disorder	1.171 (0.328–4.183)	0.81
Dissociation, DES total score[b]	1.116 (1.014–1.226)	**0.03**

[a] *Missing values processed by Multiple Account Assignment (MAA).*
[b] *Coefficient for additional consultation (continuous variable).*
DES, dissociative experiences scale; OR, odds ratio; CI, confidence interval.
Bold values correspond to significant results.

Determining Factors of TES? A Multivariate Analysis

Three factors appeared as determining factors of TES: the existence of a previous trauma ($p = 0.008$), a history of at least one psychiatric disorder ($p = 0.03$), and a high total score on the DES ($p = 0.03$) (**Table 4**).

Postepileptic Seizure Posttraumatic Stress Disorder

One-third ($n = 16$) of patients who experienced a TES developed a provisional PS-PTSD, which represented 14.95% of our total population. Due to the small number of patients, we did not perform comparative or multivariate analyses.

DISCUSSION

Half of the 107 patients had at least one TES, and one-third of patients in the TES group developed a potential/provisional PS-PTSD, which was 14.95% of our total population PRFE. Two previous studies have shown that an epileptic seizure could be experienced as traumatic. Labudda et al. (18) found that only 5% of included patients had PTSD in a population of difficult-to-treat individuals who had not been treated by surgery. In contrast, Chung and Allen (17) concluded that 51% of the 71 patients with all types of epilepsy met PTSD criteria. We found intermediary results. These differences between studies might be due to the methodological differences (such as assessment of PTSD). In our study, we did an exhaustive psychiatric interview by using event checklist to assess if patients experienced one or more traumatic events; then, the four core-symptoms of PTSD (avoidance, negative changes in mood and cognition, reexperience, and hyper-arousal) were sought by interview, which allowed us to justify PTSD diagnosis, according to DSM-V criteria. Moreover, patients who reported symptoms were assessed through the use of PCL-5 in order to rate their severity. Chung et al. (33) did the PTSD diagnosis based on PDS DSM-3 version. The PTSD

diagnosis is therefore only based on a self-reported questionnaire without a standardized psychiatric interview. Moreover, the authors asked the participants to complete PDS regarding their most traumatic seizure without checking if this event represent a traumatic experience based on DSM criteria. Therefore, we believed that, there might be an overvaluation or the prevalence of the patients with post-seizure PTSD. Moreover, we believe that there is also an overvaluation for the control group with 24% of participants with PTSD. Regarding Labudda et al. (18), the authors also used the PDS self-questionnaire. The authors asked the participants to remember their worst seizure and if they could identify one or more extraordinarily upsetting seizure. If the patients could identify a distressing seizure, then they checked if this event represented a traumatic experience according to DSM-4. We believe that their methodological approach is *a priori* much more restrictive. We also believe that differences in the PS-PTSD rates among the three studies arose from the fact that populations were not comparable: our study included specifically patients with pharmacoresistant focal epilepsy. By contrast, the two other studies included patients with epilepsy, whether it concerned drug-resistant epilepsy or not.

Trauma History

Additional studies suggested that there are multidirectional links between trauma and epilepsy. The patients with epilepsy who perceived stress as a trigger for seizures were more likely to have a history of childhood maltreatment (34, 35). In a study of pharmacoresistant epilepsy patients, 75% reported having experienced a traumatic event other than a seizure, and 20% reported that their first seizure arrived in a traumatic context and showed more PTSD symptoms (33). In our study, we showed that patients with TES had more past trauma.

As a result of a traumatic history, TES patients reported more regular dissociative experiences in daily life. We assumed that the patients who have higher dissociative tendencies in their everyday life have already experienced regularly some altered forms of consciousness, automatic behaviors, etc. Therefore, perhaps, for these patients, experiencing a loss of consciousness during an epileptic seizure is more traumatic. We suppose that these patients who have higher level of dissociation might experience more traumatic seizures compared to patients with lower level of dissociation.

On a neurobiological perspective, the hypothalamo–pituitary–adrenal (HPA) axis is activated in stressful situations, followed by the release of corticosteroid hormones. Increased activity in the HPA axis has been observed in early life traumas (36). Chronic or repeated stress could exacerbate epileptogenesis, inducing a greater predisposition for further stress experiences to trigger seizures (37). People who underwent maltreatment during childhood have a reduction of the hippocampus volume by ∼6% (38, 39). A smaller hippocampus could result in less efficient mnesic integration of the traumatic event in its chronology, leading to pathological intrusions. Amygdala overactivation induces fear and hypervigilance symptoms of PTSD. Therefore, a previous trauma alters these functions and could weaken a patient who may perceive a second unpredictable event, such as an epileptic seizure, as a new trauma.

Psychiatric Comorbidities

Suffering from epilepsy and anxious disorder might increase the risk of subjectively experiencing an epileptic seizure as more traumatic as a result of a catastrophic scenario made by anticipation or after a seizure. TES could be a consequence of this anxiety, or even of depression.

Moreover, the link between psychiatric comorbidities and epilepsy could be a consequence of TES. Therefore, experienced TES might increase the risk of developing a psychiatric pathology, especially if this experience induces social isolation. These psychiatric comorbidities might also be a confounding factor with trauma history, which is known to ensure these psychiatric comorbidities even before seizure appearance.

Our study showed that half of the patients who experienced a traumatic seizure had anticipatory anxiety about a seizure, a subjective symptom described as a day-to-day persistent fear, dread, or worries to have a seizure. A previous study demonstrated that this anticipatory anxiety was not correlated with the objective severity, frequency, or localization of seizures but was related to trauma history (40). A traumatic experience could induce more anticipatory anxiety, avoidance behavior, and ictal anxiety among patients with TES. We found that the TES group has experienced higher rates of peri-ictal psychiatric symptoms compared to the non-TES group. Possibly, having a TES could increase the seizure related anxiety and consequently the peri-ictal complications. However, we do not have a chronological data and therefore we could not demonstrate any causal links. Alternatively, general mood and anxiety disorders that were more frequent in TES patients could increase the likelihood of peri-ictal symptoms (41).

Chung and Allen (17) demonstrated that alexithymia was more common among patients with TES. Similarly, our results showed that one-third of TES patients had a diagnosis of alexithymia. Alexithymia might constitute a defense mechanism for these people to protect themselves from anxiety, fear, and negative emotions that a seizure could generate. Alexithymia was also associated with higher rates of affective disorders (42). Bewley et al. (41) suggested that alexithymia could be due to neurologic deficits induced by epilepsy, such as right cortical lesions, dysfunction of the right cerebral hemisphere, or frontal lobe dysfunction (43). Alexithymia was also described in link with trauma: perhaps people who have difficulties verbalizing their emotions could be more vulnerable in front of a danger or another perturbating situation.

Quality of Life

In our study, TES patients had a significantly lower score on the social functioning dimension of the QOLIE-31 and seemed more concerned about their seizures, which could explain the higher level of anticipatory anxiety. A decrease in social interactions might be the consequence of the traumatic experience of seizures, or that altered social interactions involve social isolation due to psychiatric disease (44). Alternatively, this social alteration could also be induced by trauma. Trauma creates a feeling of unsafety. Furthermore, TES patients have slightly more tendency to suffer from the side effects of antiepileptic drugs (45, 46).

Our results showed that TES was not significantly correlated with the type of seizure frequency, severity, or localization. However, we found that TES patients tended to have more frequent focal to bilateral tonic–clonic seizures and presented a higher incidence of fall during seizure. These could increase the severity of the seizures and therefore could be considered as important contributing factors for TES.

Moreover, there was a link between TES and duration of the disease. The time since onset of epilepsy was shorter in the TES group than in the non-TES group. Possibly, there was a memorization bias because TES was closer in time, so patients might remember them more precisely. It could also reflect a habituation phenomenon; people with a longer history of epilepsy would be more psychologically prepared for a seizure that is experienced as less traumatic than those whose onset is more recent. Alternatively, patients in the TES group might have an earlier consultation for their seizure because of their traumatic nature. An earlier management of the seizures might also explain this onset difference.

Furthermore, most of the patients examined herein had temporal epilepsy, which is related to the hippocampus. In some forms of focal epilepsy, as in temporal epilepsy, hippocampal sclerosis is present, which could also induce symptoms of trauma and PTSD by the mechanism that we described above. Further studies focusing on structural hippocampal and amygdala abnormalities in patients with TES could contribute to our current knowledge on TES pathophysiology.

This study has some limitations, such as a low number of included patients (107) and a small number for multidimensional analysis of PS-PTSD. Further studies are necessary to confirm these links in larger samples. Moreover, our study sample included only the patients with PRFE. Therefore, our findings are not representative of people with general idiopathic or drug responsive epilepsy. Our results must be interpreted with caution. The participants may have been affected by memorization bias. There could be some confounding factors between a TES vulnerability predisposition and its consequences. Conscious awareness during seizures is an important factor for traumatically experienced seizures. The memory of seizure might influence the stress related to it. In the current study, we did not evaluate the level of consciousness. Further studies should investigate the patient's consciousness during seizure. Moreover, we did not investigate precisely the seizure type (focal or focal to bilateral tonic–clonic seizures) causing TES among our patients.

Epileptic seizure could be experienced as traumatic in some patients with PRFE and even induce PTSD. These clinical entities should be explored systematically in clinical practice because its identification and treatment could improve the quality of life of patients with epilepsy. Some therapeutic methods, such as EMDR, cognitive–behavioral therapy, and hypnosis, could be interesting to explore. The neurobiological causes of the links between epilepsy and traumatic events unrelated to epilepsy should also be examined.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethical local comitee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

J-PV, CH, LM, and LT conceived of the presented idea and helped supervise the project and designed the study. SM and DV developed the theory and included patients and wrote the manuscript. AT included patients. WE-H and DE wrote the manuscript. JC and SS designed the model and the computational framework and analyzed the data. LM and RS devised the project. CH designed and directed the project. All authors contributed to the article and approved the submitted version.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.669411/full#supplementary-material

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Anxiety and Depression in Newly Diagnosed Epilepsy: A Matter of Psychological History?

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Purpose: Anxiety and depression are highly prevalent in patients with epilepsy (PWE), and these symptoms can even precede the onset of the pathology. We aimed to define the prevalence of anxiety and depressive symptoms at the time of the epilepsy diagnosis and the factors related to their presence in newly diagnosed adult patients.

Methods: One hundred and twelve newly diagnosed patients were assessed, usually in the week after diagnosis. Patients were untreated at this time. We used the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E, cut-off $\geq$15) and the Generalized Anxiety Disorder 7-Item scale (GAD-7, cut-off >7). A semi-structured interview was conducted to collect sociodemographic and epilepsy data and patients' psychiatric history. We first compared patients with and without anxiety symptoms, then patients with and without depressive symptoms.

Results: According to the GAD-7 scale, the prevalence of anxiety symptoms at the time of diagnosis was 35%. Patients with anxiety symptoms had significantly more psychiatric history (26%, $p = 0.001$) and more history of psychological trauma (51%, $p = 0.003$) than patients with no anxiety symptoms. According to the NDDI-E scores, the prevalence of depressive symptoms at the time of the diagnosis was 11%. Patients with depressive symptoms had significantly more psychiatric history (43%, $p < 0.001$) and more history of psychological trauma (65%, $p = 0.007$) than patients with no depressive symptoms. No difference between groups was found for other sociodemographic variables (age and gender), epilepsy characteristics (number of seizures prior to diagnosis, time from first seizure to diagnosis, type of epilepsy, and localization in focal epilepsy), or neurological comorbidities.

Conclusions: Anxiety symptoms are common whereas depressive symptoms are less prevalent at the time of diagnosis. It appears essential to be aware of anxiety and depression in newly diagnosed epileptic patients. They should be screened and routinely monitored, especially those patients with a history of psychological trauma and/or psychiatric disorders. Longitudinal follow-up is required to identify whether these factors and anxiety and depression themselves have an impact on the future course of care.

Keywords: epilepsy, newly diagnosed, anxiety, depression, new-onset

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INTRODUCTION

Epilepsy is a chronic multifactorial neurological disease encompassing psychological factors, as described in the International League Against Epilepsy (ILAE) definition: "epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition" (1). The ILAE definition highlights the relevance of considering the psychological dimension of epilepsy.

Patients with epilepsy (PWE) also have a higher risk of developing psychiatric comorbidities, which can affect one-third of patients (2). Compared with controls, PWE are more likely to suffer from depression, with a relative risk ranging from 1.43 (3) to 2.7 (4). The estimated prevalence of depression is around 23.1% and comorbid anxiety affects 20.2% of PWE (5, 6). These studies looked at all types of epilepsy combined (drug-resistant and drug-sensitive epilepsy), whereas the risk of experiencing psychiatric comorbidities is four times higher in drug-resistant epilepsy (7, 8). Conversely, people with mood and anxiety disorders have a seven-fold increase in the risk of developing epilepsy (9–13).

These data highlight a bidirectional correlation between epilepsy and mood/anxiety disorder (14). Psychiatric disorders in epilepsy have specific characteristics that clinicians need to consider at the time of assessment (6). Psychiatric symptoms are classified according to their temporal relationship to the seizures: periictal (chronologically linked with a seizure) or interictal symptoms (no chronological link with a seizure) (15). It is noteworthy that psychiatric disorders are associated with impaired quality of life (QoL) and increased frequency of seizures (16, 17). Consideration and assessment of psychiatric comorbidities is therefore essential. In this study, we propose to do this as early as possible in the history of epilepsy.

Anxiety and depressive disorders have been extensively studied in drug-resistant epileptic patients who often have longstanding epilepsy and still have seizures. This is a specific population, and the results cannot be extended to all PWE. There are fewer studies in drug-sensitive or newly diagnosed patients (18–21). We know that anxiety and depression can even precede the onset of the epilepsy (22): in a population of 3,773 PWE and 14,025 matched controls, the PWE were found to be more likely to have depression, notably during the 3 years preceding the diagnosis of epilepsy. There thus appears to be a clear bidirectional link between psychiatric comorbidities and epilepsy. Screening for anxiety and depression should therefore be conducted at an early stage.

Studies report a prevalence of anxiety ranging from 19 to 42.6% in newly diagnosed epilepsy (NDE) (18–21). The prevalence of depression varies from 11 to 44.7% in this population (18–21). There is therefore a wide disparity in prevalence between studies, which is surely related to the populations studied [NDE, new-onset epilepsy (NOE), and/or first seizure], the different tools used [mostly the Hospital Anxiety and Depression Scale (HADS) but also the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), and the Generalized Anxiety Disorder-7 (GAD-7) scale], and the cut-off points chosen [e.g., 14 for GAD-7 in the study by Lane et al. (19)].

To our knowledge, the factors related to anxiety and depression at the time of epilepsy diagnosis have not been extensively studied (18, 21).

Anti-epileptic drugs (AEDs) are well-known to induce psychiatric disorders in PWE (23–25). Up to 15% of patients can be expected to have psychiatric symptoms of iatrogenic origin (26). Antiepileptic drugs induce several types of psychiatric disorders, including anxiety, depression, irritability, hallucinations, and delusions. These symptoms vary in duration and occur from a few hours to several weeks after the introduction of treatment (15). This is a major confounding factor that is difficult to control in PWE studies. The opportunity to focus on newly diagnosed patients who are not currently taking AEDs is therefore novel and valuable.

We aimed to define the prevalence of anxiety and depression symptoms and their related factors in a sample of adult patients with NDE who were not being treated with AED.

MATERIALS AND METHODS

Study Design and Participants

This is an observational prospective monocentric study. Participants were recruited from Nancy Hospital Epilepsy Unit between June 2017 and March 2021. The study design was approved by the Regional Ethical Standards Committee on Human Experimentation (France, CPP no. 20.07.23.36832). Subjects were aged over 16 years and had NDE. Diagnosis and syndrome classification were based on clinical history and electroencephalogram findings according to the ILAE (27). Newly diagnosed epilepsy means that diagnosis is recent, but seizures may have gone unrecognized for over a year. We considered NDE to include NOE, which corresponds to the onset of seizures within the last year. Patients were excluded if they had experienced provoked seizures, had a history of drug/alcohol misuse, or had previously used AEDs. All patients gave their non-opposition for inclusion in this study.

Data Collected

Patients were assessed at the time of diagnosis (during the week after diagnosis) and were untreated at this time.

Demographic Data

Demographic data were collected by means of an interview, in which we gathered information on age, gender, and level of education.

Epilepsy Data

We collected classification of seizure type (focal with lateralization, or generalized), number of seizures prior to diagnosis, time between the first seizure and diagnosis, and lesions on MRI.

Neurological Data

We collected data on patient MRIs and neurological comorbidities (stroke, traumatic brain injury, etc.).

Psychiatric Data

Psychiatric data were obtained with particular focus on psychiatric history and treatment. A semi-structured interview was conducted, with questions addressing patients' history of depression, anxiety disorders, suicide attempts, use of anti-depressants, medication for anxiety and/or psychotherapy, and psychiatric hospitalization. We considered that there was a mentioned psychiatric history if the patient refers any one of these issues.

We also actively screened for traumatic events (natural disasters, accident, deliberate violence, abuse, harassment, sudden death, etc.).

Validated Scales in Epilepsy

We used the NDDI-E (28) and the GAD-7 (29) to investigate the presence of depressive and anxiety symptoms, respectively. The NDDI-E and the GAD-7 are both validated screening tools for such symptoms in epilepsy (29). We used cut-off scores of 15 for the NDDI-E and 7 for the GAD-7, forming our study groups according to these scales. Participants with an NDDI-E score of over 15 and a GAD-7 score of over 7 were included in the depressive symptoms group and the anxiety symptoms group, respectively.

Other Psychometric Scales

In addition, we used the State-Trait Anxiety Inventory (STAI) to measure patients' state and trait anxiety. A score of 35 or less is considered very low, 36–45 low, 46–55 medium, 56–65 high, and above 65, very high. For depression, we also used the Beck Short Form Depression Inventory (BDI). A score of 0–4 indicates no depression, 4–7 indicates mild depression, 8–15 indicates moderate depression, and 16 and above indicates severe depression.

Data Analyses

We compared demographic data, medical data, and psychiatric data according to the presence or absence of depressive or anxiety symptoms at the time of diagnosis. Sociodemographic and clinical data are displayed as mean, SD, and median (med) for numeric variables. For nominal variables, we used patient numbers or percentages. Differences in mean values were calculated using Student's *t*-test (after ensuring normality and equality of variance) or the Mann–Whitney *U*-test for independent samples. For nominal variables, we used the χ^2-test or Fisher's exact test. *P*-value $\leq$0.05 was considered significant. Data were analyzed using Jamovi 1.6.15.

RESULTS

Description of Cohort

One hundred and twelve patients were included. Seventy-six patients were enrolled prior to the worldwide COVID pandemic. As summarized in **Table 1**, 62 females and 50 males were included, with a mean age of 45.11 $\pm$ 21.38 years and a mean duration of education of 11.93 $\pm$ 2.47 years.

TABLE 1 | Sociodemographic and medical data (n = 112).

Gender (*n*, %)	
Male	50 (45%)
Female	62 (55%)
Age [mean (SD)]	45.11 (21.38)
Duration of education [mean (SD)]	11.93 (2.47)
Time between first seizure and diagnosis in months [mean (SD)]	19.14 (44.68)
Number of seizures before diagnosis [mean (SD)]	42.33 (208.95)
New-onset epilepsy (*n*, %)	76 (68%)
Newly diagnosed epilepsy (*n*, %)	36 (32%)
Type of epilepsy (*n*, %)	
Focal	87 (80%)
Generalized	22 (20%)
Lateralization of epilepsy in focal epilepsy (*n*, %)	
Left	40 (59%)
Right	28 (41%)
Neurological comorbidities (*n*, %)	
Yes	40 (36%)
No	82 (64%)
Lesions on MRI (*n*, %)	
Yes	38 (40%)
No	59 (60%)
Psychiatric history (*n*, %)	
Yes	13 (12%)
No	97 (88%)
Psychological trauma mentioned (*n*, %)	
Yes	35 (33%)
No	72 (67%)
Anxiety symptoms (*n*, %)	
GAD-7 >7	39 (35%)
State STAI $\geq$46	16 (16.5%)
Trait STAI $\geq$46	28 (29%)
Depressive symptoms (*n*, %)	
NDDI-E $\geq$15	14 (12.5%)
Short-form BDI $\geq$10	11 (11%)

Epileptic Data

Eighty percent of patients had focal epilepsy (41% right-sided and 76% temporal) and 68% had NOE. The mean time between first seizure and diagnosis was 19.14 $\pm$ 44.68 months, but the median was 6. The mean number of seizures before diagnosis was 42.33 $\pm$ 208.95, but the median was 3. The majority of patients had only focal seizures (68%). Generalized seizures were less frequent and most patients had <4 (mean of 1) except for two patients who had, respectively, 10 and 52 absence-type seizures before diagnosis.

Medical Data

Forty percent of patients had a lesion found on MRI (atrophy, vascular damage, cavernoma, dysplasia, cyst, polymicrogyria, etc.) and 36% of patients had a neurological comorbidity (stroke, traumatic brain injury, etc.).

Psychiatric Data

Twelve percent of patients had psychiatric history: nine had depression (two with a suicide attempt), one had experienced burn-out, one had a generalized anxiety disorder, one had an eating disorder, and one had post-traumatic stress disorder. Four of these patients are currently being treated with psychopharmacological treatments. No other patients in this study are being treated with this medication.

Thirty-three percent of patients mentioned a history of psychological trauma. Most (14 patients) cited interpersonal violence (domestic violence, harassment, stabbing, child abuse, etc.), the sudden death of a relative, or a serious illness leading to death (13 patients). Seven patients also cited accidents (car, train) and one cited a natural disaster (fire).

The prevalence of anxiety symptoms at the time of diagnosis was 35% according to the GAD-7 scale and was quite similar for patients included before and after the start of the COVID pandemic ($p = 0.913$). According to the STAI scale, state anxiety had a prevalence of 16.5% at the time of diagnosis and trait anxiety, 29%.

The prevalence of depression symptoms at the time of diagnosis was 12.5% according to the NDDI-E and was quite similar for patients included before and after the start of the COVID pandemic ($p = 0.375$). At the time of diagnosis, 11% of patients had symptoms of depression according to the short-form BDI.

Comparison of Groups According to Anxiety Symptoms

We compared patients with anxiety symptoms (defined by the GAD-7 score) ($n = 39$) and without ($n = 73$) such symptoms. The presence of psychiatric history (26 vs. 4%, $p = 0.001$) and at least one psychological trauma (51 vs. 23%, $p = 0.003$) was overrepresented in patients with anxiety symptoms (**Table 2**). We found no difference in other sociodemographic variables (age and gender) or in the characteristics of the epilepsy [number of seizures prior to diagnosis, time from first seizure to diagnosis, side ($p = 0.462$), and type of epilepsy].

Comparison of Groups According to Depressive Symptoms

We compared patients with depressive symptoms (as defined by their NDDI-E scores) ($n = 14$) and without ($n = 98$) such symptoms. The presence of a psychiatric history (43 vs. 7%, $p < 0.001$) and psychological trauma (64 vs. 28%, $p = 0.007$) was over-represented in patients with depressive symptoms (**Table 3**). We found no difference in other sociodemographic variables (age and gender) or in the characteristics of the epilepsy [number of seizures prior to diagnosis, time from first seizure to diagnosis, side ($p = 0.297$), and type of epilepsy].

Supplementary Data

Supplementary data provides results for patients with no neurological comorbidities (82 patients). This research will be extended to the study of cognitive aspects, for which the separation is important. There are no significant differences for this group between patients with or without anxiety symptoms. However, the presence of a psychiatric history ($p = 0.027$) and psychological trauma ($p = 0.035$) was still over-represented in patients with depressive symptoms.

DISCUSSION

The main findings of this study show that patients who have experienced psychological trauma or who have a psychiatric history are more likely to present anxiety and depressive symptoms at the time of diagnosis. It is important to emphasize that patients were not being treated with AED at the time of the assessment, to exclude AED-induced depression or anxiety.

Prevalence of Depressive and Anxiety Symptoms

In this study, we assess the prevalence of anxiety and depressive symptoms in NDE patients. The prevalence of such symptoms found in our sample at the time of diagnosis is consistent with previous studies in the same population (18–21). It is noteworthy that the percentage is close to that recorded in a study of patients with drug-resistant focal epilepsy (6). Jansen et al. found that 31% of patients had psychiatric disorders even before the onset of the epilepsy. It is therefore necessary to follow up our patients to determine whether patients with these mood disorders are more likely to become drug resistant.

Interestingly, there is a significant difference between the prevalence of anxiety and depressive symptoms in our sample, whereas in most other studies they are quite similar (18, 19, 21). In these studies, anxiety and depression were mainly assessed using the HADS (18, 21). Notably in the study by Lee et al. (18), anxiety and depression were assessed using the HADS and their prevalence was similar. With other tools, Lane et al. found a higher prevalence of depression symptoms (33%) with anxiety symptoms occurring less frequently (23%) (19). This study was based on patients who had experienced potentially epileptic events but who had not received a diagnosis of epilepsy. Although they used the GAD-7 and the NDDI-E, the cut-off used for the GAD-7 was 14, which may have influenced the scores recorded (19). Moreover, in this study, 30% of the patients had regularly taken psychoactive substances.

Our results therefore confirm the presence of anxiety and/or depressive symptoms at the onset of epilepsy, or even beforehand. The issue of precise time frame is really complex to address because patients have to retrieve their information retrospectively. Longitudinal follow-up will enlighten us on this issue.

Qualitatively, several close relatives of the patients in this sample were able to report changes in their partner or child (irritability, changes of mood such as melancholia) in the previous year, even though no particular event had occurred. The patients themselves were sometimes very confused by these changes, which they could not explain. They did not report a link with the seizure(s) they experienced, especially since such changes may have occurred before the seizure(s). As an example, one patient said that he had had regular mood swings without understanding the underlying reason within the last year, even

TABLE 2 | Sociodemographic and medical data according to the presence or absence of anxiety symptoms.

	Patients with anxiety symptoms ($n = 39$)	Patients without anxiety symptoms ($n = 73$)	p
Gender (*n*, %)			
Male	13 (33%)	37 (51%)	0.078[a]
Female	26 (67%)	36 (49%)	
Age [mean (SD)]	43.2 (19.71)	46.2 (22.28)	0.482[b]
(med)	41	46	
Duration of education [mean (SD)]	12 (2.54)	11.9 (2.44)	0.887[b]
(med)	12	11	
Time between first seizure and diagnosis in months [mean (SD)]	16.9 (23.59)	20.3 (52.53)	0.710[b]
(med)	6	6	
Number of seizures before diagnosis [mean (SD)]	97.6 (351.21)	13.9 (38.18)	0.903[c]
(med)	3	3	
New-onset epilepsy (*n*, %)	26 (67%)	50 (68.5%)	0.844[a]
Newly diagnosed epilepsy (*n*, %)	13 (33%)	23 (31.5%)	
Type of epilepsy (*n*, %)			
Focal	28 (78%)	59 (81%)	0.710[a]
Generalized	8 (22%)	14 (19%)	
Lateralization of epilepsy in focal epilepsy (*n*, %)			
Left	11 (48%)	29 (64%)	0.188[a]
Right	12 (52%)	16 (36%)	
Neurological comorbidities (*n*, %)			
Yes	14 (36%)	22 (30%)	0.534[a]
No	25 (64%)	51 (70%)	
Lesions on MRI (*n*, %)			
Yes	13 (38%)	25 (40%)	0.889[a]
No	21 (62%)	38 (60%)	
Psychiatric history (*n*, %)			
Yes	10 (26%)	3 (4%)	0.001*[d]
No	28 (74%)	69 (96%)	
Psychological trauma mentioned (*n*, %)			
Yes	19 (51%)	16 (23%)	0.003*[a]
No	18 (49%)	54 (77%)	

*$p < 0.05$; [a]*Chi-square test*; [b]*Student's t-test*; [c]*Mann-Whitney U-test*; [d]*Fisher's exact test.*

before the first seizure. There was no change in his everyday life. Mood swings in PWE, especially temporal lobe epilepsy, is a known disorder described by Blumer, so-called interictal dysphoric disorder (30).

Gender did not emerge significantly, although there is a tendency for patients with anxiety to be mainly female. This gender difference has been reported in the general population in anxiety and depressive disorders (31, 32) but not in PWE (33). Our results are therefore in line with those obtained previously in other studies. Unexpectedly, our result as regards gender did not achieve significance for depressive symptoms. This is inconsistent with studies on this topic, which suggest that women report more depressive symptoms than men in PWE (33). This result can be explained by the small number of patients with depressive symptoms ($n = 14$), which makes the statistical analyses less powerful. Further investigation with more patients is required. This finding could also imply that there is no gender-related difference at an initial stage of the disease and that this difference occurs as the disease progresses. This will be explored in the longitudinal follow-up of these patients.

Specificity of Patients With a History of Psychological Trauma and Psychiatric Disorders

In our sample, 33% of patients reported psychological trauma, which appeared to be related to the occurrence of anxiety and/or depressive symptoms at the time of diagnosis. The link between psychological trauma and psychiatric disorders is well-established (34). We also know that psychological trauma may influence epileptogenesis (35). For example, patients with post-traumatic stress disorder are 3.7 times more likely to

TABLE 3 | Sociodemographic and medical data according to the presence or absence of depressive symptoms.

	Patients with depressive symptoms (*n* = 14)	Patients without depressive symptoms (*n* = 98)	*p*
Gender (*n*, %)			
Male	4 (29%)	46 (47%)	0.256[d]
Female	10 (71%)	52 (53%)	
Age [mean (SD)]	39.9 (16.77)	45.9 (21.93)	0.328[b]
(med)	39	45.9	
Duration of education [mean (SD)]	12.6 (2.5)	11.8 (2.46)	0.249[b]
(med)	12	11	
Time between first seizure and diagnosis in months [mean (SD)]	23.4 (23.48)	18.5 (47.01)	0.708[b]
(med)	11.5	6	
Number of seizures before diagnosis [mean (SD)]	172.7 (551.51)	24.1 (86.13)	0.375[c]
(med)	3	3	
New-onset epilepsy (*n*, %)	7 (50%)	69 (70%)	0.126[a]
Newly diagnosed epilepsy (*n*, %)	7 (50%)	29 (30%)	
Type of epilepsy (*n*, %)			
Focal	11 (79%)	76 (80%)	0.901[d]
Generalized	3 (21%)	19 (20%)	
Lateralization of epilepsy in focal epilepsy (*n*, %)			
Left	4 (40%)	36 (62%)	0.297[d]
Right	6 (60%)	22 (38%)	
Neurological comorbidities (*n*, %)			
Yes	6 (43%)	30 (31%)	0.359[a]
No	8 (57%)	68 (69%)	
Lesions on MRI (*n*, %)			
Yes	7 (54%)	31 (37%)	0.244[a]
No	6 (46%)	53 (63%)	
Psychiatric history (*n*, %)			
Yes	6 (43%)	7 (7%)	<0.001[*a]
No	8 (57%)	89 (93%)	
Psychological trauma mentioned (*n*, %)			
Yes	9 (64%)	26 (28%)	0.007[*a]
No	5 (36%)	67 (72%)	

*$p < 0.05$; [a]*Chi-square test;* [b]*Student's t-test;* [c]*Mann-Whitney U-test;* [d]*Fisher's exact test.*

develop epilepsy than age- and gender-matched controls (36). Moreover, psychological trauma can influence the course of epilepsy and potentially its severity. For example, the rate of psychological trauma is higher in our previous study with focal drug-resistant epileptic patients (42.5%) (6). Seizure frequency is greater in children with epilepsy living in war zones than in those living in peaceful areas (37). Hence, screening for history of psychological trauma can be particularly relevant in patients at the onset of their epilepsy. Patients with a history of psychotrauma may also be at higher risk for depressive and/or anxious symptoms when a diagnosis of epilepsy is confirmed. Such an announcement can be perceived as a very stressful experience.

We also found that previous psychiatric comorbidity was implicated in the occurrence of anxiety and/or depressive symptoms in NDE. We assume that probably such symptoms may be a consequence of previous psychiatric disorders. We can surmise that these symptoms reflect the patient's psychiatric history (residual symptoms, active symptomatology, vulnerability induced by previous disorders). However, in patients with no mentioned psychiatric history but with anxiety and depressive symptoms, we cannot exclude that these symptoms are the potential expression of an underlying undiagnosed psychiatric disorder. The time frame and the recording of the free interval could not be obtained easily due to the memory bias of patients.

Evaluation and Information

Considering the high prevalence of anxiety and depressive symptoms compared with the normal population, routine screening as recommended by guidelines is essential (2, 38). There are a number of validated screening tools such as the GAD-7 and the NDDI-E (28, 29) that are suitable for PWE.

These scales are concise and easy to use, allowing for their adoption by all clinicians. They act as a mediator between the patient and the clinician, providing the patient with the opportunity to mention things that they would not have expressed spontaneously. It is equally important to provide patients and their relatives with information and to provide psycho-education right from the first consultation. This can help to eliminate any stigmas that may be developing and have an impact on these patients' psychiatric comorbidities (18). Furthermore, the information should be given routinely as psychiatric comorbidities in epilepsy patients influence QoL and seizure outcome (16, 17).

It is therefore crucial to assess this aspect, to follow up, in particular, those patients with psychiatric comorbidities and who have experienced psychological trauma, and to advise them of the considerable adverse impact that such comorbidities may have on the outcome of their epilepsy.

During the assessment, some patients mentioned having a fear of being judged because they have epilepsy. They also mention the fear of the consequences that this could have on their work, especially since they can no longer drive. The emergence of these fears at the time of diagnosis must be explored and followed up.

There is a clear issue of early identification and prompt treatment of psychiatric and psychological aspects (2).

LIMITATIONS

Our study has several limitations. The number of patients is small in some cases due to division into several groups for statistical analysis. A larger sample size will also lead to more powerful statistical analysis.

Moreover, the assessment was most often conducted within a week of diagnosis. Anxiety related to the diagnosis may still be very marked and may increase the prevalence of anxiety in our sample. We are aware that this epileptic pathology can have a negative connotation and carry stigma. This can lead to negative social relationships. In addition, epilepsy often implies a decrease of employability, or even to a driving prohibition. These things can cause major anxiety at the time of diagnosis. One advantage of this timing is that these patients were not yet on antiepileptic drugs when they were included. It also provided an opportunity for remote psychoeducation and allowed patients to ask any questions they had about epilepsy.

We did not have the exact duration between the start of a thymic disorder and the epilepsy because most of the patients cannot find the time period themselves.

In our study, we have not assessed particularly ictal anxiety (such as fear and agitation that have occasionally been reported in PWE as the only manifestation of focal seizures) (39). We are well-aware that it can be observed in focal epilepsies, especially in temporal epilepsy, but we decided to focus on interictal anxiety assessed by the GAD-7.

About a third of the patients were enrolled after the onset of the COVID pandemic, but this does not seem to have had an impact on the prevalence of depressive and anxiety symptoms.

PERSPECTIVES

Findings of psychiatric comorbidities at the time of diagnosis and even beforehand need to be recognized by neurologists when the epilepsy diagnosis is confirmed, as well as by psychiatrists who need to be aware that epilepsy may be preceded by symptoms of depression and anxiety. We focused on the prevalence of depressive and anxiety symptoms at the time of diagnosis, but it will be necessary to follow these patients over time and ascertain which factors are associated with their presence and especially their persistence over time. There are few long-term longitudinal studies and more are required to provide answers to these questions. These studies show that the prevalence of depression and anxiety decreases 1 year after diagnosis. Sociodemographic factors do not appear to be the best predictors of the persistence of these comorbidities; this role is fulfilled by psychiatric history and seizure frequency, however (18, 20, 21). Psychiatric history was mentioned in only one study in NDE, and it encourages us to question patients more thoroughly about psychological trauma and psychiatric history (20). We assume that patients who already have a psychiatric history are more mentally vulnerable. Indeed, once the patient is treated and recovers, he or she often achieves a healthy balance that allows him or her to return to a normal life. Epilepsy disrupts the state of mind they had previously achieved, making them more sensitive, and increasing the presence of depressive and anxiety symptoms. Longitudinal follow-up of these patients will help us to identify whether experiencing a traumatic event is a contributing factor to the development of drug-resistant epilepsy.

The decrease in the prevalence of anxiety disorders at 1 year after diagnosis described in the literature may highlight a normal process of anxiety in response to the diagnosis (18, 21). These studies used HADS to assess depression and anxiety. It would be interesting to analyze in more detail the specificity of our screening tools for the NDE population in particular.

This evidence of the possible presence of anxiety/mood disorders in NDE should be recorded by all clinicians working with this population and especially by neuropsychologists. Indeed, as cognitive assessment of NDE patients is increasingly frequent, these psychiatric aspects need to be considered, especially as we know that they can have an impact on cognitive performance [see Forthoffer et al. for a brief review (40)].

CONCLUSION

Anxiety symptoms are common whereas depressive symptoms are less prevalent at the time of diagnosis. Patients with psychological trauma or with a psychiatric history are more likely to present anxiety and depressive symptoms at the time of diagnosis. The number of seizures prior to diagnosis and the type of epilepsy appeared to be unrelated to depressive and anxiety symptoms. It seems essential to be aware of anxiety and depression in NDE patients. They should be screened and need to be routinely monitored, especially those patients who have experienced psychological trauma and/or who have a psychiatric history. Longitudinal follow-up is required to identify whether

these factors and anxiety and depression themselves have an impact on the future course of care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité de Protection des Personnes Sud-Est IV no. 20.07.23.36832. Written informed consent to participate in this study was provided by the participants' legal guardian/ next of kin.

AUTHOR CONTRIBUTIONS

NF: helped in initiating and designing the study, drafting the paper, and deciding on the analytical strategy. AT: provided a critical review of the draft. HB: provided a critical review of the draft. LM: provided a critical review of the draft. CH: assisted with data management and drafting the paper. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.744377/full#supplementary-material

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Investigation of Anxiety, Depression, Sleep, and Family Function in Caregivers of Children With Epilepsy

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Objective: Epilepsy is a chronic disease that places a heavy burden on caregivers. Previous studies have shown that caregivers of epilepsy patients often experience anxiety and depression; however, few comprehensive studies have assessed their sleep quality and family function. Based on the current understanding of the anxiety and depression state of caregivers in children with epilepsy, we further explored the caregivers' sleep and family function and evaluated the predictors of the depression state of caregivers.

Methods: In this cross-sectional online anonymous survey, we sent an online questionnaire to the caregivers of children with epilepsy who visited our hospital. The QR code of the questionnaire was scanned at the follow-up course to conduct an online survey. The questionnaire contained questions about sociodemographic and clinical information, the Self-rating Anxiety Scale, Self-rating Depression Scale, Pittsburgh Sleep Quality Index, and the Family Assessment Device.

Results: A total of 308 caregivers of children with epilepsy aged 0–12 years were included in this study. The mean age of children with epilepsy was 4.8 ± 3.18 years, and the average illness duration was 34.2 ± 29.18 months. Further, 47.1% of the children took three or more anti-seizure medications, and 43.2% were on ketogenic diet therapy. We found that in 77.9% of the cases, the subjects were the mothers, in 89% there was more than one co-caregiver, and in 51.9%, financial help was required. Further, 63.6% of the caregivers thought they could not get enough access to disease knowledge education, and 83.7% perceived epilepsy was a terrible disease. Our results also showed that 65.6% of the caregivers were in depression status, 41.9% were in anxiety status, and 49.0% had poor sleep quality. The proportion of unhealthy family functioning in each subscale was 45.1–96.1%, and the unhealthy behavior control function accounted for 96.1%. Binary logistic regression analysis of the data showed that without co-caregivers [odds ratio (OR), 5.193], free of anxiety status (OR, 0.063), good sleep quality (OR, 0.446), healthy family role dimension (OR, 0.344), and healthy family general functional dimension (OR, 0.259) were predictors of depression status in caregivers of children with epilepsy.

Conclusion: Anxiety and depression status are common in caregivers of children with epilepsy, with depression status being more prominent. Moreover, a considerable proportion of caregivers had poor sleep quality and unhealthy family function. The caregivers' anxiety status, sleep quality, family role dimension, family general function dimension, and the number of co-caregivers were predictors of depression status in caregivers. In clinical practice, caregivers' anxiety and depression status, poor sleep quality, and unhealthy family functioning should be addressed along with the treatment of children with epilepsy.

Keywords: children with epilepsy, caregiver, depression, anxiety, sleep, family function

INTRODUCTION

Epilepsy is a common chronic neurological disorder in children, with a prevalence of 3.2–5.5‰ in developed countries, 3.9–44‰ in developing countries (1), and 3.9–5.1‰ in China (2). Epilepsy in children is often associated with developmental abnormalities in the brain, leading to the impaired motor, perceptual, and cognitive development (3, 4). As children develop physically and psychologically, sick children often develop psychobehavioral abnormalities, such as attention-deficit/hyperactivity disorder, autism, and mood disorders that affect the child's education, future work, and marital status (5). In addition to comprehensive care for the child, caregivers of children with epilepsy also need to deal with developmental problems, educational and marital problems, and the stigma caused by the disease (6). It has been shown that most parents of children with epilepsy have negative perceptions of others' reactions (53.3%). They often experienced a sense of shame, self-blame, fear, anxiety, and depression. Parents often feared divulging their child's epilepsy to their friends and relatives. And they also limit family's social interaction, which also increased their parenting pressure (7).

Anxiety and depression are common among caregivers of children with epilepsy, and previous studies reported proportion of depressive symptoms ranging 21.6–34.9%, anxiety status in 14.5% of caregivers, and poor sleep quality in 37.6% of caregivers (8–11). A study that evaluated the impact of severe pediatric epilepsy on experienced stress and psychopathology in parents in Denmark showed that among 152 respondents, the incidence of depression was 34.9%, of which 15.8% had severe depressive symptoms and 19% had moderate depressive symptoms; 14.5% of the parents were in a state of anxiety (8).

In China, a survey conducted by Peking Union Medical College Hospital in 2009 showed that compared with the healthy control group, parents of children with epilepsy had more severe anxiety and depression, which were related to low quality of life (9). A recent study in Hunan Province, China, assessed the sleep quality, anxiety, and depression of 234 parents of children with epilepsy and 230 parents of healthy children; 23.51% of the parents of children with epilepsy had depressive symptoms. The symptoms of anxiety and depression were more severe than those of healthy children, and sleep quality was worse (10). A study in Shandong Province, China, also showed that 21.6% of the parents of children with epilepsy had moderate to severe depressive symptoms, and 37.6% had poor sleep quality (11).

As mentioned previously, epilepsy caregivers often suffered from anxiety, depression, and poor sleep quality. Studies suggested that seizures' frequency, severity, and unpredictability compose of epilepsy burden on families (12). The main influencing factors of caregivers' stress are the child's emotional–behavioral problems and social difficulties, caregivers' control over their own situation, social support (8), and family resilience (11).

Based on an investigation of the anxiety and depression status of caregivers in children with epilepsy, this study further explored caregivers' sleep quality and family function and evaluated the predictors of depression status in caregivers. It was the first time to evaluate the caregiver's psychological status comprehensively from different dimensions. Then, we could take more accurate and targeted measures to help caregivers adjust their own state in order to improve caregivers' ability of raising children with epilepsy. This study assumed that abnormal emotion was common in epileptic caregivers, highly related to the disease state of epileptic children, caregivers' own condition, and family support.

MATERIALS AND METHODS

This was a cross-sectional anonymous web-based study from April 2021 to May 2021. The recruitment was performed using convenience sampling. The invitation links to online questionnaires were sent via the medical record follow-up system. Caregivers of children with epilepsy at the hospital also could complete the questionnaire online by scanning the QR code of the questionnaire directly.

Participants

Inclusion criteria were as follows: caregivers of children with epilepsy aged 0–12 years, children with a diagnosis of epilepsy certified by neurologists, and were treated in the Epilepsy Center of Shenzhen Children's Hospital, and caregivers who agreed to cooperate with online surveys.

Caregivers who refused or were unable to provide consent or were illiterate or unable to read and fill in the questionnaire were excluded. Children with epilepsy coexisting with other chronic diseases (i.e., heart disease, tumors, leukemia, congenital heart disease, diabetes), which could affect the family function and mental states of caregivers, were excluded from this study.

A total of 308 caregivers were enrolled in the study, including 65 fathers and 240 mothers, and 308 children were involved. The average age of children with epilepsy was 4.8 ± 3.18 years, with the proportions of the age groups 0–3, 3–6, and 6–12 years being almost the same, with boys and non–only children being more common.

Instrument

General Information

A self-made questionnaire was used to collect sociodemographic and clinical information such as disease status of children with epilepsy, employment status of caregivers, family income, caregivers' view of the disease, ability to pay for the disease, and so on.

Self-Rating Depression Scale

It is a 20-item scale to evaluate the presence and degree of the status of depression in adults within the past week. Each of the 20 items is given a severity score from 1 (none or a little of the time) to 4 (most of or all the time), but 10 items need to be scored in reverse. The raw scores obtained on the 20 items range from 20 to 80, and the standard score is converted to a whole number that ranges from 25 to 100. As the score rises, the severity of depression increases (13). The scale has been widely used in diagnostic evaluation, curative effect evaluation, and epidemiological investigation since it was introduced to China in 1985. In the Chinese norm, depression status is considered when the standard score was more than 53 within the past week (14).

Self-Rating Anxiety Scale

Similarly to Self-rating Depression Scale, the Self-rating Anxiety Scale (SAS) is a 20-item scale to evaluate the presence and degree of anxiety status in adults within the past week. Each of the 20 items is given a severity score from 1 (none or a little of the time) to 4 (most or all of the time), and 5 items need to be scored in reverse. The raw score obtained on the 20 items ranges from 20 to 80, and the standard score is converted to a whole number that ranges from 25 to 100. As the score rises, the severity of anxiety increases (13). A standard score of more than 50 (Chinese norm) in SAS is considered as anxiety status (14).

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month time interval. Eighteen self-assessment items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score. Each component score ranges from 0 to 3, and the global score ranges from 0 to 21. The higher the score, the worse the sleep quality (15). Xianchen et al. had proved the applicability of the Chinese version in 1996. This scale is widely used to evaluate sleep quality in clinical practice and research. The cutoff scores of the poor sleep quality is 7 in the Chinese norm (16).

The Family Assessment Device

The Family Assessment Device (FAD) is a 60-item questionnaire based on the McMaster model, which measures family functioning. FAD includes seven dimensions: problem solving, communication, roles, affective responsiveness, affective involvement, behavior control, and general functioning. Higher scores indicate worse family functioning. Clinical cutoff scores were used to distinguish between healthy and unhealthy family functioning on each dimension. The cutoff scores of problem solving, communication, roles, affective responsiveness, affective involvement, behavior control, and general functioning were 2.2, 2.2, 2.3, 2.2, 2.1, 1.9, and 2.0. The Chinese cutoff score of FAD has not yet been established. Cutoff scores above were used in this study to differentiate healthy and unhealthy family functioning on each dimension (14).

Statistical Analysis

Statistical analysis using IBM SPSS Statistics software (version 23.0) was performed with a significance level defined at 0.05. All demographic data were analyzed descriptively, with nominal data presented as frequencies and percentages and continuous data presented as means and standard variations [mean ± standard deviation (SD)].

First, the data were extracted and transferred to standard data from the detailed interview in the first part of the questionnaire. Descriptive statistics were applied to analyze the sociodemographic and clinical information of children with epilepsy and caregivers, mood, sleep, and family function of caregivers. The means, SDs, and frequencies were calculated. Second, the caregivers of children with epilepsy were divided into two groups according to whether they had depression status or not. The proportion of each group in variables was tested by the χ^2 test. Third, based on the result of the previous χ^2 test, variables with significant differences were selected. Logistic regression analysis was carried out to identify the factors that predicted depression status in caregivers of children with epilepsy.

Ethics Approval

The study was approved by the Shenzhen Children Hospital Ethics Committee (ethics approval no.: 2021079).

RESULTS

Sociodemographic and Clinical Information of Epileptic Children and Caregivers

Demographic and Disease Information of Children With Epilepsy

The average age of the children was 4.8 ± 3.18 years, and the average disease duration was 34.2 ± 29.18 months, 47.1% of the children were taking three or more anti-seizure medications, 84.1% could strictly comply with the medical prescription, and 21.1% of the children still had seizures every day. In addition to drug therapy, the proportion of ketogenic diet therapy accounted for 43.2%; 64.9% of the children suffered

from comorbid global developmental delay/mental retardation (**Supplementary Table 1**).

Demographic Information of Caregivers of Children With Epilepsy

Of the caregivers of children with epilepsy, 77.9% were mothers, 89% had co-caregivers, and 51.9% wanted financial help; 84.4% of caregivers were satisfied with the physician's explanation of the disease and treatment, but 63.6% felt that they did not have adequate access to education about the disease; 83.7% of the caregivers considered epilepsy to be a terrible disease, but 60.1% were confident in the future of the child, such as control of the disease and living a normal life (**Supplementary Table 1**).

Anxiety, Depression Status, Sleep Quality, and Family Functioning of Caregivers in Children With Epilepsy

The average scores of anxiety and depression status and the proportion of abnormal status caregivers of children with epilepsy were high.

Depression status accounted for 65.6% of all caregivers, and anxiety status accounted for 41.9%; 49.0% of the caregivers had poor sleep quality. The scores of family functioning of seven dimensions were from 2.2 to 2.6. The percentage of unhealthy family functioning dimension was from 45.1 to 96.1%, of which the unhealthy behavior control dimension was the highest (96.1%) (**Table 1**).

The Related Factors of Depression in Caregivers of Children With Epilepsy

Caregivers of children with epilepsy were divided into two groups according to whether they had a depression status or not, and the results were compared between groups (χ^2 test).

Compared with the non-depression status group, significant differences existed in the following aspects in the depression group: taken anti-seizure medications, ketogenic diet, frequency of seizures, reduced frequency of seizures, and comorbidities of global developmental delay/intellectual disability in their children with epilepsy ($p < 0.05$). The employment status of caregivers, number of co-caregivers, monthly income of families, ability to pay for treatment of epilepsy, attitude toward epilepsy, promising attitude toward the children's future, and desired kinds of assistance were also significantly different between the two groups ($p < 0.05$) (**Tables 2**, **3**).

In the depression status group, proportions of anxiety status, poor sleep quality, unhealthy family functioning dimensions of problem solving, communication, roles, affective involvement, and general function were significantly higher ($p < 0.05$) (**Table 4**).

TABLE 1 | Anxiety and depression status, sleep quality and family functioning of caregivers ($n = 308$).

	Mean ± SD	No. of caregivers abnormal status, *n* (%)
SDS standard score	57.5 ± 11.78	202 (65.6)
SAS standard score	48.8 ± 11.27	129 (41.9)
PSQ global score	7.7 ± 3.70	151 (49.0)
FAD: roles	2.53 ± 0.399	222 (72.1)
FAD: communication	2.46 ± 0.399	206 (66.9)
FAD: behavior control	2.45 ± 0.399	296 (96.1)
FAD: problem solving	2.24 ± 0.571	139 (45.1)
FAD: affective responsiveness	2.61 ± 0.476	239 (77.6)
FAD: affective involvement	2.48 ± 0.430	232 (75.3)
FAD: general function	2.37 ± 0.486	244 (79.2)

SDS, Self-rating Depression Scale; SAS, Self-rating Anxiety Scale; PSQI, Pittsburgh Sleep Quality Index; FAD, Family Assessment Device.

Predictive Factors of Depression Status in Caregivers of Children With Epilepsy (Logistic Regression Analysis)

Factors with significant differences in the comparison of the presence and absence of depression status were included in a binary logistic regression analysis. In the full model containing all predictors: $\chi^2 = 1.574$, $p = 0.991 > 0.05$, the model correctly classified 85.7% of cases. Without co-caregivers [odds ratio (OR), 5.193], free of anxiety status (OR, 0.063), good sleep quality (OR, 0.446), healthy family role function (OR, 0.344), and healthy family general function (OR, 0.259) were predictors of depression status in caregivers of children with epilepsy (**Table 5**).

DISCUSSION

This study found that anxiety and depression status were common among caregivers of children with epilepsy, with depression status being more prominent. In addition, a considerable proportion of caregivers had poor sleep quality and unhealthy family function. Caregivers' anxiety status, sleep quality, family role dimension, general family function dimension, and the number of co-caregivers were predictors of depression status in caregivers.

It is evident that we included children with epilepsy with more complex conditions. Among the children with epilepsy included in this study, 47.1% took more than three drugs, and 84.1% could strictly abide by the doctor's advice, but 21.1% still had seizures every day. In addition to drug therapy, ketogenic diet therapy was administered to 43.2% of the children; 64.9% suffered from global developmental delay/intellectual disability, probably because our hospital is a national tertiary care epilepsy center (in China, epilepsy centers are classified into levels 1, 2, and 3; level 3 is the most advanced), and children with long-term follow-up visits have more complex situations, and maybe also because caregivers of children with drug-resistant epilepsy visited the hospital frequently and were more willing to participate in the survey.

In this study, the caregivers of children with epilepsy were predominantly mothers, most had co-caregivers, and approximately half of the caregivers wanted financial help. The majority of caregivers were satisfied with the physician's explanation of the disease and treatment, but 63.6% felt that they

TABLE 2 | Comparison between caregivers without depression status and those with depression status ($n = 308$) (Pearson χ^2 test) (the general information of caregivers included).

	No-depression status group, *n* (%)	Depression status group, *n* (%)	χ^2	*p*
Relationship			2.597	0.273
Father	26 (24.5)	39 (75.5)		
Mother	80 (19.3)	160 (79.2)		
Employment			7.037	0.030
Full-time work	49 (46.2)	68 (33.7)		
Part-time work	21 (19.8)	34 (16.8)		
Unemployment	36 (34.0)	100 (49.5)		
No. of co-caregivers			16.628	< 0.001
0	3 (2.8)	31 (15.3)		
1	40 (37.7)	91 (45.0)		
≥2	63 (59.4)	80 (39.6)		
Educational			1.154	0.764
Junior degree or below	34 (32.1)	69 (34.2)		
High school degree	32 (30.2)	68 (33.7)		
Bachelor's degree	36 (34.0)	60 (29.7)		
Master's degree or above	4 (3.8)	5 (2.5)		
Total income per month (yuan)			18.015	< 0.001
≤5,000	48 (45.3)	109 (54.0)		
5,000–10,000	32 (30.2)	78 (38.6)		
10,000–20,000	15 (14.2)	10 (5.0)		
≥20,000	11 (10.4)	5 (2.5)		
Medical expenses payment			18.889	< 0.001
Able to cover	63 (59.4)	68 (33.7)		
Unable to cover	43 (40.6)	134 (66.3)		
Is epilepsy terrible?			17.436	< 0.001
Yes	81 (76.4)	188 (93.1)		
No	25 (23.6)	14 (6.9)		
Promising attitude toward the child future?			12.316	< 0.001
Yes	78 (73.6)	107 (53.0)		
No	28 (26.4)	95 (47.0)		
Needed assistance			14.721	0.002
Economic	40 (37.7)	120 (59.4)		
Education for children	37 (34.9)	43 (21.3)		
Knowledge for the epilepsy	23 (21.7)	26 (12.9)		
Other	6 (5.7)	13 (6.4)		

did not have adequate access to education about the disease; 83.7% of the caregivers considered epilepsy to be a terrible disease, but 60.1% were confident in the future of the child, such as control of disease and living a normal life. As in previous studies, most caregivers were mothers, with a high proportion caring for their children full-time (8). In addition, caregivers of children with epilepsy in this study felt that access to education about the disease was inadequate, which is also consistent with the results of previous studies. Studies conducted in Greece and the United Kingdom showed that caregivers were satisfied with the initial information received from doctors or hospitals about seizures and treatment. However, caregivers often had difficulty to get expertise about epilepsy and needed more access to available social resources and emotional support (17, 18). Parents of children with epilepsy, in Malaysia, also reported a need for epilepsy-related information, ongoing care, and parental support groups (19). The results suggested that we should develop multiple approaches to educate caregivers about epilepsy and help them to seek more social resources, such as community lectures on epilepsy-related disorders and help from social workers or welfare funds.

The mean scores and the proportion of abnormal states were higher among caregivers of children with epilepsy in this study. Depression status accounted for 65.6% of the caregivers, 41.9% of caregivers having anxiety status, and 49.0% having poor sleep quality. The prevalence of depression status in caregivers was much higher than the positive rate of 3.84% for depression in the medical examination population in Shenzhen, China (20). It was also higher than the point prevalence of 3.6% of depression disorders in China's mental health survey (21). The prevalence

TABLE 3 | Comparison between caregivers without depression status and those with depression status ($n = 308$) (Pearson χ^2 test) (the disease information of children with epilepsy included).

	No-depression status group, *n* (%)	Depression status group, *n* (%)	χ^2	*p*
No. of anti-seizure medications			18.680	< 0.001
0	4 (3.8)	3 (1.5)		
1	41 (38.7)	43 (21.3)		
2	28 (26.4)	44 (21.8)		
≥3	33 (31.1)	112 (55.4)		
Seizure frequency			17.800	0.001
Everyday	11 (10.4)	54 (26.7)		
Every week	5 (4.7)	13 (6.4)		
Every month	15 (14.2)	38 (18.8)		
Every year	27 (25.5)	43 (21.3)		
Seizure-free	48 (45.3)	54 (26.7)		
Ketogenic diet treatment			6.804	0.009
Yes	35 (33.0)	98 (48.5)		
No	71 (67.0)	104 (51.5)		
Reduction in the frequency of seizures			13.012	0.005
Total	45 (42.5)	47 (23.3)		
90–99%	18 (17.0)	37 (18.3)		
50–90%	19 (17.9)	48 (23.8)		
<50%	24 (22.6)	70 (34.7)		
With global developmental delay/intellectual disability			9.808	0.002
Yes	56 (53.3)	144 (71.3)		
No	49 (46.7)	58 (28.7)		
With autism spectrum disorder			0.200	0.655
Yes	5 (4.7)	12 (5.9)		
No	101 (95.3)	190 (94.1)		

of anxiety status in caregivers was also much higher than the point prevalence of 5.0% of anxiety disorders in China's mental health survey (21). Our results generally coincide with previous studies that reported proportion of depressive symptoms ranging from 21.6 to 34.9%, anxiety status in 14.5% of caregivers, and poor sleep quality in 37.6% of caregivers (8, 9, 11, 22). There was a higher proportion of depression status, anxiety status, and poorer sleep quality among caregivers in our study. The results might be related to the fact that the caregivers we included were caring for children with drug-resistant epilepsy and that a higher proportion of primary caregivers were mothers. Studies had shown that mothers of children with epilepsy have more anxiety and depression than fathers, mainly related to the frequency and duration of the children's seizures (22).

This study also found that the proportion of unhealthy family functioning of caregivers of children with epilepsy ranged from 45.1 to 96.1%, and the highest of which was the behavioral control function (96.1%). The primary function of the family is to provide specific environmental conditions for the healthy development of the physical, psychological, and social aspects of family members. The failure of the family to achieve its essential functions can easily lead to various problems in family members (23). This study suggested that unhealthy family functioning was common in the families of children with complex epilepsy, and the caregivers needed help at the family level.

There were significant differences in the aspects of the severity of epilepsy, the attitude toward epilepsy, the number of co-caregivers, the employment of the caregivers, and so on, when they were divided into groups according to whether they had a depression status or not. There were also significant differences in anxiety status, poor sleep quality, and unhealthy family function in the depression status group. Based on the results above, binary logistic regression analysis showed that anxiety status, poor sleep quality, unhealthy family role function, and unhealthy family general family function increased the prevalence of caregiver depression status. The presence of co-caregivers (≥1) decreased the incidence of caregiver depression status.

Our results showed that the severity of the children's disease was not a predictor of caregivers' depression status. Previous studies had shown that the frequency, severity, and unpredictability of seizures brought a burden on families (12). The degree of anxiety and depression of the child's mother was mainly related to the frequency and duration of the child's seizures (24). This difference might result from that our subjects were caregivers of childhood epilepsy and the high proportion of children with drug-resistant epilepsy. On this basis, group comparisons were made based on the presence or absence of depression status in the caregivers, and then the predictors of caregiver depression were analyzed, resulting in a finding that

TABLE 4 | Comparison between caregivers without depression status and those with depression status ($n = 308$) (Pearson χ^2) (the consequences of scales included).

	No-depression status group, *n* (%)	Depression status group, *n* (%)	χ^2	*p*
Anxiety status			78.282	< 0.001
Anxiety status	8 (7.5)	121 (59.9)		
Free of anxiety status	98 (92.5)	81 (40.1)		
Sleep quality			45.022	< 0.001
Poor sleep quality	24 (22.6)	127 (62.9)		
Good sleep quality	82 (77.4)	75 (37.1)		
Family functioning of				
Problem solving			18.483	< 0.001
Healthy	76 (71.7)	93 (46.0)		
Unhealthy	30 (28.3)	109 (54.0)		
Communication			20.799	< 0.001
Health	53 (50.0)	49 (24.3)		
Unhealthy	53 (50.0)	153 (75.7)		
Roles			35.871	< 0.001
Healthy	52 (49.1)	34 (16.8)		
Unhealthy	54 (50.9)	168 (83.2)		
Affective responsiveness			14.534	< 0.001
Healthy	37 (34.9)	32 (15.8)		
Unhealthy	69 (65.1)	170 (84.2)		
Affective involvement			6.053	0.014
Healthy	35 (33.0)	41 (20.3)		
Unhealthy	71 (67.0)	161 (79.7)		
Behavior control			3.165	0.075
Healthy	7 (6.6)	5 (2.5)		
Unhealthy	99 (93.4)	197 (97.5)		
General function			31.459	< 0.001
Healthy	41 (38.7)	23 (11.4)		
Unhealthy	65 (61.3)	179 (88.6)		

FAD, Family Assessment Device; PSQI, Pittsburgh Sleep Quality Index; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale.

TABLE 5 | Predictors of depression status in caregivers (logistic regression analysis).

	B	SE	Wald	*df*	*p*	Exp (*B*)	95% CI	
							Lower	Upper
Without co-caregivers	1.647	0.837	3.872	1	0.049	5.193	1.006	26.794
1 co-caregiver	0.159	0.429	0.137	1	0.711	1.172	0.505	2.720
Adverse effect of drugs			8.631	3	0.035			
Ever	−0.205	1.442	0.020	1	0.887	0.814	0.048	13.751
Suffering	0.702	1.486	0.223	1	0.637	2.017	0.110	37.109
Never	−0.859	1.468	0.343	1	0.558	0.423	0.024	7.516
Free of anxiety status	−2.760	0.508	29.517	1	<0.001	0.063	0.023	0.171
Good sleep quality	−0.807	0.403	4.008	1	0.045	0.446	0.203	0.983
Healthy family functioning: roles	−1.068	0.447	5.718	1	0.017	0.344	0.143	0.825
Healthy family functioning: general function	−1.350	0.610	4.902	1	0.027	0.259	0.079	0.857
Constant	3.328	2.183	2.324	1	0.127	27.889		

the child's illness was not significant in predicting the caregiver's depression status.

A Danish study investigating the mental status and stress levels of parents of children with severe epilepsy showed that the increased caregiver stress was associated with the younger age of the child, a higher level of the child's difficulties such as emotional and behavioral problems, and social difficulties. Seizure type, seizure frequency, epilepsy category, and age at seizure onset were not significantly associated with the level of the caregiver's stress. Caregivers' social support and the experience of having control over life circumstances were associated with a lower level of caregivers' stress. When all related variables were analyzed by standard multiple regression analysis, only the child's difficulties, caregivers' control of their own situation, and social support were significant predictors of caregivers' stress level (8). Another study in Qilu Hospital of Shandong University in China also showed that family resilience explained 3.5 and 14.9% of sleep quality and depression. The better the family resilience, the better the quality of sleep and the less the depression among caregivers. Interventions to improve family resilience may enhance sleep quality, reduce depression, and improve family parenting of children with epilepsy (11).

Similarly, this study also suggested that caregivers' own status and family functioning were predictors of the caregiver's depression status. And this is the first time to investigate family function among caregivers of childhood epilepsy in China. As shown in the study, the clinical staff should help caregivers to identify their family problems and assist them to improve the family function.

Although we tried our best to expand our sample size, this was a single-center study. In addition, this study used a web-based questionnaire, which was completed by the respondents individually. Some participants could not obtain timely instructions on how to fill out the questionnaire, and some information was not filled out in a standard manner, which might affect the accuracy of some responses. Therefore, we chose the widely used self-assessment scales to minimize bias.

CONCLUSION

Anxiety and depression were prevalent among caregivers of children with epilepsy, with depression status being more prominent. In addition, a significant proportion of caregivers had poor sleep quality and unhealthy family functioning. The caregiver's own anxiety status and sleep quality, family role function and general function, and the number of co-caregivers were predictors of caregiver depression status. In clinical practice, the above situation should be addressed alongside the treatment of children with epilepsy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Shenzhen Children's Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MeZ conceived of the analysis. HZ, MaZ, YF, SH, and JH contributed to the data collection and analysis. MeZ and HZ wrote the first draft of the manuscript. JL provided critical feedback on the first draft. MeZ, HZ, and JL managed the production process. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.744017/full#supplementary-material

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Mood Disturbances, Anxiety, and Impact on Quality of Life in Patients Admitted to Epilepsy Monitoring Units

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Introduction: The overall combined prevalence of anxiety and depression in patients with epilepsy has been estimated at 20.2 and 22.9%, respectively, and is considered more severe in drug-refractory epilepsy. Patients admitted to epilepsy monitoring units constitute a particular group. Also, patients with psychogenic non-epileptic seizures can reach more than 20% of all admissions. This study aims to characterize these symptoms in a large cohort of patients admitted for evaluation in a tertiary epilepsy center.

Materials and Methods: The study was conducted among 493 consecutive patients (age: 38.78 ± 12.7, 57% females) admitted for long-term video EEG from January 2013 to February 2021. Demographic, clinical, and mood disorder patients' data were collected. Anxiety and depression symptoms were assessed through the Hospital Anxiety Depression Scale (HADS-A and HADS-D), the State Trait Anxiety Inventory (STAI), and Beck Depression Inventory (BDI-II). Quality of life was determined using the QOLIE-10. Patients were divided into three groups: patients with epilepsy ($n = 395$), psychogenic non-epileptic seizures (PNES) ($n = 56$), and combined ($n = 33$). A univariate and multivariate regression analysis was performed for variables associated with quality of life.

Results: Of 493 patients, 45.0% had structural etiology, and considering epilepsy classification, 43.6% were of temporal lobe origin. In addition, 32.45% of patients had a previous psychiatric history, 49.9% of patients had depressive symptoms in BDI, and 30.9% according to HADS-D; 56.42 and 52.63% of patients presented pathological anxiety scores in STAI-T and STAI-S, respectively; and 44.78% according to HADS-A. PNES and combined groups revealed a higher incidence of pathologic BDI scores (64.29 and 78.79%, $p < 0.001$) as well as pathologic HADS-A scores ($p = 0.001$). Anxiety and depression pathologic results are more prevalent in females, HADS-A (females = 50.7%, males = 36.8%; $p = 0.0027$) and BDI > 13 (females = 56.6%, males = 41.0%; $p = 0.0006$). QOLIE-10 showed that 71% of the patients had their quality of life affected with significantly higher scores in the combined group than in the epilepsy and PNES groups ($p = 0.0015$).

Conclusions: Subjective anxiety, depression, and reduced quality of life are highly prevalent in patients with refractory epilepsy. These symptoms are more evident when PNES are associated with epilepsy and more severe among female patients. Most of the cases were not previously diagnosed. These factors should be considered in everyday clinical practice, and specific approaches might be adapted depending on the patient's profile.

Keywords: epilepsy, anxiety, depression, quality of life, epilepsy monitoring unit

INTRODUCTION

Anxiety and depression are frequent among patients with epilepsy (PWE) and constitute one of the most important comorbidities (1). Moreover, psychiatric disorders represent one of the principal modulating factors of the quality of life in PWE acting independently even of the seizure control itself (2). There is an agreement that principally depression but also anxiety are the main psychiatric comorbidities although the prevalence appears to be highly variable depending on the populations studied. However, the relevance of psychiatric comorbidities and the impact on quality of life in PWE has been consistent in different cultural contexts (3–5).

Contrary to the general concept of a higher prevalence of depression in PWE, recently it has been postulated that anxiety may be even more prevalent than depressive symptoms (6). Current analysis based on population studies in PWE described an overall prevalence of 23.1% for depression, and anxiety disorders ranged from 4.4 to 52.1% (7–9). On the other hand, when the studies carried out in patients with refractory epilepsy are analyzed, depression varies between 4.5 and 30%, and anxiety disorders are between 5 and 28% (10–13). A recent meta-analysis reports that the global pooled prevalence of anxiety disorders in PWE was 20.2%, and the overall pooled prevalence of depressive disorders was 22.9% (14).

Patients admitted for long-term video-EEG monitoring (LT-VEEGM) probably represent a different group. Drug-refractory epilepsy patients principally comprise them and less frequently differential diagnostic cases. Still, a significant percentage of patients admitted to an epilepsy monitoring unit (EMU) suffer from psychogenic non-epileptic seizures (PNES), and a non-negligible group presents an association of both pathologies. Diverse studies report that between 20 and 40% of patients admitted to an EMU suffer from PNES (15). In turn, ca. 9–11% of patients with PNES also present with epileptic seizures (16, 17).

Health personnel responsible for this group of patients are confronted not uniquely with epilepsies that are difficult to manage and also with a group of patients with psychiatric comorbidities probably differing from those reported in general population studies, which also determine their quality of life beyond epilepsy. In addition, the identification of psychiatric comorbidities is essential for defining multidimensional therapeutic strategies, preventing serious psychiatric complications and prognostic factors when making surgical decisions (6).

The objective of this study was to analyze the prevalence of anxiety and depression symptoms and to establish the impact on quality of life in a large sample of consecutive patients admitted for LT-VEEGM in our EMU.

MATERIALS AND METHODS

Participants

The inclusion criteria for this study were admission to the EMU due to refractory epilepsy or differential diagnosis, aged 16 years or older, and having completed the evaluation tests. Exclusion criteria included intellectual disability (estimated IQ lower than 70), unwillingness to participate in the study, or insufficient proficiency in the Spanish language.

From January 2013 to February 2021, 836 patients were evaluated in the EMU of Hospital del Mar (Barcelona, Spain), a national reference center for refractory epilepsy and member of the European Reference Network EPI-Care. Finally, 493 consecutive (mean age: 38.78 $\pm$ 12.7 years, 57% females) patients were included in the study.

Clinical and Sociodemographic Variables

Clinical data included medical records, seizure type, age at onset, seizure duration, current antiseizure medication (ASM) history, etiology, epilepsy localization, and history of psychiatric illnesses obtained from electronic clinical files and referenced by the patient. Sociodemographic data included age, gender, marital status, occupation, and educational level. Patients were subsequently classified into three groups: PWE ($n = 395$), PNES ($n = 56$), and combined (PWE + PNES, $n = 33$), and nine patients were not diagnosed and excluded from the analysis. These patient groups represent the totality of patients admitted to our EMU, which allows comprehensive research and may be helpful for comparison purposes.

Epilepsy Variables

The group of PWE was analyzed to assess differences in the prevalence of psychiatric symptoms between focal vs. generalized epilepsies. Within focal epilepsies, prevalence in the temporal lobe vs. extratemporal epilepsy group was compared. The combined group was discarded from the analysis to avoid confounders.

Psychiatric Assessment

The psychiatric evaluation was carried out using validated tests designed to measure levels of depression and anxiety. At the same

time, the quality of life of the patients was assessed to evaluate the impact of the above symptoms on this important measure of well-being. Anxiety and depression symptoms were assessed through the Hospital Anxiety and Depression Scale (HADS), the State Trait Anxiety Inventory (STAI), and Beck Depression Inventory II (BDI-II) (18–21). Quality of life was determined using the Quality of Life in Epilepsy-10 (QOLIE-10), validated for the Spanish population (22, 23).

The PNES diagnosis was obtained after a consensual decision between epileptologists and psychiatrists. In our EMU, PNES are first detected by the epilepsy team as they occur during VEEGM. Immediately afterward, a referral psychiatrist with experience in epilepsy evaluates the behavioral aspects of the semiology and visits the patient during admission, establishing a specific treatment plan.

The HADS is a 14-item questionnaire designed to detect states of anxiety and depression symptoms in hospitalized patients. The HADS produces two scales, one for anxiety (HADS-A) and one for depression (HADS-D), and scores $\geq$8 on either scale indicate a pathologic case. The STAI is a 40-item, self-report scale assessing separate dimensions of "state" and "trait" anxiety. Items are rated on a 4-point Likert scale with higher scores indicating greater levels of anxiety. The BDI-II is a 21-item measure estimating the frequency and severity of depressive symptoms. Each item consists of four self-evaluative statements scored 0 to 3 with increasing scores indicating greater depression severity. The QOLIE-10 is a 10-item, self-report measure covering general and epilepsy-specific domains (medication effects, mental health, role functioning, and seizure worry) and scored on a 10 (normal) to 50 (very high) scale. BDI-II is the most widely used scale for detecting depression. Together with the HADS, it constitutes two of the three instruments approved by the National Institute for Health and Clinical Excellence to measure the severity of initial depression and response to treatment. Cutting scores for the different scales are reported in **Table 1**.

Ethics Committee

The protocol, informed consent, and any related relevant documents were examined and approved by the Clinical Research Ethics Committee (CEIC-Parc de Salut Mar). All patients signed an informed consent for the use of their data in this protocol. The study met the international and national good clinical practice as required by the principles of the Declaration of Helsinki of 2008 of the World Medical Association and the current legislation on protection of personal data (Organic Law 3/2018, of December 5, on the Protection of Personal Data and the Guarantee of Digital Rights).

Data Analysis

The omnibus normality test (*scipy.stats.normaltest*) was carried out to examine the normality of the data. Chi-square and Fisher's exact statistics were used to compare proportions. Depending on the normality of data, *t*-test, Mann–Whitney, or Kruskal–Wallis tests for continuous variables were conducted to compare scores among the diagnostic groups. Multiple comparisons were corrected with Bonferroni adjustments. To determine the relationship between demographic, clinical, and mood factors and quality of life, a stepwise regression analysis on QOLIE-10 scores was conducted. The criteria for factor inclusion and exclusion were set at $p = 0.01$ and $p = 0.05$, respectively, and a list-wise deletion was used in the multivariate analysis. Statistical analyses were performed using SPSS21 (Armonk, NY, USA) and the scientific python library (*scipy*) with the level of significance set at $p < 0.05$ (two-sided) unless otherwise stated.

RESULTS

Of the population of 493 patients (57% female), 395 (80.12%) had epilepsy, 56 (11.36%) presented with PNES, and 33 (6.69%) had concurrent epilepsy and PNES (**Tables 2**, **3**). Nine patients (1.83%) were not diagnosed and were not included in the group's comparison analyses. Of the total group with epilepsy (428 patients), 7.7% has PNES. Likewise, of the total group with PNES (89 patients), 37% has epilepsy.

Diagnostic groups were balanced for age (KW, $p = 0.68$) and education (chi^2, $p = 0.32$), but not so regarding gender (chi^2, $p < 0.001$ with females more prevalent in the PNES and the combined groups), epilepsy onset (KW, $p = 0.001$), epilepsy duration (KW, $p = 0.001$), marital status (chi^2, $p = 0.001$), and employment (chi^2, $p = 0.002$). Patients' mean age at evaluation was 38.78 years (SD 12.79, 95% CI [37.65–39.91]), the mean age of epilepsy onset was 18.20 years (SD 13.52, 95% CI [16.98–19.43]), and the average duration of epilepsy was 20.43 years (SD 13.95, 95% CI [19.16–21.69]). Epilepsy duration was calculated as the interval (in years) from age at seizure onset to age at evaluation. A structural etiology was observed in 222 (45.0%) cases, and considering epilepsy classification, 215 (43.6%) were of temporal origin. In addition, 279 (61.18%) patients were on treatment with one or more ASMs with a median number of three [2–3] drugs. LEV was the most frequent ASM, being prescribed to 217 (44.0%) patients. Psychiatry disorders were previously diagnosed in 160 patients (32.45%) with mood disorders being the most prevalent (91 cases, 18.46%).

TABLE 1 | Cutoff points of the inventory scales.

	BDI-II	STAI-T	STAI-S	HADS-A	HADS-D	QOLIE-10
Normal	0–13	0–20 (Males) 0–26 (Females)	0–20 (Males) 0–23 (Females)	0–7	0–7	10–20
Pathologic	>13	>20 (Males) >26 (Females)	>20 (Males) >23 (Females)	>7	>7	>20

TABLE 2 | Clinical and sociodemographic characteristics of the patients included in the analysis ($N = 493$).

	Total	Epilepsy	PNES	Combined	*p*-value
N, %	493 (100)	395 (80.12)	56 (11.36)	33 (6.69)	
Mean age at evaluation, years (SD)	38.78 (12.79)	38.55 (13.01)	39.98 (11.40)	40.03 (11.97)	0.68
Gender, *n* (%)					0.001
Females	281 (57.0)	207 (52.41)	43 (78.79)	25 (75.76)	
Males	212 (43.0)	188 (47.59)	13 (23.21)	8 (24.24)	
Marital status, *n* (%)					0.001
Single	222 (45.03)	195 (49.37)	14 (25.00)	9 (27.27)	
Married	216 (43.81)	162 (41.01)	35 (62.50)	16 (48.48)	
Widowed	8 (1.62)	6 (1.52)		1 (3.03)	
Divorced	39 (7.91)	25 (6.33)	6 (10.71)	7 (21.21)	
Couple	3 (0.61)	3 (0.76)	–	–	
Education, *n* (%)					0.32
Illiterate	3 (0.61)	3 (0.76)	–	–	
Primary	79 (16.02)	58 (14.68)	10 (17.86)	11 (33.33)	
Secondary	149 (30.22)	115 (29.11)	21 (37.50)	9 (27.27)	
Third cycle	145 (29.41)	119 (30.13)	15 (26.79)	7 (21.21)	
University	104 (21.10)	88 (22.28)	9 (16.07)	6 (18.18)	
Special education	5 (1.01)	5 (1.27)	–	–	
Occupation, *n* (%)					0.002
Employed	202 (40.97)	172 (43.54)	18 (32.14)	8 (24.24)	
Unemployed	155 (31.14)	116 (29.37)	21 (37.50)	16 (48.48)	
Retired	13 (2.64)	13 (3.29)	–	–	
Pensioner	77 (15.62)	52 (13.16)	15 (26.79)	8 (24.24)	
Student	41 (8.32)	38 (9.62)	1 (1.79)	1 (3.03)	
History of psychiatric disorders, *n* (%)					<0.001
Alcoholism	4 (0.81)	4 (1.01)	–	–	
Mood disorder	91 (18.46)	58 (14.68)	18 (32.14)	16 (48.48)	
Multiple	11 (2.23)	4 (1.01)	4 (7.14)	3 (9.09)	
No	316 (64.10)	285 (72.15)	18 (32.14)	9 (27.27)	
Not defined	6 (1.22)	2 (0.51)	2 (3.57)	1 (3.03)	
TOC	1 (0.20)	1 (0.25)	–	–	
Personality disorder	45 (9.13)	29 (7.34)	11 (19.54)	3 (9.09)	
Peri-ictal psychosis	2 (0.41)	2 (0.51)	–	–	
Number of ASMs, median (range)	3 (2, 3)	3 (2, 3)	2 (1–3)	2.5 (2, 3)	<0.001

Prevalence of Anxiety and Depression in the Total Population

A series of D'Agostino K^2 tests revealed a non-normal distribution for QOLIE-10 ($K^2 = 15.962$, $p < 0.001$), BDI-II ($K^2 = 45.720$, $p < 0.001$), HADS-D ($K^2 = 26.718$, $p < 0.001$), HADS-A ($K^2 = 21.766$, $p < 0.001$), STAI-S ($K^2 = 16.324$, $p < 0.001$), STAI-T ($K^2 = 29.839$, $p < 0.001$).

Depressive symptoms in the BDI-II (14 or above) were observed in 246/493 (49.90%) of the patients and 144/467 (30.84%) according to HADS-D (8 or above). The mean scores were 15.69 (SD 11.53) for BDI-II and 5.53 (SD 4.06) for the HADS-D scale (**Tables 4**, **5**). Females had significantly higher BDI-II scores (females: 17.49, SD = 12.13; males: 13.31, SD = 10.24, $p = 0.0002$), whereas the difference was not significant for the HADS-D scores (females: 5.80, SD = 4.36; males: 5.19, SD = 3.59, $p = 0.28$) (**Figure 1**).

Pathologic anxiety scores in the STAI-S and the HADS-A were present in 240/456 (52.63%) and 210/469 (44.78%) patients, respectively. The mean STAI-S score was 24.25 (SD 12.65), whereas the mean HADS-A score was 7.52 (SD 4.09). Females had significantly higher anxiety scores in both the STAI-S (females: 25.86, SD = 13.11; males: 22.16, SD = 11.71, $p = 0.003$), and in the HADS-A inventory (females: 8.16, SD = 4.15; males: 6.66, SD = 3.87, $p < 0.001$) (**Figure 1**).

Differences in the Prevalence of Anxiety and Depression Scores per Diagnostic Group

In our series, 360 patients had focal epilepsy (73.0%), and 17 were generalized (3.44%). Within the group of focal epilepsies, 215 (59.7%) were categorized as temporal lobe epilepsy (TLE), and 128 (35.5%) were grouped within the extratemporal group (**Table 3**). Across TLE and extratemporal epilepsies, no difference

TABLE 3 | Clinical characteristics of the patients.

	Epilepsy ($n = 395$)	Combined ($n = 33$)	*p*-value
Epilepsy etiology, *n* (%)			0.010
Genetic	15 (3.80)	–	
Structural/metabolic	209 (52.91)	13 (39.39)	
Unknown	96 (24.30)	6 (18.18)	
Epilepsy location, *n* (%)			<0.001
Generalized	17 (4.30)	–	
Frontal	72 (18.23)	2 (6.06)	
Insular	5 (1.27)	–	
Multifocal	16 (4.05)	–	
Unclassifiable	13 (3.29)	3 (9.09)	
Occipital	16 (4.05)	1 (3.03)	
Parietal	32 (8.10)	1 (3.03)	
Temporal	201 (50.89)	14 (42.42)	
Epilepsy onset age, mean (SD)	17.15 (12.83)	22.63 (14.57)	0.001
Seizure history in years, mean (SD)	21.24 (13.74)	17.86 (12.41)	0.001

in the prevalence of pathologic scores was found for all the scales employed (all $p > 0.05$).

The PNES and combined groups revealed a higher incidence of pathologic BDI-II scores (64.29 and 78.79%, $p < 0.001$) as well as pathologic HADS-A scores ($p = 0.001$). The combined group showed a higher incidence of pathologic HADS-D scores (65.62%, $p < 0.001$). Pathologic anxiety and depression results were more prevalent in females, HADS-A (females = 50.7%; males = 36.8%; $p = 0.0027$) and BDI-II>13 (females = 56.6%; males = 41.0%; $p = 0.0006$) (**Figure 2**), but no gender differences could be observed for the HADS-D and STAI scales. A significant difference in the number of ASMs was observed for the PNES group, which, on average, was on less medication ($p < 0.001$).

Quality of Life (QOLIE-10)

According to the QOLIE-10 scores (21 or above), 347/486 patients (71.40%) had their quality of life affected. The mean QOLIE-10 score was 25.90 (SD 7.83) with females showing a slightly higher incidence of pathologic QOLIE-10 scores (females = 74.73%, males = 66.99%, $p = 0.06$) (**Figure 1**). No significant difference in the prevalence of pathologic scores was found across diagnostic groups ($p = 0.13$) (**Figure 2**).

Significant bivariate relations were observed between QOLIE-10 scores and the measures of depression, including the BDI-II and the HADS-D scale ($R^2 = 0.399$ and $R^2 = 0.374$, respectively, both $p < 0.001$). Increased endorsement of mood symptoms is associated with lower quality of life (**Figure 3**). A significant bivariate association was also observed between QOLIE-10 scores and measures of anxiety, including the HADS-A and the STAI-S inventories ($R^2 = 0.302$ and $R^2 = 0.228$, respectively, both $p < 0.001$). Increasing anxiety is similarly associated with a reduction in quality of life (**Figure 3**).

Depression and anxiety affect QoL independently. The partial correlations between QOLIE-10 and the two depression inventories remain significant after controlling for the two anxiety scales (BDI-II controlled for HADS-A, $R^2 = 0.163$; BDI-II controlled for STAI-S, $R^2 = 0.223$; HADS-D controlled for HADS-A, $R^2 = 0.396$; HADS-D controlled for STAI-S, $R^2 = 0.199$. All $p < 0.001$). Similarly, the partial correlations between the anxiety scores and the QOLIE-10 remain significant after controlling for the depression factor (HADS-A controlled for BDI-II, $R^2 = 0.054$; HADS-A controlled for HADS-D, $R^2 = 0.077$; STAI-S controlled for BDI-II, $R^2 = 0.043$; STAI-S controlled for HADS-D, $R^2 = 0.036$. All ps < 0.001).

We used multivariate stepwise regression to quantify the relative explanatory power of the different demographic, clinical, and mood factors on QOLIE-10 scores. The QoL score was significantly predicted ($R^2 = 0.477$, $p < 0.001$) by a regression model, including the age of the patient, the age of epilepsy begins, the number of ASMs, depression (BDI-II, HADS-D scores), and anxiety scores (STAI-T) as latent factors.

DISCUSSION

Patients admitted to epilepsy monitoring units constitute a group of patients with unique characteristics. The presence of drug resistance and clinical features allow grouping and differentiating them even from outpatients, especially considering the diagnostic context. The admissions usually last a week in adult patients although they tend to be shorter for children. Admission times for invasive epilepsy procedures are even longer, lasting 2 or 3 weeks. During this time frame, medical efforts aim to answer epileptological questions, and subtle psychiatric disorders are usually overlooked (24). Throughout this period, patients are seen by nurses, medical technologists, neurologists, neurophysiologists, and health care teams indirectly related to epilepsy for whom the awareness of specific comorbidities is perhaps even more unknown.

Taking into consideration psychiatric comorbidities during the diagnostic process and subsequent discharge is relevant from several aspects. When the health care team is aware of psychiatric symptomatology, it can help establish a more empathetic physician–patient relationship and improve the patient's compliance to receive instructions, understand specific diagnostic procedures, and describe symptoms that psychiatric modulators can influence. In our series, 32.45% of the patients had a history of psychiatric mood disorders. The prevalence at the time of admission was higher, being between 30.84 and 49.9% for depressive symptoms, according to the scale used, and between 44.78 and 52.63% for anxiety symptoms. This finding is consistent with previous reports describing that psychiatric disorders are underdiagnosed in epilepsy (9). The determination of psychiatric comorbidity should influence a change in the choice of ASM with suitable characteristics for this comorbidity and the eventual indication of a specific psychiatric treatment under the specialist's control. Severe psychiatric symptoms, especially suicide risk, must be detected to establish adequate preventive measures (25, 26). On the other hand, the severity of the preexisting psychiatric pathology can be seriously affected after surgical procedures when this comorbidity is overlooked (27).

TABLE 4 | Prevalence or frequency of depression, anxiety, and quality of life per diagnostic groups.

	Total		Epilepsy		PNES		Combined	
	Normal	Pathologic	Normal	Pathologic	Normal	Pathologic	Normal	Pathologic
BDI-II	247 (50.10)	246 (49.90)	215 (54.43)	180 (45.57)	20 (35.71)	36 (64.29)	7 (21.21)	26 (78.79)
STAI-T	214 (43.58)	277 (56.42)	181 (46.06)	212 (53.94)	22 (39.29)	34 (60.71)	8 (24.24)	25 (75.76)
STAI-S	216 (47.37)	240 (52.63)	184 (50.27)	186 (49.73)	21 (43.75)	27 (56.25)	9 (30.00)	21 (70.00)
HADS-A	259 (55.22)	210 (44.78)	222 (58.73)	156 (41.27)	23 (46.00)	27 (54.00)	5 (55.56)	4 (44.44)
HADS-D	323 (69.16)	144 (30.84)	270 (71.62)	107 (28.38)	34 (69.39)	15 (30.61)	11 (34.38)	21 (65.62)
QOLIE-10	139 (28.60)	347 (71.40)	119 (30.51)	271 (69.49)	13 (23.64)	42 (76.36)	5 (15.62)	27 (84.38)

TABLE 5 | Average scores on anxiety, depression, and quality of life inventories per diagnostic groups.

	Total		Epilepsy		PNES		Combined	
	N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)
BDI-II	493	15.69 (11.53)	395	14.42 (11.01)	56	19.69 (11.77)	33	24.88 (12.18)
STAI-T	491	26.36 (11.66)	393	25.33 (11.48)	56	28.75 (12.33)	33	34.06 (9.83)
STAI-S	456	24.25 (12.65)	370	23.21 (12.38)	48	26.91 (13.20)	30	31.43 (12.06)
HADS-A	469	7.52 (4.09)	378	7.16 (4.03)	50	8.04 (3,95)	32	10.68 (3.71)
HADS-D	467	5.53 (4.06)	377	5.26 (3.81)	49	5.75 (4.71)	32	8.71 (4.30)
QOLIE-10	486	25.90 (7.83)	390	25.37 (7.74)	55	27.11 (7.71)	32	30.12 (7.59)

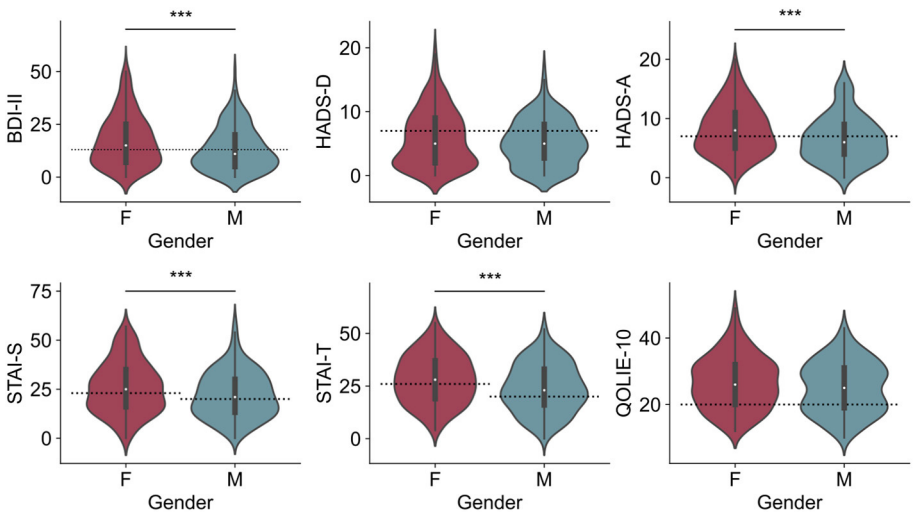

FIGURE 1 | Median of scores on the inventory scales according to gender. BDI, HADS-A, STAI-S, and STAI-T scores were significantly higher in female patients. ***$p < 0.01$.

In our sample, we did not find a significant correlation between the number of ASMs and the prevalence of psychiatric symptoms or quality of life. However, other groups, using specific tools such as the Epitrack, a test specifically designed to evaluate cognitive side effects of medication, have found a negative correlation between them and the number of ASMs in TLE patients (28). A significant difference was only observed in the number of ASMs for the PNES group, which, on average, was on less medication. In the same line, other groups have found similar differences in this regard (24).

Several studies analyze the prevalence of psychiatric symptoms by epilepsy subtype. Some studies show a higher prevalence of mood disorders in TLE, arguing the involvement of mesial temporal structures part of the limbic system (29–31). However, many other studies find no differences during their lifetime (3, 32, 33). Methodological factors could explain these discrepancies. Various diagnostic instruments are used for psychiatric evaluation, ranging from questionnaires to more objective and reliable clinical diagnostic assessments. On the other hand, the diagnostic criteria for focal epilepsies can be

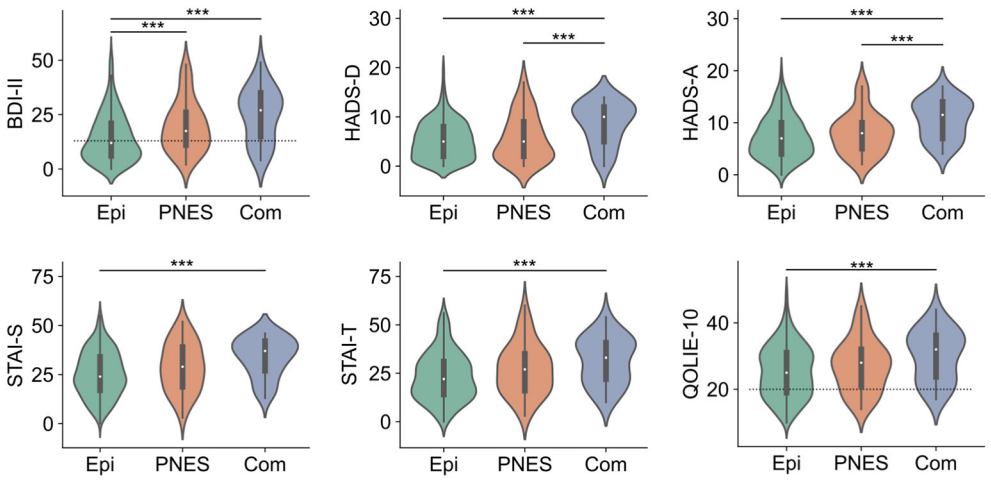

FIGURE 2 | Inventory scores according to the diagnostic group. Epi, epilepsy group; PNES, psychogenic non-epileptic seizure group; Com, combined group. ***$p < 0.01$.

inhomogeneous, depending on the setting in which the patient is evaluated. Finally, another confounding factor may be the use of diverse ASMs that can, in turn, modulate psychiatric factors in patients. The psychiatric findings of the studies are, therefore, difficult to compare (32). In our series, no differences were found between the prevalence of symptoms of depression or anxiety in TLE vs. extratemporal focal epilepsies despite the large number of patients evaluated. Nor were significant changes seen in the comparison between generalized and focal epilepsies. Only the duration of epilepsy in the PWE group was a risk factor for the appearance of symptoms. Therefore, our results support the hypothesis of a multifactorial cause in patients with refractory epilepsy (24).

Another relevant finding of this study is the gender differences found in the prevalence of psychiatric symptoms. The analysis of our series reveals that the BDI-II scores showed significant differences; that is, females had a higher incidence of pathological BDI-II scores than males (F: 56.58%, M: 41.04%). However, the comparison of HADS-D scores was not significant. Similarly, anxiety domains showed differences in pathologic HADS-A scores. Female patients revealed a higher incidence of pathologic HADS-A scores (50.75%) than male patients (36.82%) and scored higher also in STAI-S. Considering differences in quality of life by gender, a significant gap was also observed. Females (74.91%) had higher pathologic QOLIE-10 scores than males (66.5%). Recent studies also report similar results, suggesting that gender-specific approaches can be taken (34).

Besides epilepsy, a substantial number of the patients admitted to EMUs present with PNES, and a smaller group displays an association of both pathologies (35, 36). It is shown that PNES patients manifest functional, anatomical, and autonomic brain changes compared with healthy subjects and epilepsy patients without PNES (37–40). On the other hand, it is suggested that a wide range of psychopathologies may be the basis of PNES and that their treatment could improve clinical outcomes, avoiding the perpetuation of ongoing psychogenic seizures (35). In our series, 11.36% of patients presented isolated PNES, and another 6.69% had concurrent epilepsy and PNES, the total prevalence of PNES was 18.05%, which is consistent with previous reports (24, 33, 41). Of the total group with epilepsy (428 patients), 7.7% had PNES. Likewise, of the total group with PNES (89 patients), 37% had epilepsy. A recent metanalysis shows that the pooled frequency of epilepsy among those with PNES was 22% compared with 12% of PNES among those with epilepsy (42). In other words, in our case of EMU patients, the prevalence of epilepsy in PNES is approximately double among PWE, and that of PNES in PWE is around half. This could be explained by more selective screening of patients by excluding PNES before admission to UMEs compared with the general epilepsy population.

Furthermore, most studies exclude the mixed pathology group from their analyses. However, in our experience, it constitutes a clinical entity differentiated from patients with epilepsy or PNES alone. Our results suggest it is relevant to analyze this group separately.

When considering the prevalence of psychiatric symptoms in patients admitted to UMEs, a recent study of 101 patients detected that PNES patients scored significantly higher on the depression and anxiety scales than PWE. In addition, the overall QOLIE-31 score was worse for PWE than for PNES (3, 24). A different study including 200 participants shows that PNES patients have higher self-reported anxiety and depression levels but similar QoL to PWE (24).

In our comparative group analysis of depression rating scales, we observed that the PNES and combined groups have a higher incidence of pathologic BDI-II scores. BDI-II scores were significantly higher in the PNES (64.29%) and combined groups (78.79%) than the epilepsy group (45.57%). Similarly, HADS-D scores were significantly higher in the combined group (65.62%) than the epilepsy group (28.38%) and the PNES group (30.61%).

In relation to anxiety scores between the groups, a significant association of the pathological HADS-A scores is demonstrated, showing that the PNES and the combined group also have a

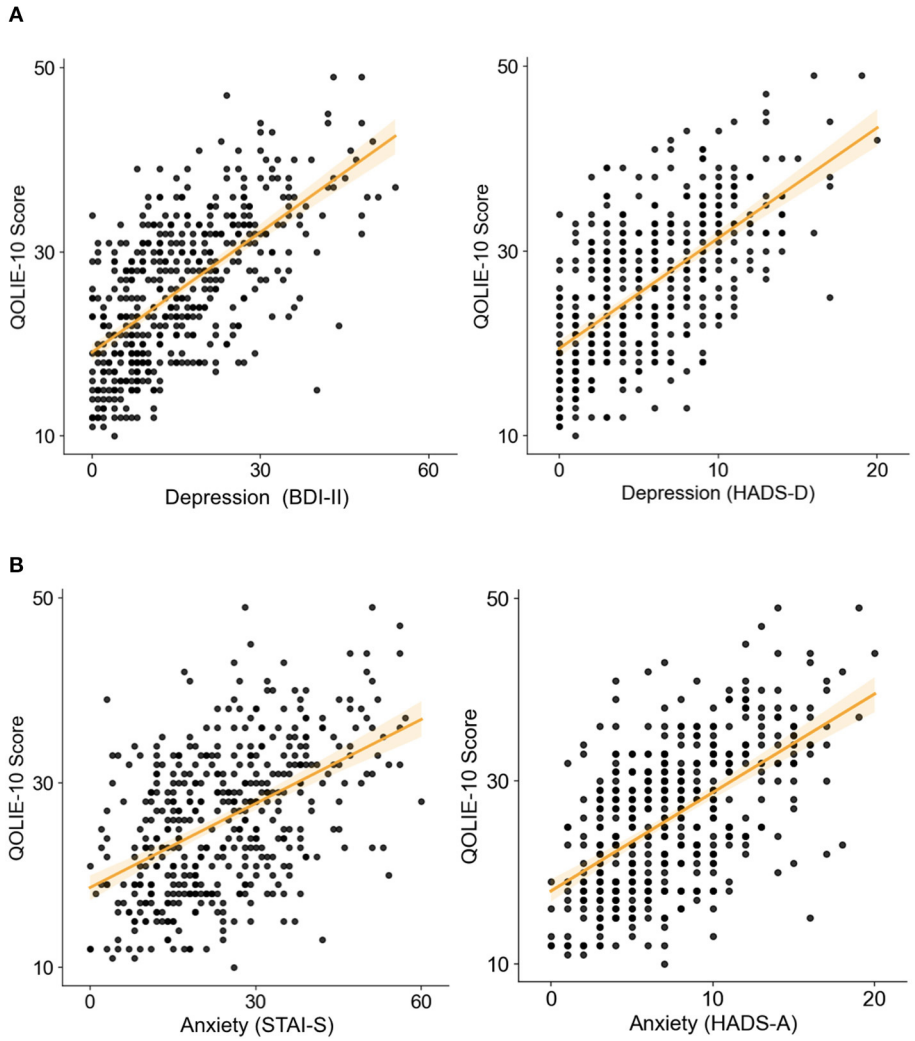

FIGURE 3 | Inferior health-related quality of life is significantly associated with increased symptoms of depression and anxiety (higher score means lower perceived quality of life). Correlation between Quality of Life in Epilepsy Inventory-10 (QOLIE-10) overall score and scores of **(A left)** Beck Depression Inventory-II (BDI-II), **(A right)** Hospital-Anxiety and Depression-Scale (HADS) depression subscale, **(B left)** State-Trait-Anxiety-Inventory (STAI), and **(B right)** HADS anxiety subscale (all with $p < 0.001$).

higher incidence of pathological scores than the epilepsy group. HADS-A scores were also significantly higher in the combined group (71.88%) than in the PNES group (54%) and the epilepsy group (41.27%). On the other hand, The STAI-T score was significantly higher in the combined group (75.76%) than in the epilepsy group (53.94%) as were the STAI-S scores (70 and 50.27%, respectively).

Finally, these differences also corresponded with worsening in the quality of life of the patients. QOLIE-10 scores positively correlate with BDI-II scores and STAI-T. Partial correlations revealed significant independent relations between anxiety and depression and QoL, suggesting that the quality of life is affected similarly by both symptoms. Using multiple regression procedures, we also found that psychiatric comorbidities are relevant latent predictors of QoL associated with the patient's age, the age at which epilepsy was first diagnosed, and the number of ASMs. In the comparative analysis of groups, the QOLIE demonstrated pathological values in the group with epilepsy, PNES, and combined of 69.49, 76.36, and 84.38%, respectively. QOLIE-10 scores were also significantly higher in the combined group than in the epilepsy group.

These data confirm that patients with PNES have higher rates of depression than patients with isolated epilepsy, which has been previously reported (24). Moreover, we also found that patients suffering from both pathologies (epilepsy + PNES) present even higher ranges of depression and anxiety than patients with isolated psychogenic seizures or epilepsy. To interpret this difference, we propose a perspective within a broader framework, that is, a dual pathological model of the functional substrates of PNES and focal epilepsy. There is growing evidence from biomarker studies in PNES, suggesting that structural and functional changes observed in the brain may act as predisposing

or precipitating factors for PNES. These changes could be secondary to early emotional trauma (37, 43). On the other hand, modern concepts of focal epilepsy interpret epileptogenicity based on the interaction of abnormal brain networks (44). How both etiological substrates interact is unknown, but they could theoretically explain the differences observed in the prevalence of psychiatric phenomena.

Our study has several limitations. First, it is a monocentric study with the constraints that this entails. Second, the scales used are for general psychiatric use and have not been designed explicitly for epilepsy. For this, using specifically developed scales, such as EpiTrack or the Neurological Disorders Depression Inventory for Epilepsy, could have provided more specific data. Third, we have not controlled the evolution of the patients, which could have provided important information regarding prognostic factors. Finally, our sample is based on the prospective collection of psychiatric symptoms using scales properly validated in Spanish but does not include clinical psychiatric diagnosis obtained through a specialized medical evaluation. Neuropsychiatric tests can identify people with anxiety and depression, but the results may be inconsistent with the clinical psychiatric evaluation. False negative screening tests can incorrectly assure that patients do not have a depressive or anxiety disorder, especially in patients with PNES (45). In our sample, only patients with PNES received, per protocol, a formal psychiatric evaluation at the time of VEEGM.

In conclusion, our study comprehends a large record of patients admitted to EMUs. Anxiety and depression symptoms are present in at least half of them with a direct negative effect on the quality of life of patients. Even more, anxiety symptoms seem to be more prevalent than depression. It provides valuable information comparing diagnostic groups, revealing that patients who have epilepsy associated with PNES present the highest rates of depression and anxiety. In addition, our analysis confirms that female patients show severer symptomatic and a worse QoL. Finally, it is evidenced that both depression and anxiety symptoms can independently affect the QoL of patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Clinical Research Ethics Committee (CEIC-Parc de Salut Mar). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RR was responsible for the study concept, methodology design, and medical writing. EP and AB were responsible for data collecting. BC was responsible for data collecting and statistical analysis. CP-E was responsible for data collecting, manuscript reviewing, and neuropsychological analysis. LP was responsible for data collecting and manuscript reviewing. AP contributed with data collecting and manuscript reviewing. RZ contributed with the statistical analysis, methodology, medical writing, and reviewing the article. All authors contributed to the article and approved the submitted version.

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Predictors of Comorbid Anxiety Symptoms After a New Diagnosis of Epilepsy: A Prospective 12-Month Follow-Up Observation

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Objectives: We aimed to identify the factors contributing to comorbid anxiety symptoms over a 12-month follow-up period in Chinese adults with newly diagnosed epilepsy.

Methods: Adult patients with newly diagnosed epilepsy (PWNDE) were recruited from First Hospital, Jilin University. Anxiety symptoms were assessed using the Generalized Anxiety Disorder-7 questionnaire (GAD-7; Chinese version) at 12 months. Multivariate stepwise logistic regression analysis was employed to identify the predictors for anxiety symptoms at 12 months.

Results: A total of 157 PWNDE completed the study and were included in the final analysis. The percentage of participants with anxiety symptoms significantly decreased from 31.2% at baseline to 23.6% at 12 months ($p = 0.027$). Multivariate stepwise logistic regression analysis indicated that depressive symptoms at baseline [odds ratio (OR) 3.877 (95% confidence interval (CI) 1.683–8.933); $P = 0.001$] and the number of antiseizure medications (ASMs) during the follow-up period [OR 2.814 (95% CI 1.365–5.803); $P = 0.005$] were independent factors contributing to comorbid anxiety symptoms at 12 months.

Conclusion: Depressive symptoms at baseline and the number of ASMs during the follow-up period were significant predictors of comorbid anxiety symptoms 12 months after a diagnosis of epilepsy.

Keywords: epilepsy, 12-month follow-up, depressive symptoms, anxiety symptom, number of ASMs

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INTRODUCTION

Epilepsy is a common severe brain disease that affects more than 70 million individuals worldwide (1, 2). Epilepsy rarely stands alone, and patients with epilepsy (PWE) always have one or several additional comorbidities (3–5). Epilepsy tends to be linked to psychiatric comorbidities, such as mood, anxiety, and psychotic disorders (6–9). Anxiety is a highly prevalent psychiatric comorbidity in PWE, and the incidence of anxiety is similar to that of depression (10–13). Among various populations, a total of 5–52.1% of PWE reported anxiety (14). Anxiety has been identified as a risk factor for poor quality of life, suicide risk, and poor seizure control in patients (15–18). It is of vital importance to identify the risk factors contributing to anxiety symptoms to improve preventive

strategies. Physicians would benefit from information regarding which patients may be at higher risk for anxiety symptoms.

Although multiple studies aimed to identify the risk factors, including demographics and clinical characteristics, for anxiety in PWE, their findings were controversial (10, 11, 14, 19, 20). Female gender and depression were the most consistent risk factors associated with comorbid anxiety in PWE across studies. However, most of the previous studies employed a cross-sectional study design and were based on patients with chronic epilepsy. One major limitation is that this study design did not allow us to establish specific causal interpretations. Lee et al. recently reported that higher levels of anxiety symptoms at 1 year after the diagnosis of epilepsy could be predicted by higher neuroticism, stigma, and lower self-esteem (21). To date, there have been limited data investigating the risk factors for the development of anxiety symptoms in PWNDE. In this study, we aimed to identify the factors contributing to comorbid anxiety symptoms over a 12-month follow-up period in Chinese adults with newly diagnosed epilepsy.

METHODS

Subjects

We conducted a prospective cohort study of PWNDE managed via an epilepsy management programme at the Epilepsy Clinic of First Hospital, Jilin University in Jilin Province. Adult PWNDE treated and followed up in our hospital between March 2017 and April 2020 were invited to participate in the current study. The diagnosis of epilepsy by a neurologist conformed to the International League Against Epilepsy (ILAE) criteria (22). Participants had never been treated with an ASM. The additional inclusion criteria were as follows: (1) 18 years of age or older; (2) physical, mental, and language abilities to complete the interview and questionnaires; and (3) willingness to participate. Exclusion criteria were as follows: (1) <18 years old; (2) a history of non-epileptic seizures; (3) a severe brain disease other than epilepsy (e.g., dementia and Parkinson's disease), a serious physical disease (e.g., significant hepatic, renal, or cardiopulmonary condition), or a psychiatric disorder (e.g., schizophrenia or lifelong anxiety); and (4) a history of intellectual disability or language disability. Written informed consent was obtained from all participants or their legal representatives. This study was approved by the Ethics Committee of First Hospital, Jilin University.

Data Collection

Demographic and clinical variables were collected and recorded by a face-to-face structured interview at the time of diagnosis. We recorded demographic data, such as age, sex, marital status, educational level, occupational status, residence, and per capita monthly family income. Clinical variables [e.g., age at seizure onset, duration >6 months before diagnosis, seizure type, presence of generalized tonic-clonic seizure (GTCS) before diagnosis, and total of 5 or more seizures] were also obtained. Seizure type was classified as generalized, focal or unclassified onset. Formal follow-up outcome assessments were undertaken at 3, 6, and 12 months after enrolment. At each visit, patients and their relatives were questioned regarding seizure recurrence, medication compliance, and changes. Seizure-related variables during the 12-month follow-up, including the number of seizures and number of ASMs, were recorded. At the time of diagnosis (baseline), depressive and anxiety symptoms were assessed using the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E; Chinese version) (23) and the 7-item Generalized Anxiety Disorder-7 questionnaire (GAD-7; Chinese version) (24), respectively. Anxiety symptoms were reassessed at the end of the 12-month follow-up.

Questionnaires

Assessment of Anxiety and Depressive Symptoms

We adopted the Chinese version of the GAD-7 to assess anxiety symptoms in PWE (24). This instrument was validated for Chinese PWE with a suggested cut-off point of >6, with a sensitivity of 94% and a specificity of 91.4% (24). Cronbach's alpha was good for the Chinese version of the GAD-7 (alpha = 0.888). This questionnaire has seven self-rated questions, with each score ranging from zero to three (25). A continuous anxiety symptom severity score ranging from 0 to 21 was calculated. A higher GAD-7 score indicated more severe anxiety symptoms. The GAD-7 total score accurately distinguished those who had anxiety symptoms (GAD-7 total score >6) from those without anxiety symptoms (GAD-7 $\leq$6) (24).

The Chinese version of the NDDI-E (C-NDDI-E) scale is a rapid and user-friendly test used to evaluate depressive symptoms, which indicates the possibility of having comorbid depressive symptoms in PWE over the past 2 weeks (23). This questionnaire was validated for Chinese PWE with a suggested cut-off point of >12, with a sensitivity of 0.926 and a specificity of 0.804. Cronbach's alpha was good for the C-NDDI-E (alpha = 0.825) (23). The NDDI-E consists of a total of six self-rated questions, with each question offering four possible answers, which are scored from 1 to 4 points, generating a total score from 6 to 24 points, with higher scores indicating higher levels of depressive symptoms (26). A cut-off score of >12 indicates depressive symptoms in PWE (23). The NDDI-E and GAD-7 are not substitutes for clinical interviews and the Diagnostic and Statistical Manual (4th ed.) diagnosis, but they are reliable and validated self-report measures of anxiety and depressive symptoms in PWE, which have been widely used in mainland China (11, 14, 27).

Statistical Analysis

The dependent variable was the presence or absence of comorbid anxiety symptoms at the end of the 12-month follow-up. Independent variables included characteristics at baseline and during the follow-up period. To confirm the factors contributing to the comorbid anxiety symptoms at 12 months, anxiety and depressive symptoms at baseline were also included as independent variables. Continuous data are presented as the means $\pm$ standard deviations (SDs) or medians [interquartile ranges (IQRs)] depending on the normal or non-normal distribution of the data assessed with the Kolmogorov-Smirnov test. Continuous variables were compared by Student's *t*-tests or Mann-Whitney *U*-tests. Categorical data are displayed as

TABLE 1 | Patient characteristics.

Variable	Individuals who completed the study ($n = 157$)
Sociodemographic variables	
Age (years), mean ± SD	35.34 ± 14.24
Female, *n* (%)	66 (42.0)
Educational level, *n* (%)	
University and above	45 (28.7)
Middle school	102 (65.0)
Primary school and below	10 (6.4)
Marital status-married, *n* (%)	101 (64.3)
Unemployed, *n* (%)	36 (22.9)
Residence-rural area, *n* (%)	59 (37.6)
Per capita monthly family income (Yuan), *n* (%)	
<1,000	21 (13.4)
1,000–5,000	108 (68.8)
>5,000	28 (17.8)
Seizure-related variables at baseline	
Age at onset (years), median (IQR)	29 (18, 42)
Duration >6 months before diagnosis, *n* (%)	97 (61.8)
Seizure type, *n* (%)	
Focal	119 (75.8)
Generalized	24 (15.3)
Unclassified	14 (8.9)
Presence of GTCS before diagnosis, *n* (%)	98 (62.4)
Number of 5 or more seizures, *n* (%)	76 (48.4)
Depression and anxiety symptoms at baseline	
C-NDDI-E >12, *n* (%)	39 (24.8)
GAD-7 >6, *n* (%)	39 (31.2)
Seizure-related variables at 12 months follow-up	
Number of seizures, *n* (%)	
0	95 (60.5)
1–11	32 (20.4)
≥12	30 (19.1)
Number of ASMs, *n* (%)	
1	121 (77.1)
2	32 (20.4)
≥3	4 (2.5)

GTCS, generalized tonic–clonic seizures; C-NDDI-E, Chinese version of Neurological Disorders Depression Inventory for Epilepsy; GAD-7, Generalized Anxiety Disorder-7 questionnaire; ASMs, antiseizure medications; SD, standard deviation; IQR, interquartile range; n, number.

numbers with percentages and were compared by chi-squared tests or Fisher's exact tests. The Wilcoxon rank sum test and McNemar test were used to compare anxiety symptoms between baseline and 12 months after a diagnosis of epilepsy. Using multivariate analyses, the independent contribution of the study variables was assessed. Variables with a $P < 0.05$ in the univariate analyses were subsequently included in the multivariate stepwise logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was utilized to test the overall prognostic accuracy of the significant predictors of anxiety symptoms at 12 months. The area under the curve (AUC) was calculated.

TABLE 2 | Comparison of anxiety symptoms between baseline and 12 months after a diagnosis of epilepsy ($n = 157$).

	At baseline	At 12 months	*P*-value
GAD-7 score, median (IQR)	4 (1, 8)	3 (0, 6)	0.005
GAD-7 >6, *n* (%)	49 (31.2)	37 (23.6)	0.027

GAD-7, Generalized Anxiety Disorder-7 questionnaire; IQR, interquartile range; n, number.

All data were analyzed with SPSS 25.0 (SPSS Inc., Chicago, IL, USA). A probability value of $p \leq 0.05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

A total of 157 PWNDE completed the study at the end of the 12-month follow-up period and were included in the final analysis. In this sample, 66 (42%) patients were women. The participants had a mean age of 35.34 ± 14.24 years. The demographic and clinical information of the participants is described in **Table 1**. Of the 157 PWNDE, 61.8% of them had a disease duration >6 months before diagnosis, and 48.4% of them had 5 or more seizures before treatment with ASMs. A total of 39 (24.8%) patients had depressive symptoms (C-NDDI-E >12), and 39 (31.2%) patients had anxiety symptoms (GAD-7 score >6) at the time of epilepsy diagnosis. Additionally, 62 (39.5%) patients experienced more than one epileptic seizure, and 22.9% of the patients were taking two or more ASMs during the follow-up period.

Prevalence of Anxiety Symptoms at Baseline and at 12 Months

At the time of diagnosis, 31.2% of the 157 patients had comorbid anxiety symptoms. At the end of the 12-month follow-up period, the percentage of participants with anxiety symptoms significantly decreased from 31.2% at baseline to 23.6% at 12 months ($p = 0.027$; **Table 2**). Additionally, the median GAD-7 score significantly decreased from 4 at baseline to 3 at 12 months ($p = 0.005$).

Factors Associated With Anxiety Symptoms at 12 Months

Univariate analyses indicated that comorbid anxiety symptoms at 12 months were significantly associated with depressive symptoms ($p = 0.003$) and anxiety symptoms ($p = 0.027$) at baseline (**Table 3**). Additionally, the number of seizures ($p = 0.017$) and number of ASMs ($p = 0.041$) during the follow-up period were risk factors contributing to comorbid anxiety symptoms at 12 months after diagnosis. Per capita monthly family income also tended to be associated with comorbid anxiety symptoms at 12 months, but the association did not reach statistical significance ($p = 0.057$). There was no significant difference between those with and without anxiety symptoms at 12 months in terms of demographic or seizure-related variables at baseline.

TABLE 3 | Comparison of patient characteristics between patients with and without anxiety symptoms at 12 months.

Variable	Anxiety symptoms at 12 months follow-up		
	Yes ($n = 37$)	No ($n = 120$)	*P*-value
Sociodemographic variables at baseline			
Age (years), mean ± SD	35.41 ± 15.04	35.32 ± 14.06	0.974
Female, *n* (%)	18 (48.6)	48 (40.0)	0.351
Educational level, *n* (%)			
University and above	9 (24.3)	36 (30.0)	0.442
Middle school	25 (67.6)	77 (64.2)	
Primary school and below	3 (8.1)	7 (5.8)	
Marital status-Married, *n* (%)	22 (59.5)	79 (65.8)	0.479
Unemployed, *n* (%)	27 (73.0)	94 (78.3)	0.498
Residence-rural area, *n* (%)	15 (40.5)	44 (36.7)	0.671
Per capita monthly family income (Yuan), *n* (%)			
<1,000	9 (24.3)	12 (10.0)	0.057
1,000–5,000	23 (62.2)	85 (70.8)	
>5,000	5 (13.5)	23 (19.2)	
Seizure-related variables at baseline			
Age at onset (years), median (IQR)	28 (18, 42)	30 (19, 43)	0.532
Duration >6 months before diagnosis, *n* (%)	23 (62.2)	74 (61.7)	0.957
Seizure type, *n* (%)			
Focal	28 (75.7)	91 (75.8)	0.805
Generalized	6 (16.2)	18 (15.0)	
Unclassified	3 (8.1)	11 (9.2)	
Presence of GTCS before diagnosis, *n* (%)	27 (73.0)	71 (59.2)	0.13
Number of 5 or more seizures, *n* (%)	18 (48.6)	58 (48.3)	0.973
Depression and anxiety symptoms at baseline			
C-NDDI-E >12, *n* (%)	16 (43.2)	23 (19.2)	0.003
GAD-7 >6, *n* (%)	17 (45.9)	32 (26.7)	0.027
Seizure-related variables at 12 months follow-up			
Number of seizures, *n* (%)			
0	15 (40.5)	80 (66.7)	0.017
1–11	11 (29.7)	21 (17.5)	
≥12	11 (29.7)	19 (15.8)	
Number of ASMs, *n* (%)			
1	23 (62.2)	98 (81.7)	0.041
2	12 (32.4)	20 (16.7)	
≥3	2 (5.4)	2 (1.7)	

GTCS, generalized tonic–clonic seizures; C-NDDI-E, Chinese version of Neurological Disorders Depression Inventory for Epilepsy; GAD-7, Generalized Anxiety Disorder-7 questionnaire; ASMs, antiseizure medications; SD, standard deviation; IQR, interquartile range; n, number.

Independent Factors Contributing to Anxiety Symptoms at 12 Months

Variables with a $P < 0.05$ in the univariate analyses were included in the multivariate stepwise logistic regression analysis. Multivariate stepwise logistic regression analysis indicated that depressive symptoms at baseline [odds ratio (OR) 3.877 (95% confidence interval (CI) 1.683–8.933); $P = 0.001$] and the number of ASMs during the follow-up period [OR 2.814 (95% CI 1.365–5.803); $P = 0.005$] were independent risk factors contributing to comorbid anxiety symptoms at 12 months (**Table 4**).

TABLE 4 | Multiple logistic regression for predictors of anxiety symptoms at the end of the 12-month follow-up period.

Variable	Anxiety symptoms at 12 months follow-up		
	OR	95% CI	*P*-value
Depression and anxiety symptoms at baseline			
C-NDDI-E >12, *n* (%)	3.877	1.683–8.933	0.001
Seizure-related variables at 12 months follow-up			
Number of ASMs	2.814	1.365–5.803	0.005

C-NDDI-E, Chinese version of Neurological Disorders Depression Inventory for Epilepsy; ASMs, antiseizure medications; OR, odds ratio; CI, confidence interval.

The Predictive Value of Depressive Symptom Levels and the Number of ASMs for Anxiety Symptoms at 12 Months

With an AUC of 0.684 (95% CI 0.583–0.785), depressive symptom scores (NDDI-E scores) showed a significantly greater discriminatory ability compared with that of the number of ASMs (AUC 0.599; 95% CI 0.490–0.709) to predict anxiety symptoms at 12 months (**Figure 1**).

DISCUSSION

Multiple cross-sectional studies of comorbid anxiety symptoms have been conducted on patients with chronic epilepsy (10, 14, 20, 28), but limited evidence has investigated the predictors for the development of anxiety symptoms in PWNDE (21). We aimed to identify the risk factors contributing to anxiety symptoms after a diagnosis of epilepsy. There were two main findings in this study. First, the incidence of comorbid anxiety symptoms decreased from 31.2% at baseline to 23.6% at the end of the 12-month follow-up period. Second, depressive symptoms at baseline and the number of ASMs during the follow-up period were independent risk factors for comorbid anxiety symptoms after 12 months of a diagnosis of epilepsy.

In this cohort, 31.2% of PWNDE had anxiety symptoms at baseline, which is lower than the 44.7% reported by Lee et al. in Korean adults with new-onset epilepsy using the Hospital Anxiety Depression Scale (HADS) (21). A prospective cohort study from Australia on PWNDE reported that anxiety was prevalent in 29% of the total participants at the time of diagnosis (29), which is similar to our reported incidence of comorbid anxiety symptoms. Notably, this may represent cross-cultural differences across studies. Another possible explanation is that the screening instruments for anxiety symptoms varied among studies. In this cohort, we also found that anxiety symptoms were prevalent in 31.2% of PWNDE at baseline, and they decreased

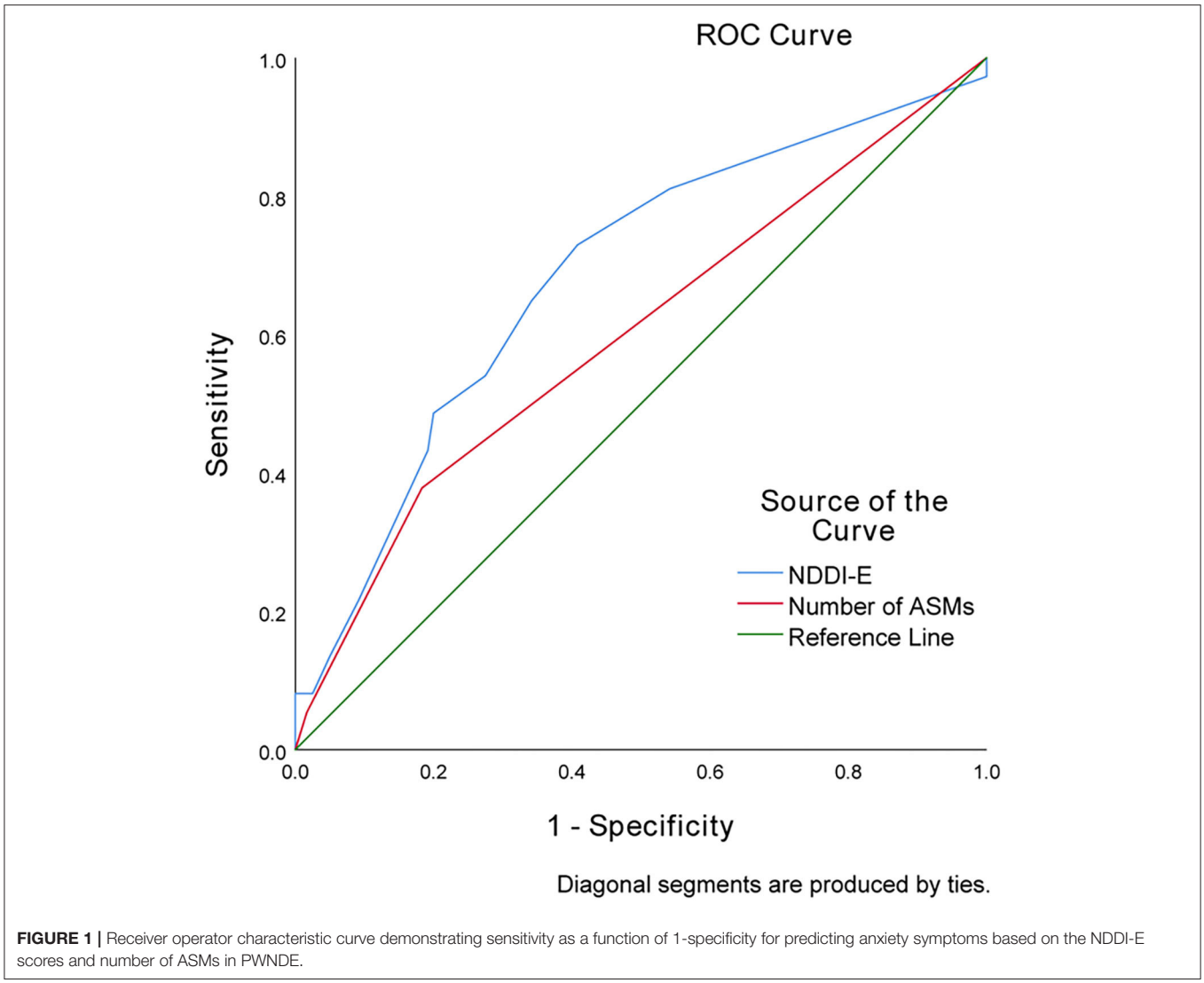

FIGURE 1 | Receiver operator characteristic curve demonstrating sensitivity as a function of 1-specificity for predicting anxiety symptoms based on the NDDI-E scores and number of ASMs in PWNDE.

over the follow-up period. These symptoms remained in 23.6% of patients at 12 months. A similar decrease in the incidence of anxiety over time was also reported by Lee et al. (21). In a recent prospective study from Australia with the aim of assessing mood trajectories after a first seizure, Velissaris et al. (30) found that anxiety trajectories decreased over time, and a patient's sense of poor control early after diagnosis was the main predictor of anxiety trajectories (31). Even decreasing anxiety trajectories over time were observed by prior investigations, and the influencing factor varied (21, 30). There may be cross-cultural differences in the major concerns of PWE in their daily life. For example, the most common concerns of adult PWE in West China were worries about seizures, maintaining a job, and the heritability of epilepsy (32). Anxiety/depression, age, and degree of discrimination were the main factors associated with the levels of concern in Korean patients with epilepsy (33).

In the present study, we revealed that the number of ASMs during the follow-up period was one of the most significant predictors of comorbid anxiety symptoms at 12 months. Our finding is in agreement with Oguz et al. (34) and Williams et al. (35), and they identified polytherapy as a significant risk factor for anxiety in children and adolescents with epilepsy (8). Anxiety has been strongly associated with the adverse side effects of ASMs (36, 37). The use of polytherapy may lead to more adverse effects from medications, which may contribute to anxiety in PWE (38). However, a 12-month follow-up study of 98 adults with new-onset epilepsy from South Korea reported that polytherapy was not a risk factor contributing to higher levels of anxiety symptoms (21). Additionally, the negative effects of some ASMs, such as phenobarbital, on mood have been identified (39). Data on the type of ASMs prescribed in PWE were not reported by those investigations, which may partly explain the controversial results.

This study also suggested that depressive symptoms at baseline emerged as another important predictor of anxiety symptoms at 12 months. In a prospective cohort study involving 439 individuals from Australia, Xu et al. provided evidence that a history of psychiatric disorder had a strong association with

psychological distress in PWNDE (29). Additionally, it has been reported by recent cross-sectional studies that there may be a relationship between psychological distress and anxiety symptoms (29). Pre-pregnancy depression and/or anxiety was a risk factor associated with peripartum depression and/or anxiety in PWE (40). Prior evidence indicated that lifetime mood disorder was a predictor for seizure recurrence in adults with a single unprovoked seizure or newly diagnosed epilepsy (41). Similarly, higher levels of neuropsychiatric symptomatology were associated with a higher risk of seizure recurrence in patients newly treated with ASMs (42). Psychological distress appeared to persist due to seizure recurrence in the high anxiety group (30). Additionally, the mental health of PWE is significantly associated with the perceived stigma of the patients (43). A recent study from Italy showed that PWE were still affected by perceived stigma, which was strongly related to higher depressive symptoms (44). Thus, perceived stigma may be a significant predictor of anxiety symptoms, which requires more attention. Tombini et al. recently reported that the combination of depressive symptoms, perceived stigma, and the number of ASMs best explained the poor quality of life in PWE (45). Anxiety was a significant determinant of poor quality of life (16).

Several limitations exist for the current study. First, characteristics and follow-up data (e.g., number of seizures and educational levels) were gathered based on self-report. There is the possibility of the existence of self-report bias. Second, some variables that may contribute to the development of anxiety symptoms after a new epilepsy diagnosis (e.g., ASM type or family psychiatric history) were not available and were not analyzed in our cohort. Additionally, we do not have reliable information on counseling or psychological treatments. This variable was not included as a possible confounder, and its potential effects on our results were not assessed. Third, all participants were limited to adults with newly diagnosed epilepsy and recruited from a single centre in northeast China, which may have introduced selection bias. Thus, our findings may not be relevant to all patient groups.

CONCLUSION

In conclusion, we found that the prevalence of comorbid anxiety symptoms decreased from 31.2% at baseline to 23.6% at 12 months in PWNDE. Additionally, depressive symptoms at baseline and the number of ASMs during the follow-up period were independent risk factors for comorbid anxiety symptoms after 12 months of diagnosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of First Hospital, Jilin University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GL and WL conceived and designed the study. RZ, QC, and XZ were involved in data acquisition. RZ analyzed the data and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Psychiatric Symptoms and Parental Stress in Children and Adolescents With Epilepsy

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Introduction: The aim of this study was to identify the presence of emotional and behavioral symptoms in children and adolescents with epilepsy, to measure the stress levels in their parents, and to determine if and how parental stress was linked to emotional and behavioral symptoms of their children.

Methods: We conducted a cross-sectional observational study including 103 children and adolescents with different form of epilepsy and 93 sex-/age-matched controls. Parental stress and emotional and behavioral symptoms were assessed through two standardized questionnaires: the Parenting Stress Index (PSI) and the Child Behavior Checklist (CBCL), respectively. We also considered the following variables: age, sex, maternal education level, family history of psychiatric disorders, duration of epilepsy, seizure frequency, seizure type, and number of antiseizure medications.

Results: The statistical comparison showed that the epilepsy group obtained significantly higher scores than controls in almost all the CBCL and the PSI scales ($p < 0.05$). The correlation analysis revealed a significant relationship between the PSI Total Stress scale and the following CBCL scales: total problems, internalizing problems, and externalizing problems ($p < 0.05$). An earlier age of seizure onset was related to a greater presence of externalizing problems, total problems, and total stress ($p < 0.05$).

Conclusion: In the epilepsy group, we found higher levels of parental stress and higher presence of emotional and behavioral symptoms compared to controls, mainly represented by internalizing problems (anxiety and depression symptoms). Therefore, it is important to precociously detect these symptoms and monitor them over time, in order to prevent psychiatric problems. In addition, parents of children with epilepsy should be offered psychological support to cope with parental stress and to improve the relationship with their children.

Keywords: epilepsy, children, behavioral problems, emotional problems, parental stress

INTRODUCTION

Epilepsy is one of the most frequent chronic neurological conditions in pediatric population, with the highest incidence in the first year of life. Worldwide, over 10 million of children and adolescents under the age of 15 years suffer from epilepsy, accounting for about a quarter of the total individuals with epilepsy (1).

Children and adolescents with epilepsy exhibit emotional and behavioral problems more often than children in the general population (2–6), including depression, anxiety, psychosis, attention, and behavioral problems, as a result of both the psychosocial (unpredictability and distressing nature of the seizures, social stigma associated with epilepsy, and overprotective parental behavior) and clinical factors (etiology, age at onset of epilepsy, frequency, and severity of seizures) (7–10).

The emotional and behavioral problems in children with epilepsy may also be influenced by family factors such as socioeconomic status or psychiatric conditions in other family members (11, 12).

Several epidemiological studies, focusing on the prevalence of psychopathological symptoms in pediatric epilepsy, documented that children with epilepsy present an estimated overall risk of 21–60% for childhood psychopathology (7, 13). A review of Reilly et al. (4) reported the presence of depression in 12–14% of pediatric epilepsy in population-based studies. The authors suggested that significant variations in instruments and methods used to assess anxiety and depression in published studies could lead to variable results (4). With respect to the prevalence of anxiety in pediatric epilepsy, a study by Williams et al. (14) reported mild-to-moderate symptoms of anxiety in 23% of patients (14). However, for both the anxiety and depression, the prevalence rates appear to be higher in young people with epilepsy than the general pediatric population and in children with other chronic medical conditions not involving the central nervous system (3, 15, 16).

A recent population-based study of young people with epilepsy aged between 0 and 17 years highlighted that 43% of the subjects showed psychiatric or neurodevelopmental comorbidities. More severe forms of epilepsy were more often associated with the risk of developing psychiatric comorbidities; even milder conditions were burdened by the presence of emotional and behavioral problems (17, 18).

Psychiatric and behavioral comorbidities in these children should not be attributed exclusively to the chronicity of the disease, but the presence of some specific epilepsy-related factors, including the underlying brain dysfunction, might be supposed (19).

The mechanisms underlying the development of psychiatric comorbidities in epilepsy are supposed to be multiple and complex. Although they have not been fully clarified, it is possible to advance several hypotheses: the first one is the presence of a genetic risk shared between epilepsy and psychiatric disorders that affects the development of common neural systems. The second one is that seizures themselves can lead to the construction of inadequate cortical networks, involving the limbic and frontocentral cortex (20). Moreover, it must be considered that epilepsy is more often associated with impairments of the cognitive profile, executive functions, social cognition, and learning skills that could lead to social and scholastic difficulties (21–25). Finally, social stigma can further contribute to increasing the emotional burden in young people with epilepsy (26). With respect to the role of antiseizure medications (ASMs), some drugs seem to have a higher tolerability profile than others; generally, the reduction of the seizures and a better control of the disease are associated with a more favorable emotional and behavioral profile (22, 27–30).

Psychiatric comorbidities and emotional and behavioral problems place a significant burden on patients and their families and complicate the clinical management of epilepsy (31).

Chronic diseases in children, such as diabetes, asthma, and autism, can generate parental stress; therefore, having children with epilepsy, characterized by unpredictable crisis onset, can cause treatment-related stress in their parents (32, 33).

Our cross-sectional observational study aimed to evaluate the presence of emotional and behavioral symptoms in children and adolescents with epilepsy through a standardized neuropsychological assessment compared to sex-/age-matched controls. We also aimed to explore the correlation between these symptoms and epidemiological and clinical variables (sex, age, etiology of epilepsy, age at onset of epilepsy, epilepsy duration, seizure type, seizure frequency, number of ASMs, and family history of psychiatric condition).

The secondary aim of this study was to measure the stress level in parents of children with epilepsy and to determine if and how parental stress is linked to emotional and behavioral symptoms of their children.

MATERIALS AND METHODS

Study Design

We conducted a cross-sectional observational study that aimed to explore emotional and behavioral symptoms in young patients with epilepsy and the stress levels in their parents.

Participants

We consecutively enrolled children and adolescents aged between 6 and 18 years, diagnosed with different types of epilepsy at the Child and Adolescent Neuropsychiatry Unit of the University of Salerno, from June 2019 to February 2021.

The diagnosis was made by two expert clinicians, according to the most recent classification of the International League Against Epilepsy (ILAE) (2017) (34), based on the electroencephalogram (EEG) findings and on the typical clinical features of the seizures. The MRI study supported the diagnosis if it was needed.

We also recruited a control group, homogeneous by sex, age, and socioeconomic status, among children and adolescents belonging to a screening project for learning difficulties. These subjects were healthy children without any presence of medical, neurological, and psychiatric conditions.

In all the patients of the control group, the diagnosis of epilepsy was excluded and all had a normal EEG.

Exclusion criteria in both the groups were the presence of additional neurological [cerebral palsy, moderate-to-severe intellectual disability according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria, neurodegenerative diseases, or migraine], psychiatric (anxiety, depression, and psychosis), or other relevant medical conditions (endocrinological, metabolic, hepatic, cardiac, or renal disorders).

Two standardized neuropsychological questionnaires were administered to the parents of all the children by a single child neuropsychiatrist, evaluating emotional and behavioral problems of child and parental stress level.

We also recorded the following clinical variables: age at onset of epilepsy, disease duration, epileptic seizure frequency, lobe and side of epileptic seizure onset, and ASMs numbers.

A clear and detailed explanation about the purposes and the procedures of this study was provided to all the participants and their parents. Parents provided their informed consent in written form. The procedure was approved by the local ethics committee "Campania Sud," according to the rules of good clinical practice, in keeping with the Declaration of Helsinki.

Table 1 shows the main sample characteristics.

TABLE 1 | Demographic and clinical characteristics.

	Epilepsy group	Control group	Statistics
N	103	93	
Sex			
Male	60 (58%)	52 (56%)	$\chi^2 = 0.109$
Female	43 (42%)	41 (44%)	$p = 0.741$
Age in years (M ± SD)	12.54 ±3.87	11.84 ± 3.51	$U = 4355.5$
			$p = 0.272$
Maternal Education (years)	12.44 ± 6.72	13.84 ± 6.98	$U = 4656$
			$p = 0.214$
Familiar history of psychiatric disorders	19 (19%)	12 (13%)	$\chi^2 = 1.127$
			$p = 0.288$
Epilepsy characteristics			
Age at onset (M ± SD)	9.04 ±3.21		
Epilepsy duration in year (M ± SD)	3.30±3.84		
Etiology			
Genetic	10 (10%)		
Symptomatic	12 (12%)		
Unknown	81 (78%)		
Seizure frequency			
Monthly	59 (57%)		
Weekly	20 (19%)		
Daily	8 (8%)		
Seizure free	16 (16%)		
Seizure type			
Focal	42 (42%)		
Generalized	26 (25%)		
Unknown	35 (33%)		
Drug therapy			
Mono	44 (43%)		
Poli	59 (57%)		
Number of ASMs (M ± SD)	1.18 ± 0.84		
MRI positive	12 (12%)		
-	6 cortical dysplasia 6 hypoxic-ischemic damage		

N, sample size; M, mean; ASM, antiseizure medication.

Neuropsychological Assessment

Child Behavior Checklist for Ages 6–18 (CBCL/6–18)

The CBCL/6-18 (35) is a standardized questionnaire for parents that evaluate emotional, social, and behavioral problems in children aged between 6 and 18 years. The questionnaire consists of 113 questions, to which parents can answer with a Likert scale ranging from 0 to 2 (0 = not true, 1 = somewhat or sometimes true, and 2 = very true or often true). Raw scores are converted to T-scores, weighted by sex and age. It is possible to obtain the scores of three main scales ("internalizing problems," "externalizing problems," and "total problems"), six scales based on the DSM-IV ("affective problems," "anxiety problems," "somatic problems," "attention deficit hyperactivity disorder (ADHD) problems," "oppositional defiant problems," and "conduct problems"), and eight empirically-based syndrome scales ("anxious/depressed," "withdrawn/depressed," "somatic complaints," "social problems," "attention problems," "rule-breaking behavior," and "aggressive behavior") in which a T-score ≤ 64 indicates non-clinical symptoms, a T-score between 65 and 69 indicates a borderline range, and a T-score ≥ 70 indicates clinical symptoms.

Parenting Stress Index-Short Form (PSI-SF)

The PSI (36, 37) is a standardized questionnaire for parents that measure the level of stress in the dyad parent-child. The short form of PSI consists of 36 items, to which parents attribute a score on a Likert scale ranging from "5 = strongly agree" to "1 = strongly disagree."

This self-report is organized in different subscales: parental distress (PD), parent-child dysfunctional interaction (P-CDI), and difficult child (DC), which evaluate the level of distress a caregiver is experiencing in his/her parental role, the satisfaction in the relationship with their own child, and, lastly, how difficult the management of the child is perceived to be.

The test also allows to evaluate the Total Stress (TS) scale. The TS is obtained by adding the relative scores of the three subscales (PD, P-CDI, and DC).

Raw scores are converted in age-weighted scores. A higher score suggests a higher stress level and a score above 85 indicates clinically significant parental stress.

Statistical Analysis

All the neuropsychological scores were expressed as mean ± SD. The percentage of participants scoring lower than the normal (<2 SD) was evaluated. In order to verify the data distribution, the Kolmogorov–Smirnov normality test was preliminarily performed. The presence of data not normally distributed forced us to employ non-parametric tests for our analysis. The

comparison of proportions was made using the chi-squared test, whereas the comparison of the mean scores was performed using the Mann–Whitney *U* test (independent sample).

The two-tailed Spearman's rank correlation test was employed to evaluate the relationship between different variables. All the data were analyzed using Statistical Package for the Social Science (SPSS) software (version 25.0, SPSS Incorporation, Armonk, New York, USA) (IBM Corporation released, 2017); p-values ≤ 0.05 are considered as statistically significant.

RESULTS

Sample Characteristics

We recruited 103 children ($n = 38$; age < 12 years) and adolescents ($n = 65$; age ≥ 12 years) diagnosed with epilepsy (mean age = 12.34 years, $SD = 3.87$ years) and 93 sex-/age-matched controls (mean age = 11.84 years, $SD = 3.52$ years) (**Figure 1**).

All the demographic and clinical characteristics of the participants such as age, sex, level of maternal education, seizure types, seizure frequency, age at onset of epilepsy, epilepsy duration, MRI findings, and ASMs number are shown in **Table 1**. The epilepsy group and the control group did not significantly differ in the main demographic characteristics (**Table 1**).

A family history of psychiatric disorders was found in 19% of the subjects with epilepsy. The mean age of epilepsy onset was 9.04 (±3.21) years, with a mean disease duration of 3.30 (±3.84) years. In most cases, the etiology of epilepsy was unknown; in 10%, we found a genetic mutation, in 6%, we found a cortical dysplasia, and in the remaining 6%, we found a hypoxic-ischemic damage. All the patients were in drug therapy with ASMs (43% monotherapy and 57% polytherapy).

Seizure type and frequency were shown in **Table 1**.

Emotional and Behavioral Symptoms in the Epilepsy Group vs. the Control Group

Analyzing the CBCL Total Problems scale, we found that 25/103 (24%) of patients with epilepsy obtained a score higher than the norm (T-score ≥ 70), against 8/93 (9%) of controls.

Internalizing problems were present in 30/103 (29%) and externalizing problems were present in 20/103 (19%) of children and adolescents with epilepsy vs. 7/93 (7%) and 6/93 (6%) of the controls, respectively. The remaining clinical scores percentages are given in **Table 2**.

The mean scores comparison showed that the epilepsy group obtained significantly higher scores than controls in all the CBCL scales, with the exception of the Rule-Breaking Behavior scale ($p < 0.05$).

Table 2 shows all the neuropsychological mean scores for the CBCL in both the groups and the results of statistical comparison.

Parental Stress in the Epilepsy Group vs. the Control Group

Analyzing the PSI TS scale, we found that 52/103 (50%) of parents of children with epilepsy obtained a score higher than the norm (T-score ≥ 85), against 3/93 (3%) of controls. The remaining clinical scores percentages are shown in **Table 2**.

The statistical comparison showed that the epilepsy group obtained significantly higher scores than controls in all the PSI scales ($p < 0.05$).

Table 2 shows all the neuropsychological mean scores for the PSI in both the groups and the results of the statistical comparison.

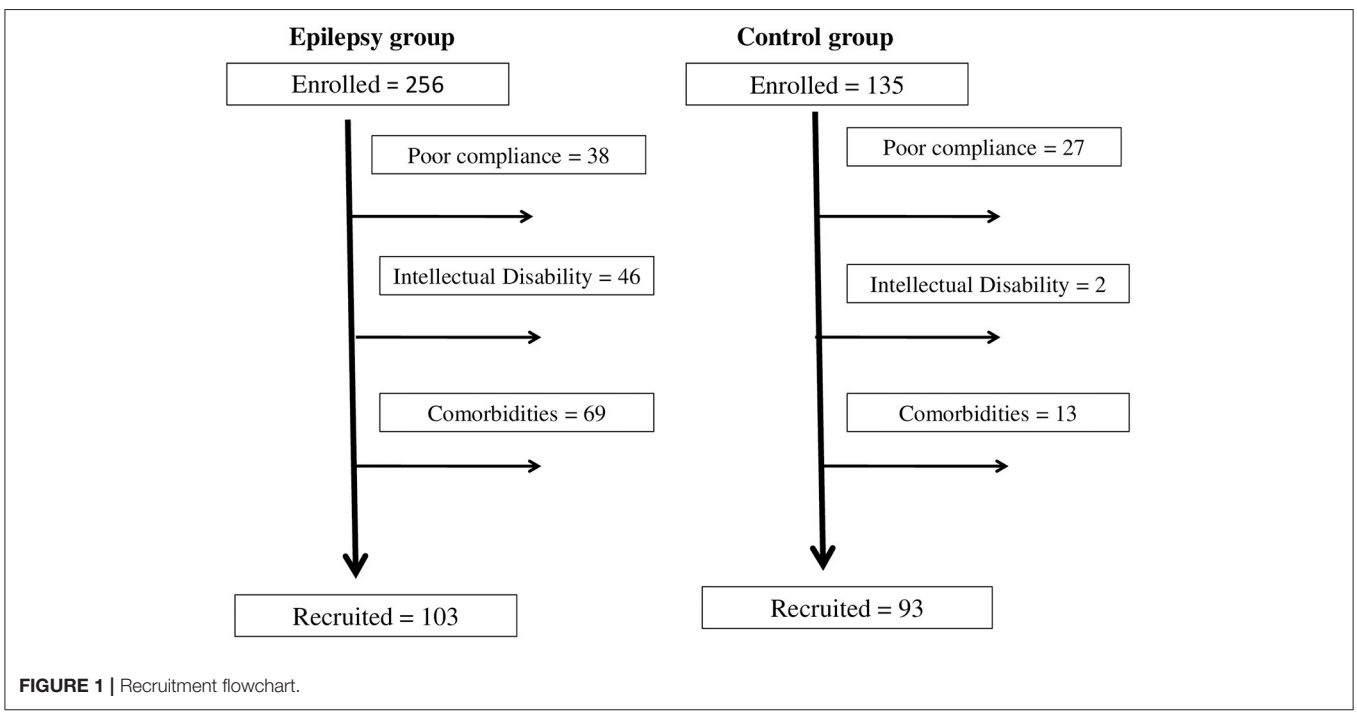

FIGURE 1 | Recruitment flowchart.

TABLE 2 | Statistical comparison between the average scores of the different groups.

	Epilepsy (m ± SD)	Control (m ± SD)	Mann-Witney		Percentage of subjects scoring in clinical range	
			U	*P*	Epilepsy	Control
CBCL						
Anxiety/depression	62. 27 ± 11.06	57.91 ± 7.37	3,808	**0.018**	29 (27%)	5 (5%)
Withdrawn/depressed	62.01 ± 10.19	56.32 ± 7.92	3,109	**0.000**	26 (25%)	5 (5%)
Somatic complaints	63.61 ± 11.23	57.97 ± 8.97	3,313	**0.000**	33 (32%)	13 (14%)
Social problems	62.57 ± 9.38	59.86 ± 9.53	3,861	**0.019**	22 (21%)	4 (4%)
Thought problems	60.28 ± 10.08	54.81 ± 6.74	3,168	**0.000**	24 (23%)	3 (3%)
Attention problems	63.56 ± 12.35	58.84 ± 10.64	3,591	**0.002**	26 (25%)	7 (7%)
Rule-breaking behavior	57.19 ± 8.52	55.10 ± 6.36	4263.5	0.181	14 (14%)	4 (4%)
Aggressive behavior	61.58 ± 13.08	54.98 ± 8.33	3061.5	**0.000**	16 (15%)	5 (5%)
Affective problems	61.68 ± 9.12	53.69 ± 8.06	1445.5	**0.000**	18 (17%)	3 (3%)
Anxiety problems	62.31 ± 7.82	54.28 ± 7.59	1,434	**0.000**	19 (18%)	4 (4%)
Somatic problems	60.91 ± 10.06	56.26 ± 9.50	2,289	**0.006**	24 (23%)	8 (9%)
ADHD problems	60.37 ± 8.82	54.56 ± 7.99	1,860	**0.000**	16 (16%)	4 (4%)
Oppositional-defiant problems	58.65 ± 8.46	53.43 ± 7.09	1908.5	**0.000**	9 (9%)	2 (2%)
Conduct problems	57.84 ± 9.65	52.77 ± 7.00	1,846	**0.000**	9 (9%)	0 (0%)
Internalizing problems	61.38 ± 13.20	56.56 ± 8.33	3564.5	**0.002**	30 (29%)	7 (7%)
Externalizing problems	57.78 ± 13.07	53.56 ± 8.67	3623.5	**0.003**	20 (19%)	6 (6%)
Total problems	61.99 ± 12.66	58.68 ± 10.00	3915.5	**0.027**	25 (24%)	8 (9%)
PSI						
PD	70.05 ± 27.41	34.55 ± 29.00	1787.5	**0.000**	46 (45%)	10 (11%)
P-CDI	79.08 ± 20.68	40.97 ± 26.68	1,365	**0.000**	59 (57%)	10 (11%)
DC	75.53 ± 24.01	39.61 ± 29.39	1,724	**0.000**	51 (49%)	11 (12%)
TS	75.83 ± 24.90	36.16 ± 26.98	1,432	**0.000**	52 (50%)	10 (10%)

$p < 0.05$ is in bold.
m, mean; CBCL, Child Behavior Checklist; PSI, Parental Stress Index; TS, Total Stress; PD, parental distress; P-CDI, parent–child dysfunctional interaction; DC, difficult child; DR, defensive response.

Correlation Analysis

The correlation analysis revealed a statistically significant positive relationship between the PSI TS scale and the following CBCL scales: total problems, internalizing problems, and externalizing problems ($p < 0.05$).

A lower age of seizure onset was correlated with a higher presence of externalizing problems, total problems, and TS ($p < 0.05$).

We did not find statistically significant correlations among the other analyzed variables (age, sex, maternal education level, family history of psychiatric disorders, duration of epilepsy, seizure frequency, seizure type, and number of ASMs) and the CBCL and the PSI.

Table 3 shows the significant results of the correlation analysis.

TABLE 3 | Correlation analysis.

	PSI	CBCL		
	Total stress	Internalizing problems	Externalizing problems	Total problems
Age at onset	$r = -0.239$		$r = -0.231$	$r = -0.210$
	$p = 0.015$		**$p = 0.019$**	**$p = 0.034$**
Internalizing	$r = 0.227$		$r = 0.722$	$r = 0.856$
problems	**$p = 0.021$**		**$p = 0.000$**	**$p = 0.000$**
Externalizing	$r = -0.222$	$r = 0.722$		$r = -0.866$
problems	**$p = 0.024$**	**$p = 0.000$**		**$p = 0.000$**
Total Problems	$r = 0.199$			
	$p = 0.044$			

$p < 0.05$ is in bold.
CBCL, Child Behavior Checklist; PSI, Parental Stress Index.

DISCUSSION AND CONCLUSION

Previous studies already highlighted the presence of both the emotional and behavioral symptoms and psychiatric problems in pediatric populations with epilepsy (38, 39). In particular, a very recent meta-analysis by Scott et al. (40) showed that over 70% of children and adolescents with epilepsy had at least one psychological symptom, with a prevalence of anxiety of 18.9% and of depression of 13.5%, in pooled data; the estimated risk of ADHD was between 2.5 and 5.5 times higher in children and adolescents with epilepsy than in controls. Serra-Pinheiro

et al. (9) reported a prevalence of 22% for mood disorders, 20.7% for anxiety, 26.8% for attention deficit, and 24.4% for disrupted disorders in a sample of children with epilepsy, while in another very recent work of Shehata and colleagues (41) on 80 children aged 6–13 years with idiopathic epilepsy the presence of depressive symptoms rose to 37.5%.

Our cross-sectional observational study aimed to evaluate the presence of emotional and behavioral symptoms in children and adolescents with epilepsy, through a standardized neuropsychological assessment, and compare them to sex-/age-matched controls. We also measured the stress level in their parents in order to determine if and how parental stress is linked to emotional and behavioral symptoms of the children.

From the analysis of the CBCL questionnaire administered to the parents, it emerged that children and adolescents with epilepsy ($n = 103$) compared to their peers ($n = 93$) had a significantly higher number of total emotional and behavioral problems (24 vs. 9%), with a slight prevalence of internalizing problems (29 vs. 7%) compared to externalizing problems (19 vs. 6%).

In the empirical CBCL scales, the most represented problems were somatic complaints (32%) and anxiety/depression (27%), followed by withdrawal/depression and attention problems. Thought problems and socialization problems were present in 23 and 21% of subjects, respectively. The presence of aggressive behavior was reported in 15% of cases and the presence of rule-breaking behavior was reported in 14% of cases (**Table 2**). The DSM-IV-oriented scales highlighted the presence of somatic problems (24%), anxiety problems (19%), affective problems (18%), ADHD problems (16%), oppositional defiant problems (9%), and conduct problems (9%) (**Table 2**).

The analysis of these results revealed a significant difference between the empirical CBCL scales compared to the DSM-IV-oriented scales. Therefore, we suggest that it would be useful to employ the DSM-IV-oriented scales instead of empirical scales, which contain elements clearly not belonging to the problem that the scale intends to evaluate.

From the statistical comparison with the control group, we found that children and adolescents with epilepsy presented significantly worse symptoms in all the emotional and behavioral areas, with the exception of the Rule-Breaking Behavior scale (**Table 2**).

This study extends and confirms the results of previous studies that explored emotional and behavioral symptoms through the CBCL in children with epilepsy.

In the study by Jones and colleagues (42), the authors found that children with recent onset epilepsy exhibited an elevated rate of the DSM-IV axis I disorders compared to controls. They showed significantly higher rates of depressive disorders (22.6 vs. 4%, $p = 0.01$), anxiety disorders (35.8 vs. 22%, $p < 0.05$), and ADHD (26.4 vs. 10%, $p = 0.01$). A subset of children with epilepsy (45%) exhibited these problems before the first recognized seizure, suggesting the potential influence of antecedent neurobiological factors that remain to be identified (42).

Our findings agree with Del Canto and colleagues (2018) (43). The authors highlighted emotional and behavioral problems in 50% of 159 children with epilepsy. Similarly, internalizing problems were more present than externalizing problems in our findings.

The cross-sectional study by Karanja et al. (44) on 177 children aged 6–12 years further confirms our results, highlighting that total emotional and behavioral symptoms were present in 46% of cases, mainly represented by attention problems, social problems, aggressive behavior, and withdrawal/depression.

Furthermore, a prospective controlled study of 43 preschool children with new onset epilepsy showed an increase in internalizing, externalizing, and total problems compared to controls both at the baseline and after 1 year of follow-up, suggesting the need to reassess these symptoms over time (45).

On the other hand, this study seemed to disagree with Cianchetti and colleagues (46) who found lower rates of anxiety (8%) and depression (9.2%) than ours in a sample of 326 children aged between 8 and 18 years. Probably, this discrepancy may be due to the different standardized neuropsychological tool, which was based on the self-assessment of child.

In this study, higher presence of total problems and internalizing problems was related to an early age of epilepsy onset, in keeping with previous studies (43, 47, 48).

The presence of emotional and behavioral problems in this study was not related to other sociodemographic variables. This finding disagreed with several literature studies, which report a significant association with age, duration of epilepsy, seizure frequency, number of ASMs, socioeconomic status, and family history of psychiatric disorders (41, 44, 45, 48–50). Possibly, our result could be attributed to the sample size that did not allow us to reach statistical significance. A future study on a larger sample will be needed.

The study by Moreira et al. (51), however, suggested no relationship between emotional and behavioral problems and other clinical variables (duration of epilepsy or number of ASMs), but highlighted a significant relationship with children IQ. It would, therefore, be interesting, in a future research, to add this parameter in our analysis.

The analysis of the PSI questionnaire detected clinical levels of total parental stress in 50% of the parents of children and adolescents with epilepsy. Clinical stress levels were detectable in the following subscales: PD (45%), P-CDI (57%), and DC (49%).

The statistical comparison showed significantly higher levels of parental stress in the parents of the group with epilepsy than in the parents of the control group.

This data are in agreement with previous studies, showing that parents of children with epilepsy experience significantly higher stress levels than general population (52, 53).

A 10-year longitudinal study that considered 356 mothers of children with epilepsy showed that 57% scored in the "at-risk" range for major depression. A supportive family environment was significantly associated with a better trend over time. Other significant factors were: seizure frequency, cognitive level of child, maternal age, and educational level (54).

The recent study by Olagunju et al. (55) showed that the perceived level of burden in 121 caregivers of adolescents with epilepsy (cases) was significantly higher than the one in caregivers of adolescents with sickle cell anemia (controls). In the cases

group, significant levels of psychological parental distress were found in 38% and significant levels of depression/anxiety were found in 39.7%.

High levels of parental stress can be explained by several factors: worries of parent about the occurrence of future seizures, possible side effects of ASMs, social stigma, and lifestyle consequences of the disease.

In our previous studies, parental stress seemed to be unrelated to the severity of epilepsy (56) and seemed to persist even after therapy withdrawal (57). Moreover, children with severe epilepsy can also present behavioral, mood, and sleep disorders, which, in turn, contribute to increase stress in parents (57).

Another significant result of this study was that parental stress levels were significantly related to emotional and behavioral symptoms in their child, involving both the internalizing and externalizing problems. On the other hand, study by van den Berg and colleagues (58) showed that only externalizing problems were related to parental stress.

We can assume that externalizing problems, such as aggressive behaviors, can lead to a difficult child management, resulting in a feeling of inadequacy of the parents. The presence of internalizing problems, such as mood disorders and anxiety disorders, on the other hand, can increase the concern about the health of child, resulting in a parent–child dysfunctional interaction (59). Individual psychological factors of the caregivers can influence the impact of epilepsy in family life and the parental stress levels (60).

The strength of this study was the recruitment of an age-matched control group and the assessment through standardized neuropsychological tests. This study had certainly many limitations such as the modest sample size and the cross-sectional design.

In conclusion, children and adolescents with epilepsy are at a higher risk of developing emotional and behavioral problems such as anxiety, depression, somatic problems, and attention problems than their peers. The presence of emotional and behavioral problems can affect the parental stress and the quality of life of the entire family.

It is important to precociously detect emotional and behavioral symptoms in children with epilepsy in order to prevent the development of future psychopathological conditions (61, 62) and support their parents by providing them with adequate coping strategies (63–65).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Campania Sud Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FO and GP conceptualized the work. GP and FP analyzed the data and drafted the manuscript. CP, VV, and CS performed psychometric measurements and analyzed the data. IP revised English language and researched the data literature. GC was involved in planning and supervised the work. All authors have agreed to this final version and participated in a meaningful way in the preparation of the manuscript.

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Intrinsic Brain Activity in Temporal Lobe Epilepsy With and Without Depression: Insights From EEG Microstates

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Background: Depression is the most common psychiatric comorbidity of temporal lobe epilepsy (TLE). In the recent years, studies have focused on the common pathogenesis of TLE and depression. However, few of the studies focused on the dynamic characteristics of TLE with depression. We tested the hypotheses that there exist abnormalities in microstates in patients with TLE with depression.

Methods: Participants were classified into patients with TLE with depression (PDS) ($n = 19$) and patients with TLE without depression (nPDS) ($n = 19$) based upon the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V). Microstate analysis was applied based on 256-channel electroencephalography (EEG) to detect the dynamic changes in whole brain. The coverage (proportion of time spent in each state), frequency of occurrence, and duration (average time of each state) were calculated.

Results: Patients with PDS showed a shorter mean microstate duration with higher mean occurrence per second compared to patients with nPDS. There was no difference between the two groups in the coverage of microstate A–D.

Conclusion: This is the first study to present the temporal fluctuations of EEG topography in comorbid depression in TLE using EEG microstate analysis. The temporal characteristics of the four canonical EEG microstates were significantly altered in patients with TLE suffer from comorbid depression.

Keywords: temporal lobe epilepsy, depression, microstates parameter, EEG, resting state

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INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent episodes of spontaneous seizures, affecting nearly 1–2% population of the world (1). Epileptic seizures are caused by the imbalance of excitatory and inhibitory neurotransmitters in central nervous system, thus leading to abnormal synchronous firing occurs in the involved neural networks of brain (2). The most prevalent type of focal epilepsy is temporal lobe epilepsy (TLE). In this population, comorbidity burden is high and psychiatric comorbidities are frequently encountered (3), such as depression, which is the most common psychiatric comorbidity.

The recently reported prevalence numbers of depression comorbidity in patients with TLE vary from 30 to 50% (4, 5). Comorbid depression has been further linked not only to high rates of suicide and decreased life expectancy, but it is also a greater risk factor for developing refractory epilepsy (5, 6).

However, the precise mechanism of comorbid depression in TLE is not yet fully elucidated. In the recent years, studies have focused on the neurobiological basis of TLE and depression, suggesting that a common pathogenesis may exist. The pathogenesis includes disorders of the endocrine system (7–10), abnormal neurotransmitter balance (11, 12), changes in immune-related biochemical indicators (13, 14), abnormal glucose metabolism (15, 16), inflammation (17), and neurogenesis (15). Spenser et al. (18) highlighted that epilepsy and depression have similar networks with postulated roles in neuropsychiatric disorders that overlap, providing a theoretical basis for the high prevalence of comorbid depression disorders in epileptic patients. Therefore, knowledge of the physiological mechanisms at an intrinsic network level is essential to patients with TLE with depression.

Most recent studies have indicated that brain neural activity changes dynamically through time and, thus, provides abundant information of neural characteristics for epilepsy and depression (19, 20). The electroencephalography (EEG) activity is segmented into limited amounts of scalp electrical topographies of certain time periods (60–120 ms) duration and then dynamically changing into a different state that remains stable again (8, 21). Each successive signal is referred to as "microstate" and transitions between microstates are thought to reflect coordinated interactions among large-scale distributed brain networks (22). In the resting state, only four specific topographies (termed microstates A, B, C, and D) are able to explain most of the global variance of EEG signals (>65%) (22). Microstate metrics included the duration (average time of each state remains stable), occurrence (the number of times it occurred per second), coverage (the percentage of total time spent in each state), and microstate syntax (transition probabilities from each microstate class to another) (23). Simultaneous EEG-functional MRI (fMRI) has reported association of the microstates A and B with phonological and visual and microstates C and D with salience and attention networks (24). Most of the studies conducted focused on fMRI and few on EEG (22). With the emergence of dense array EEG technologies, the recording of more accurate electrical source imaging has become available. Due to its advantages of submillisecond temporal, high-spatial resolution, and high signal-noise ratio, high-density EEG covering all the relevant neural regions has become more likely to reveal underlying mechanisms.

The purpose of this study was to examining deviant resting-state EEG microstate dynamics in patients with TLE with depression as compared to patients with TLE without depression. We hypothesized that in patients with TLE suffer from comorbid depression, the temporal characteristics of the four canonical microstate maps will be significantly altered. In this study, we applied 256-channel high-density EEG to reveal the microstate dynamic changes in patients with TLE with depression over time.

MATERIALS AND METHODS

Study Design and Participants

This retrospective study was based on data of patient collected from Beijing Tiantan Hospital from January 2019 to June 2021. The diagnosis was conducted by at least two well-trained neurologists. Inclusion criteria were: (i) diagnosed as TLE according to the criteria established by the International League Against Epilepsy (25); (ii) age over 18 years old; (iii) the epileptogenic zone was localized to the temporal lobe by continuous video EEG evaluation; and (iv) being seizure free for at least 72 h. Exclusion criteria were: (i) previous neurosurgery; (ii) cognitive impairment assessed using the Mini-Mental State Examination; (iii) a history of other neurological disorders, except epilepsy; and (iv) use of antidepressant medications prior to this study. Depression was ascertained using the Fifth Edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria and depressive severity was assessed using the 24-item version of the Hamilton Depression Rating Scale (HAMD24). A total of 38 patients with TLE were enrolled and divided into patients with depression (PDS, $n = 19$) and patients without depression (nPDS, $n = 19$). This study was approved by the Hospital Ethics Committee and all the patients signed informed consent forms.

Electroencephalography Acquisition and Preprocessing

Prior to EEG measurements, patients were requested to lie comfortably in the supine position and relax their facial muscles. During the acquisition, subjects remained awake with their eyes closed to reduce artifact signals due to eye movements and avoid deliberate mental activities. Data were recorded using 256-channel high-density EEG recordings (EGI System 400; Electrical Geodesic Incorporation, Oregon, USA, band pass filter: 0.1–70 Hz, sampling rate: 1,000 Hz, and impedance <30 kΩ with a recording reference at the vertex). We subjected EEG to rule out the presence of interictal EEG discharges for all the patients. For further analysis, the number of electrodes was reduced from 256 to 203 channels in order to minimize artifacts from facial or neck muscles.

Each EEG dataset was segmented into 2 s non-overlapping epochs and bad channels were removed with subsequent interpolation. If a channel was bad for 20% or more of the epochs, the channel was flagged as bad for all the epochs; if more than 15% of the channels in a single segment were labeled as bad, the whole segment was rejected. Electroencephalography epochs contaminated by movement artifacts were manually discarded from subsequent analysis. Independent component analysis was employed to remove components associated with persistent ocular and electrical artifacts. At the end, an artifact-free data were selected per subject from which estimating the parameters for the microstate analyses.

Microstate Analysis

The atomize-agglomerate hierarchical cluster (AAHC), a modified k-means to provide unique clusters for microstate analysis, was used to generate clusters of EEG topographies

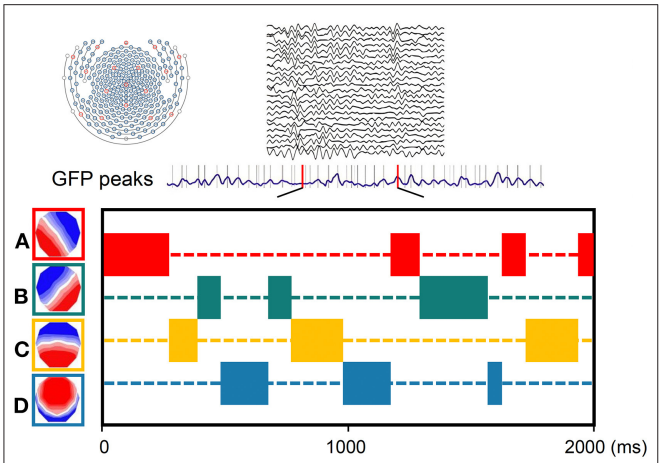

FIGURE 1 | Schematic of the method of microstate analysis. The global field power (GFP) (drawn in purple) is calculated at each instant of the 256-channel electroencephalography (EEG) recording. Original maps at the times of maximal GFP are plotted and assigned into the four group model maps labeled A, B, C, or D.

TABLE 1 | Demographic and clinical characteristics of participants.

Variable	PDS ($n = 19$)	nPDS ($n = 19$)	*P*-value
Age (year)	26.0 (23.0, 30.0)	29.0 (19.0, 31.0)	0.58
Sex			0.71
Male	13 (68%)	15 (79%)	
Female	6 (32%)	4 (21%)	
HAMD score	21.0 (15.0, 35.0)	5.0 (2.0, 6.0)	<0.01
Epilepsy duration (year)	10.0 (6.0, 15.0)	7.0 (4.0, 17.0)	0.41
Education years	12.0 (9.0, 13.0)	9.0 (8.0, 12.0)	0.46
Lateralization			0.75
Left	9 (47%)	11 (58%)	
Right	10 (53%)	8 (42%)	

PDS, patients with temporal lobe epilepsy with depression; nPDS, patients with temporal lobe epilepsy without depression; HAMD, 24-item Hamilton Depression Rating Scale.

(26). Electroencephalography was bandpass filtered (0.2–20 Hz) (27) and average rereferenced. The polarity of the topographical maps was disregarded (26, 28). The global field power (GFP) (spatial standard deviation as a function of time) is subsequently calculated across EEG channels as a function of time to quantify synchronous activity from all of the electrodes at every timepoint (29). Global field power peaks have been previously proven to represent moments of highest signal-to-noise ratios and strongest field potentials. The topographic maps are always steady during the high GFP, and immediately after, change to the next topographic map, once GFP reaches a minimum peak (30). In microstate analysis, the topographies of GFP peaks are regarded to be discrete microstates, whereas dynamic changes in EEG signals as variations of these states (23). Cluster analysis was conducted first at the individual template maps level and then at group levels. To facilitate comparisons with previous studies, we categorized the microstate maps into four categories (A–D) on

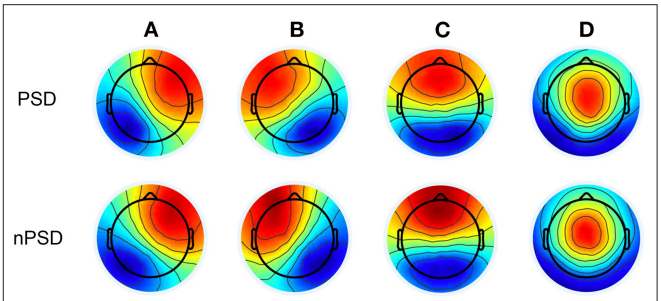

FIGURE 2 | Microstate topographic maps. PDS, patients with temporal lobe epilepsy with depression; nPDS, patients with temporal lobe epilepsy without depression.

the basis of previous study (22) (**Figure 1**). Spatial correlations between each map at group level and the topographies (maps) at the GFP peaks of the original EEG signals at individual level were calculated. Therefore, microstate maps were used to determine the backward fitting to the original map topography at each GFP peak according to maximum spatial correlation. The timepoints between two GFP peaks were obtained using nearest-neighbor interpolation. For each microstate map, four temporal parameters including duration, occurrence, coverage, and microstate syntax were calculated.

Statistical Analysis

Statistics were calculated with the SPSS Statistics version 25 (IBM Corporation, Armonk, New York USA). For the differences in microstate duration, occurrence, and coverage, data were analyzed by using the Wilcoxon rank-sum test. For the differences in microstate syntax, the non-random transition probabilities from each microstate to another were counted; these numbers were normalized to fractions of all between-class transitions of the subjects. Given four classes, we, thus, obtained for each subject 12 values for all the possible sequence doublets. False discovery rate (FDR) was used for multiple testing correction (FDR q-values < 0.01). Besides, comparisons between groups were conducted with the two-tailed t-tests. p-values < 0.05 were considered as statistically significant.

RESULTS

Demographics and Clinical Variables

Demographics and pertinent clinical data are given in **Table 1**. There were no significant differences in age, gender, years of education, course of epilepsy, and localization of TLE between patients with and without depression. The HAMD scores differed significantly between the two groups [21.0 (15.0, 35.0) vs. 6.0 (2.0, 6.0), $p < 0.01$]. As described in the methods, patients were categorized into the PDS group (HAMD score ≥ 7) and the nPDS group (HAMD score < 7).

Electroencephalography Microstate Analysis

Group dominant microstate maps are shown in **Figure 2**. They were highly similar to the categories observed in previous studies

(22). The orientation of microstate A is from right frontocentral to left occipital-parietal; the orientation of microstate B is from left frontocentral to right parieto-occipital; the orientation of microstate C is from prefrontal to occipital; the orientation of microstate D is from frontocentral to occipital. The four microstate classes are labeled accordingly and explained 77.0%

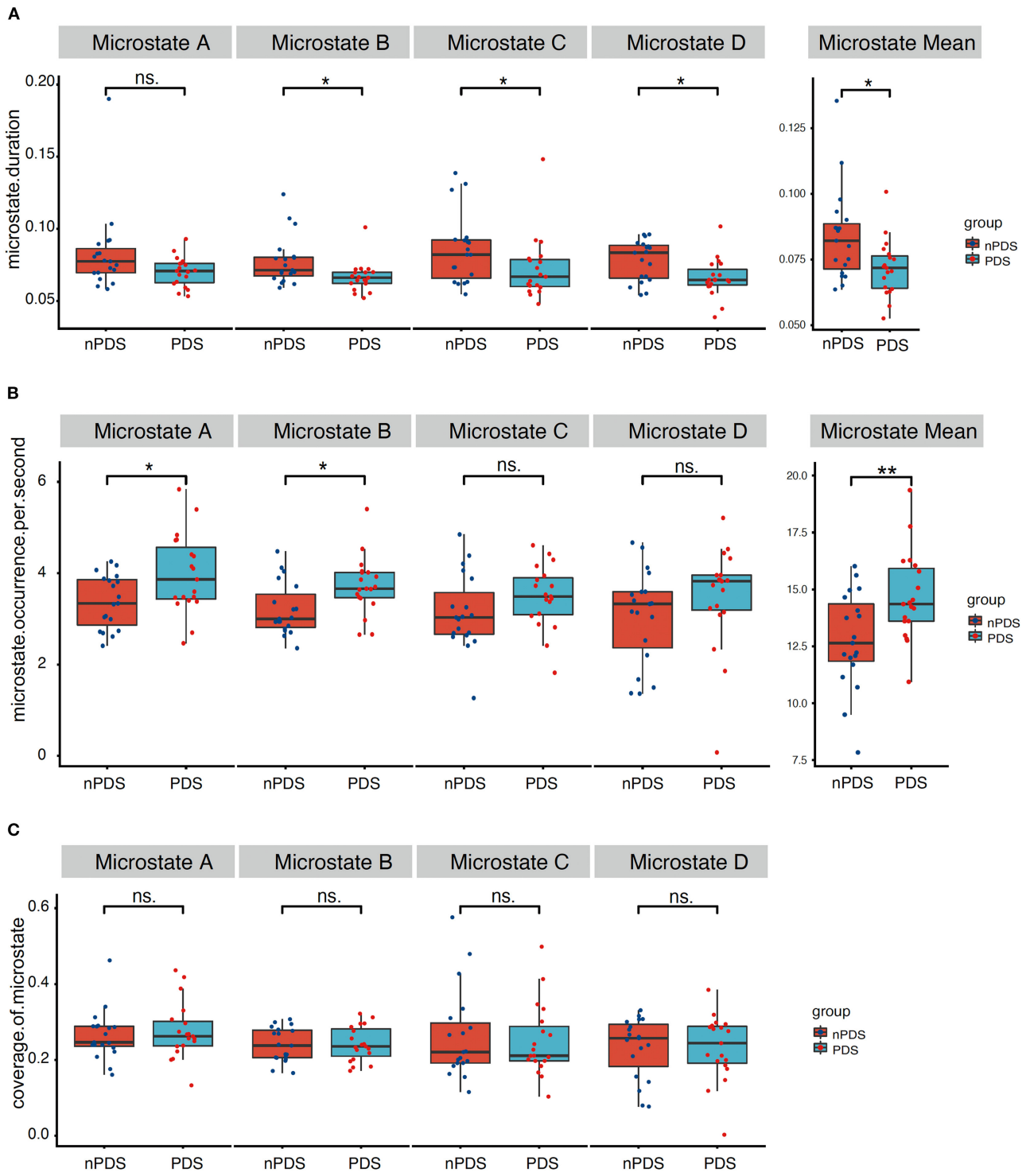

FIGURE 3 | Temporal characteristics of microstate. Comparison between the two groups of microstate duration, occurrence per second, and coverage for each microstate class separately. **(A)** correspond to the duration of microstate map A–D and mean duration, **(B)** correspond to the occurrence per second of microstate map A–D and mean occurrence, **(C)** correspond to the coverage of microstate map A–D. *p*-values result from the Wilcoxon rank-sum test between two groups. PDS, patients with temporal lobe epilepsy with depression; nPDS, patients with temporal lobe epilepsy without depression. $^{*}p < 0.05$, $^{**}p < 0.01$.

TABLE 2 | Duration of microstates A to D and mean of two groups.

	PDS ($n = 19$)	nPDS ($n = 19$)	*P*-value
A	0.071 (0.062, 0.076)	0.078 (0.069, 0.089)	0.075
B	0.066 (0.062, 0.066)	0.071 (0.066, 0.807)	0.017
C	0.067 (0.060, 0.079)	0.082 (0.063, 0.925)	0.027
D	0.065 (0.060, 0.075)	0.083 (0.065, 0.089)	0.018
mean	0.072 (0.064, 0.077)	0.082 (0.070, 0.090)	0.013

PDS, patients with temporal lobe epilepsy with depression; nPDS, patients with temporal lobe epilepsy without depression.

TABLE 3 | Occurrence per second of microstates A–D and mean of two groups.

	PDS ($n = 19$)	nPDS ($n = 19$)	*P*-value
A	3.862 (3.418, 4,644)	3.337 (2.738, 3.879)	0.030
B	3.661 (3.453, 4.018)	2.999 (2.779, 3.714)	0.020
C	3.489 (3.066, 3.945)	3.030 (2.642, 3.882)	0.096
D	3.824 (3.148, 3.959)	3.327 (2.205, 3.595)	0.140
Mean	14.353 (13.604, 16.050)	12.644 (11.696, 14.649)	0.010

PDS, patients with temporal lobe epilepsy with depression; nPDS, patients with temporal lobe epilepsy without depression.

TABLE 4 | Contribution of microstates A to D and results from comparison between two groups.

	PDS ($n = 19$)	nPDS ($n = 19$)	*P*-value
A	0.262 (0.236, 0.307)	0.247 (0.232, 0.289)	0.73
B	0.236 (0.202, 0.287)	0.238 (0.206, 0.280)	0.82
C	0.211 (0.197, 0.301)	0.221 (0.192, 0.310)	0.98
D	0.244 (0.186, 0.290)	0.257 (0.156, 0.300)	0.93

PDS, patients with temporal lobe epilepsy with depression; nPDS, patients with temporal lobe epilepsy without depression.

(SD: 3.9%) of the total variance across PDS and 78.2% (SD: 3.1%) across nPDS, respectively. These results suggested no statistical difference between these two groups ($p = 0.45$).

Figure 3 presents the duration, occurrence, and coverage for the four microstate classes. Microstate mean duration ranged from 38.8 to 190.1 ms for the different microstate classes. Patients with nPDS had longer duration on average than patients with PDS ($p = 0.013$) (**Table 2**; **Figure 3**). Microstate occurrence ranged between 0.07 and 5.84. Compared with patients with nPDS, patients with PDS displayed a less mean occurrence per second ($p = 0.010$). Proportion of total time covered by the different microstates varied from 0.3 to 57.6%. There was no difference between the two groups in the coverage of microstates A–D. In microstate A, compared with nPDS, the microstate occurrence of patients with PDS increased. But, there was no difference between the two groups with duration and coverage (**Table 4**). In microstate B, a higher occurrence per second with a shorter duration was found in patients with PDS compared with nPDS. The coverage did not reveal statistical significance between groups. In microstates C and D, the duration was shorter than in nPDS. No other temporal characteristics differed between the two groups (**Figure 1**; **Tables 2–4**). In this study, we showed the receiver operating characteristic (ROC) curves for microstate duration and occurrence (**Figure 4**). There was an adequate discrimination for patients with PDS and nPDS: on ROC analysis, all the areas under the ROC curves of both duration and occurrence shown in the figure were larger than 0.6 and were 0.73 for mean duration and 0.74 for mean occurrence.

Between any microstate measures above and the severity of depression according to the HAMD score, there was no significant correlation ($p > 0.05$).

DISCUSSION

We found a marked increase in the dynamic changes of the brain network in patients with PDS compared with patients with nPDS. Collectively, patients with PDS had shorter mean durations and higher occurrences than patients with nPDS. This is the first study to present the temporal fluctuations of EEG topography in patients with TLE with depression using EEG microstate analysis, which robustly affirmed alterations in a specific subset of subsecond functional states of brain.

To the best of our knowledge, only a handful of studies focused on spontaneous EEG microstates in TLE or depression (31–36). However, no studies are currently available that address the altered large-scale network dynamics in TLE with depression using microstate analysis. Compared to patients with nPDS, patients with PDS showed a decreased overall resting-state microstate duration of microstates B, C, and D and an increase of occurrence of microstate A and B.

Previous resting-state fMRI studies demonstrated that microstate class A was highly correlated with the auditory network (24). Involved regions included bilateral superior and middle temporal gyri, which is relevant to voice processing. Besides recognition of the brain involvement, the source of topography of EEG microstate has attracted much attention (37). Left lateral activity in temporal lobe, insula, medial prefrontal cortex, and the occipital gyri has been proposed as a major sources of microstate A (37, 38). Temporal lobe epilepsy and depression share common involved brain regions including the temporal, frontal lobes, amygdala, hippocampus, entorhinal cortex, subcortical structures including basal ganglia and thalamus, and the connecting pathways (39). The findings of fMRI studies showed the functional changes in the superior temporal gyrus in patients with a major depression (40, 41). A number of studies in the auditory domain document alterations in auditory system in major depressive disorder (MDD) (42–44). Higher occurrence of the microstate A has been shown to be related to greater depression severity in MDD. This conclusion was corroborated by our results, which showed the significant alterations of microstate A in patients with TLE with depressive symptom.

This study showed decreased duration and increased occurrence of class B in patients with PDS. Microstate B could

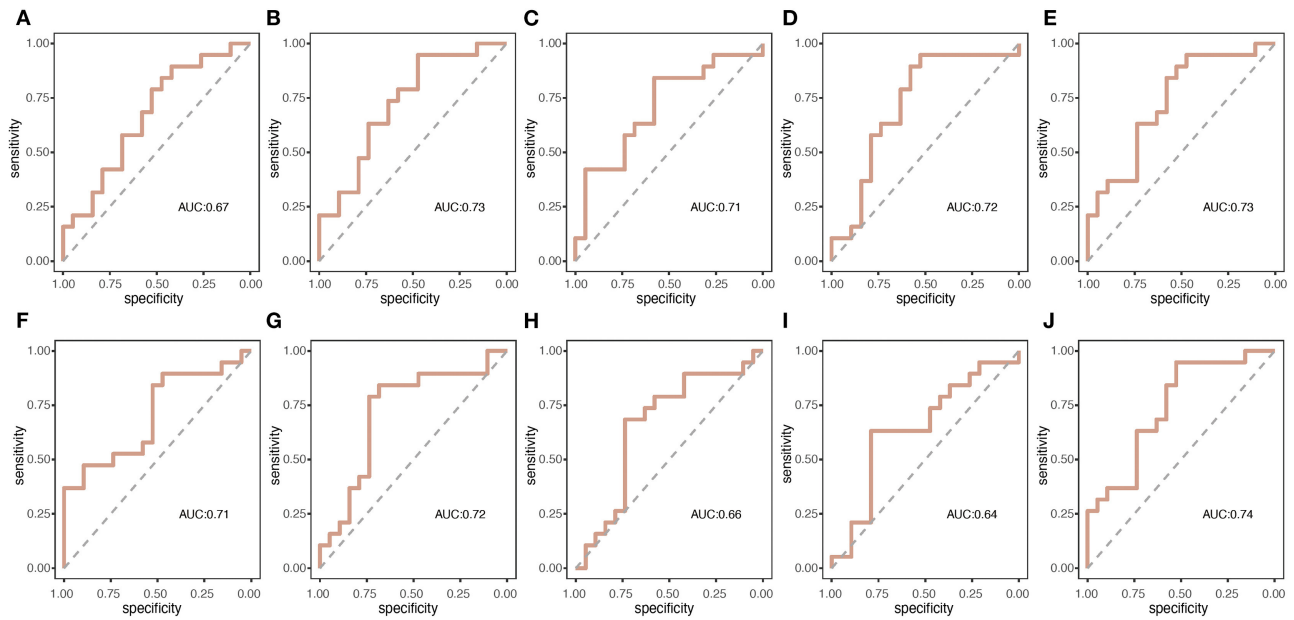

FIGURE 4 | The summary receiver operating characteristic (ROC) curves for the two groups of microstate duration and occurrence per second. **(A–E)** correspond to the duration of microstate map A–D and mean duration, respectively; **(F–J)** correspond to the occurrence per second of microstate map A–D and mean occurrence, respectively.

mirror the alterations in resting-state visual networks (24). Major depressive disorder had been reported to show abnormal functional connectivity (FC) within visual regions (45, 46). Abnormal visual and auditory networks have increasingly been recognized as a core feature of depression (47), which could explain, at least in part, by the fact that there were differences of microstates A and B between patients with PDS and nPDS.

The alterations in microstate C were not found to be unique to epilepsy. Prior microstate studies have reported increased frequency not only in epilepsy (31), but also in schizophrenia (48, 49) and syndrome of 22q11 deletion (50). Our results indicated that microstate map C could reflect the combined effect of comorbidity depression that patients living with TLE might harbor. Besides, precuneus activity often is implicated in microstate C (38) and it has been perceived in patients with TLE with MDD that the spontaneous brain activity is altered in precuneus (51). Therefore, we inferred that the alteration of microstate C in the nPDS group is likely driven by brain network involved precuneus. In addition, microstate map C is predominated by a task inhibitory alpha level (52). Intriguingly, past study has shown that depressive patients had decreased alpha (53, 54), which might be the key factor that causes vigilance in depressive behavior. Furthermore, a phenomenon that frontal EEG alpha asymmetry has been described in depressed patients (55, 56). All of the above could support the suggestion that in this study, the PDS group showed alterations of microstate C compared to the nPDS group.

Microstate D was found to be negatively related to BOLD signal changes in right-lateralized dorsal and ventral areas of the frontal-parietal networks involved in attentional reorienting and switching (22, 57). The default mode network (DMN) is disrupted in patients with TLE with MDD according to previous studies. Moreover, increased activation in the DMN including midline thalamus, precuneus, hippocampus, ventral anterior cingulate cortex, and prefrontal cortex was found in patients with TLE with depression (58), implying that midline structure is one of the key brain structures involved in the emotional modulation and hyperactivation in these regions disrupt normal emotional function. Consistent with these results, we found that microstate D showed shorter duration in patients with TLE with depression.

In addition, we found a lower duration of B to D microstates in patients with PDS. Duration is the key parameter in microstate analysis because accurate timing is of great importance to manage the flow of information the brain has to deal with at each moment to exert their functionality (59). This speaks to the increased dynamical changes of the brain network structures in patients with TLE with depressive symptom.

There was no correlation of the HAMD scores with microstate parameters. Such an observation may result from limitations to the utilization of the HAMD scale. As far as we know, most of the previous studies on depression used other depression scales such as Beck Depression Inventory-II (33) or Montgomery–Åsberg Depression Rating Scale (32) to assess correlation between depressive severity and microstate parameters. Therefore, another depression scale may have to be employed in future studies to capture this correlation.

LIMITATIONS

Several study limitations need to be acknowledged. First, the sample size may not be sufficient. Therefore, the study needs replications with larger sample sizes. Second, this study considers only temporal and not spatial dynamics or time-frequency analysis. Third, more detailed and comprehensive scales are required to assess the severity of depression. Furthermore, given that none of our patients with PDS received antidepressant therapy as EEG was recorded, we cannot come to any further conclusions with respect to the potential effect of antidepressants on the microstate parameters of patients with PDS.

CONCLUSION

We analyzed the altered resting-state EEG microstate dynamics measured with high-density EEG in TLE with comorbid depression and compared them to those without comorbid depression. Classic microstate analysis provide insight into subsecond time scale whole-brain dynamics in depression comorbidity in epilepsy. Large scale EEG microstate network alterations cast a perspective on the neuronal networks underlying depression in TLE. The high spatiotemporal resolution of high-density EEG provides a detailed understanding of functional network.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing Tiantan Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QW concepted, designed, and supervised the study. YS acquired the data, analyzed and interpreted the data, provided statistical analysis, had full access to all of the data in the study, responsible for the integrity of the data and the accuracy of the data analysis, and drafted the manuscript. GR, JR, and QW critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.753113/full#supplementary-material

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Levetiracetam Prophylaxis Therapy for Brain Tumor-Related Epilepsy (BTRE) Is Associated With a Higher Psychiatric Burden

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Purpose: Brain tumor-related epilepsy (BTRE) is a condition characterized by the development of seizures in the context of an undergoing oncological background. Levetiracetam (LEV) is a third-generation anti-seizure medication (ASM) widely used in BTRE prophylaxis. The study evaluated LEV neuropsychiatric side effects (SEs) in BTRE prophylaxis.

Method: Twenty-eight patients with brain tumors were retrospectively selected and divided into two groups. In one group, we evaluated patients with a BTRE diagnosis using LEV (BTRE-group). The other group included patients with brain tumors who never had epilepsy and used a prophylactic ASM regimen with LEV (PROPHYLAXIS-group). Neuropsychiatric SEs of LEV were monitored using the Neuropsychiatric Inventory Questionnaire (NPI-Q) at the baseline visit and the 6- and 12-month follow-up.

Results: Eighteen patients of the BTRE-group and 10 patients of the PROPHYLAXIS-group were included. Compared to the BTRE-group, the PROPHYLAXIS-group showed a higher severity of neuropsychiatric symptoms. According to Linear Mixed Models (LMM), a multiplicative effect was observed for the interaction between group treatment and time. For the caregiver distress score (CDS), only a time-effect was observed.

Conclusion: Prophylactic ASM with LEV is associated with an increased frequency of neuropsychiatric SE. Accurate epileptological evaluations in patients with brain tumors are mandatory to select who would benefit most from ASM.

Keywords: AMPA, glutamate, brain tumor epilepsy, psychiatry, side effect

INTRODUCTION

Brain tumor-related epilepsy (BTRE) is one of the most frequent neurological manifestations in the context of brain tumors. Seizures are frequently the onset symptoms in up to 40% of patients (1) with brain tumors. The prevalence of BTRE in patients with supratentorial brain tumors is up to 75%, with the highest percentage in cases of low-grade astrocytoma (2, 3). Treatment of BTRE is challenging due to the efficacy of anti-seizure medications (ASM) and the distinct side-effects

occurring in these patients that differ from non-oncological patients (4). Data on new ASM indicate a percentage of side-effects ranging from 7 to 44.4% (4).

According to some studies, the high prevalence of BTRE in patients suffering from brain tumors justifies the prophylactic use of ASM. The rationale for the procedure relates to the higher risk of developing BTRE, especially in association with brain surgery (5). The incidence of seizures is estimated to be 15–20% in patients who underwent non-traumatic, supratentorial craniotomy. According to expert opinion, the use of ASM in patients with supratentorial brain tumors should consider (6) risk-benefits assessment. According to the literature, ASM prophylactic treatment is generally recommended during the perioperative period, starting from brain tumor diagnosis and prolonged from 1 week to more than 12 months after brain surgery (7).

Levetiracetam (LEV) is a third-generation ASM that mainly blocks the SV2A presynaptic protein and decreases levels of excitatory neurotransmitters. Data in the literature highlight that LEV is associated with a favorable outcome in BTRE with a consistent reduction in seizure frequency (4, 8). LEV is also frequently used in BTRE prophylaxis, thanks to easy titration and low interaction with anti-neoplastic treatments (9). Most common side effects (SEs) of LEV include agitation, irritability, and aggressiveness. Tolerability and SEs of LEV in the context of BTRE and prophylactic treatment have been extensively evaluated throughout standard SE scales, such as Adverse Event Profile (AEP) scale and Quality of Life Questionnaire-35 (QOL-35) (4). However, these scales do not assess the psychiatric profiles of patients.

This study evaluated the psychiatric tolerability of LEV when used in prophylactic treatment compared to treatment of patients suffering from BTRE.

METHODS

Patient Demographics and Clinical Features

Adult patients with primitive brain tumors were retrospectively selected from the database of inpatients referred to the Neurology Clinic of "G. d'Annunzio" University of Chieti-Pescara from September 2018 to June 2020. The selection was made according to the following inclusion criteria: Mini-Mental State Examination (MMSE) score >24 at the time of brain tumor diagnosis, no history of psychiatric disorders, and no treatment with medications that interfere with behavioral functioning. As per routine protocol, all patients with brain tumors had undergone neuropsychiatric evaluations with Neuropsychiatric Inventory Questionnaire (NPI-Q) at the time of brain tumor diagnosis and the 6–12 month follow-up visits. Furthermore, patients had undergone a standard 21-channel-electroencephalogram (EEG) recording to confirm the diagnosis of BTRE. Diagnosis of epilepsy was reviewed based on the clinical and electrophysiological information according to International League Against Epilepsy (ILAE) diagnostic criteria. Independently of BTRE diagnosis, all patients included had been treated with oral administration of LEV. Patients were divided into two groups: patients with BTRE treated with LEV (BTRE-group) and patients without BTRE treated with LEV as prophylactic ASM (PROPHYLAXIS-group). As per standard clinical protocols, BTRE prophylaxis treatment usually lasts 12 months. Demographics, clinical, radiological, and neurophysiological data were compared between groups. In addition, mortality at 12 months was assessed in both groups. The study was approved by the local ethics committee ("G. d'Annunzio" University of Chieti-Pescara, Protocol code 2098. 11/06/2020, Protocol "Neurodem" 26/7/2018, Emend 2/8/2018). The patients/participants provided their written informed consent to participate in the study. If the patient could not read, write, or hear, informed consent was obtained from the legal guardian(s) of the patient. The present study was performed in agreement with the Declaration of Helsinki.

Neuropsychiatric Evaluation

The NPI-Q is a semi-structured clinician interview of caretakers that rates the severity and frequency of disturbance in 12 symptom domains (delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor activity, sleep disturbance, and eating disorders). For each domain, the overall impact is estimated as the product of the frequency of the psychiatric symptom (scores range 0–4) and its severity (scores range 0–3). In addition, caregivers rate the associated impact of the symptom manifestations on them using a five-point scale (caregiver distress scale, CDS).

The Neuropsychiatric Inventory Questionnaire total score represents the sum of all 12 sub-scores and ranges between 0 and 144. Scoring in subscales of the NPI-Q has been shown to strongly correlate with those in other well-validated symptomatic scales, such as the Hamilton Rating Scale for Depression (10). According to the literature, NPI-Q could be crucial in behavioral assessment in patients with brain tumors. Indeed, NPI-Q in brain tumor patients seems more appropriate than behavioral inventories implemented for psychiatric populations (e.g., Mini-International Neuropsychiatric Interview—M.I.N.I.). Furthermore, administering by-proxy neuropsychiatric tests allows detecting behavioral disturbances in patients with language impairment or anosognosia (11).

The NPI-Q was administered to the spouse or to a close first-degree relative who lived with the patient.

Statistical Analysis

Data are reported as the median plus interquartile range (IQR) or absolute number and percentage for continuous, or categorical and dichotomous variables, respectively. Differences between groups were compared using general linear models for continuous variables and with the χ^2 test for categorical and dichotomous variables. Differences in the frequency of clinical manifestations between two groups were assessed with the χ^2 test. Logistic Regression Models were used to produce odds ratio (OR), and 95% CI, to assess ASM prophylactic therapy association with mortality. To evaluate variations in scores related to the NPI-Q scale according to time (baseline, 6 and 12 months follow-up) and group (BTRE-group and

TABLE 1 | Demographics and brain tumor characteristics and treatment.

	BTRE-group *(n = 18)*	**PROPHYLAXIS-group *(n = 10)***	
Age	46.9 ± 15.5	60.7 ± 16	*p = 0.04*
Sex	11M 7F	5M 5F	*p = 0.67*
Baseline KPS [median (IQR)]	1 (0.9–1)	1 (0.9–1)	*p = 0.84*
6-months KPS [median (IQR)]	1 (0.9–1)	1 (0.9–1)	*p = 0.84*
12-months KPS [median (IQR)]	0.9 (0.8–1)	0.9 (0.8–1)	*p = 0.13*
Tumor hystology	○ Glioblastoma (WHO IV): 10 ○ Anaplastic astrocitoma (WHO III): 1 ○ Low grade astrocitoma (WHO II): 4 ○ Oligoastrocitoma: 3	○ Glioblastoma (WHO IV): 5 ○ Anaplastic astrocitoma (WHO III): 2 ○ Low grade astrocitoma (WHO II): 2 ○ Cerebral gliosarcoma: 1	*p = 0.67*
Localization	○ Frontal: 7 ○ Temporal: 7 ○ Parietal: 4	○ Frontal: 3 ○ Temporal: 3 ○ Parietal: 4	*p = 0.79*
Dimension	○ <5 cm: 9 ○ >5 cm: 9	○ <5 cm: 7 ○ >5 cm: 3	*p = 0.58*
Lateralization	○ Right 10 ○ Left 8	○ Right 4 ○ Left 6	*p = 0.62*
Type of surgery	○ GTR: 8 ○ STR: 10	○ GRS: 5 ○ STR: 5	*p = 0.67*
12-months tumor relapse	2	5	*p = 0.03*
CT/RT treatment	14	8	*p = 0.27*
12-months tumor mortality	2	5	*p = 0.03*

KPS, Karnoski Performance status; GRS, gross tumor resection; STR, sub-total tumor resection; CT, chemotherapy; RT, radiotherapy.

PROPHYLAXIS-group), Linear Mixed Models (LMMs) were used. The main effects of fixed factors and their respective interactions were assessed by model comparisons (Likelihood Ratio Tests). The intercept was added as random factors with uncorrelated random intercepts and slopes within participant and time. LMMs highlight interactive effects among predictors (i.e., whether ASM prophylactic therapy and the course of time synergically impact on NPI-Q total score of CDS score) or unravel individual effects of each predictor on a given outcome (i.e., whether ASM prophylactic therapy, independently of time, affects the risk for increased NPI-Q total score or CDS score). Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided, and statistical significance was defined at $p < 0.05$.

RESULTS

Demographics

Eighteen adult patients (mean age: 46.9 ± 15.5; men: 11) with BTRE (BTRE-group) and 10 patients (mean age: 60.7 ± 16; men: 5) under prophylactic treatment with LEV (PROPHYLAXIS-group) were eligible for the study. At the study entry, no patients showed psychiatric symptoms or cognitive impairment as assessed by the NPI-Q and MMSE scores. Sixteen patients in the BTRE-group (16/18, 89%) and 9 patients in the PROPHYLAXIS-group (9/10, 90%) were married and living together with their spouses. Two patients in the BTRE-group (2/18, 11%) and one patient in the PROPHYLAXIS-group (1/10, 10%) lived with their relatives. Two patients in the BTRE-group (2/18, 11%) and five patients in the PROPHYLAXIS-group (5/10, 50%) died due to tumor progression during follow-up. Sixteen patients in the BTRE-group (16/18, 89%) and five patients in the PROPHYLAXIS-group (5/10, 50%) completed the 12-month follow-up. Demographic data are summarized in **Table 1**.

Seizure Prevalence and Electrophysiological Assessment

In the BTRE-group, focal seizures represented the onset symptom of underlying tumor pathology in 14 patients (78%). Focal-to-bilateral seizures were reported in 4 patients (4/18, 22%). EEG evaluation in BTRE group showed focal slow activity in 9 patients (9/18, 50%), epileptiform discharges in 3 patients (3/18, 17%), lateralized periodic discharges in 1 patient (1/18, 6%), and normal EEG in 4 patients (4/18, 22%). In the PROPHYLAXIS-group, EEG analysis revealed focal slow activity in 3 patients (3/10, 30%), lateralized periodic discharges in 1 patient (1/10, 10%), whereas 4 patients showed a normal EEG (4/10, 40%). The median LEV daily dose in the BTRE-group was 2,000 mg (IQR: 1,500–2,500 mg) and 2,000 mg (IQR: 1,000–2,000 mg) in the PROPHYLAXIS-group. No differences in the titration schedule were observed when comparing the two groups. Dose adjustment was performed according to seizure frequency of the patients during the follow-up in 2 patients in the BTRE group, who experienced seizure recurrence during follow-up. Serum levels of LEV were tested and always resulted within the normal range. Blood tests showed no abnormal findings in both groups. In particular, normal levels of creatinine clearance were observed. At the 12 months follow-up visit, seizure freedom

TABLE 2 | Seizure prevalence and electrophysiological assessment features.

	BTRE-group *(n = 18)*	PROPHYLAXIS-group *(n = 10)*
Seizure type	○ Focal: 14 ○ Focal-to-bilateral: 4	NA
Seizure onset concomitant to brain tumor diagnosis	4	NA
Electroencephalogram (EEG)	○ Focal slow: 9 ○ EDs: 3 ○ LPDs: 1 ○ Normal: 4 ○ Not available: 1	○ Focal slow: 3 ○ LPDs: 1 ○ Normal: 4 ○ Not available: 2
LEV dose [median (IQR)]	2,000 mg (1,500–2,500)	2,000 mg (1,000–2,000)
12-months seizure freedom (number of patients)	16	NA

EDs, epileptic discharges; LPDs, lateralized periodic discharges.

was detected in 16 patients (16/18, 89%), whereas 2 patients (2/18, 11%) presented a reduction >50%. No seizures have been reported in the PROPHYLAXIS-group for the whole length of the follow-up period. Discontinuation of ASM or treatment dose reduction due to the onset of AE was observed neither in the BTRE-group nor in the PROPHYLAXIS-group.

Seizure prevalence and electrophysiological assessment features are summarized in **Table 2**.

Brain Tumor Characteristics and Treatment

Histological evaluation revealed a WHO IV glioblastoma in 10 patients in the BTRE-group (10/18, 55%) and 5 patients in the PROPHYLAXIS-group (5/10, 50%). Frontal localization was reported in 7 patients in the BTRE-group (7/18, 39%) and 3 in the PROPHYLAXIS-group (3/10, 30%). Tumor dimension was >5 cm in 9 patients (9/18, 50%) and 3 patients (3/10, 30%) in the BTRE-group and PROPHYLAXIS-group, respectively. Ten patients (10/18, 55%) in the BTRE-group exhibited right-side localization of the brain lesion compared to 4 patients (4/10, 40%) in the PROPHYLAXIS-group.

All patients underwent brain surgery with total resection of the neoplastic lesion in 8 patients in the BTRE-group (8/18, 44%) and 5 patients in the PROPHYLAXIS-group (5/10, 50%). All patients were treated with the current standard oncologic treatment protocols, which included radiotherapy (RT) (age >70 years: 40 Gy; age <70 years: max 60 Gy) and chemotherapy (CT) (temozolomide for 6–12 cycles during and following RT) when indicated. If needed, anti-edema treatment with corticosteroids or mannitol was administered at the brain tumor diagnosis and discontinued after 1 week. Two patients (2/18, 11%) in the BTRE-group and five patients (5/10, 50%) in the PROPHYLAXIS-group experienced tumor relapse after RT/CT treatment. Tumor relapses were observed after an average time of 7 months (IQR: 6.5–8.5). In the BTRE-group, all patients with tumor relapses underwent second surgery followed by retrial of CT with temozolomide. In the PROPHYLAXIS-group, 3 patients underwent second surgery followed by CT with temozolomide, whereas 2 patients only underwent CT retrial with temozolomide. Brain tumor characteristics and treatments are summarized in **Table 1**.

Neuropsychiatric Assessment

At baseline, according to the enrollment criteria, both groups did not present neuropsychiatric symptoms as assessed by NPI-Q. The overall incidence of neuropsychiatric symptoms at 12 months follow-up visit is reported in **Figure 1A**. Agitation (46.4%), depression (53.6%), and anxiety (35.7%) were the most frequent neuropsychiatric signs associated with LEV treatment. However, compared to the BTRE-group, the incidence and the severity of neuropsychiatric symptoms in the PROPHYLAXIS-group were higher (see **Figure 1B**). **Figure 2A** shows changes in NPI-Q total scores in the two subgroups during follow-up. Interestingly, a multiplicative effect for the interaction between group treatment for time ($p = 0.02$) was observed. When plotting death and tumor characteristics as a covariate in the Mixed Model, the results were substantially unchanged (tumor characteristics $p = 0.60$; and death rate $p = 0.79$; AIC 486 vs. 479 in the full adjusted model). The use of symptomatic treatment with diazepam in case of agitation or anxiety was reported in 4 patients in the PROPHYLAXIS-group (4/10, 40%) and 1 patient in the BTRE-group (1/18, 6%) (median: 8 mg, IQR: 5–10).

Figure 2B shows CDS changes in the two subgroups according to time. For the CDS, only a time-effect was observed, whereas no additive or multiplicative effect was found. NPI-Q-scale and CG-stress scores were not different according to brain tumor characteristics.

Mortality Risk

A total of seven deaths (7/28, 25%) were recorded in the entire study population, two of them (2/18, 11%) in the BTRE-group and five (5/10, 50%) in the PROPHYLAXIS-group (two-tailed Fisher's exact test $p = 0.03$). To assess the risk of mortality related to ASM, a Logistic Regression model was applied. In the PROPHYLAXIS-group, death could be associated with ASM with an OR = 8.00 (95% CI: 1.17–54.71). However, when in the Logistic Regression model, age and sex were considered, the association was no more statistically significant (PROPHYLAXIS-group OR = 6.10; 95% CI: 0.63–59.20). No significant association was found between tumor characteristics (i.e., tumor relapse, dimension, histology, surgical, and therapeutical approaches) and death (data not shown).

DISCUSSION

Our study indicates that patients treated with LEV as ASM prophylactic therapy show worse NPI-Q total scores and depression sub-scores when compared to patients treated with LEV in the context of BTRE. The mechanisms through which LEV can produce psychotic symptoms are largely unknown and not necessarily related to synaptic vesicle protein SV2A blockade. Supporting this notion, the recently introduced ASM Brivaracetam (BRV), a derivative

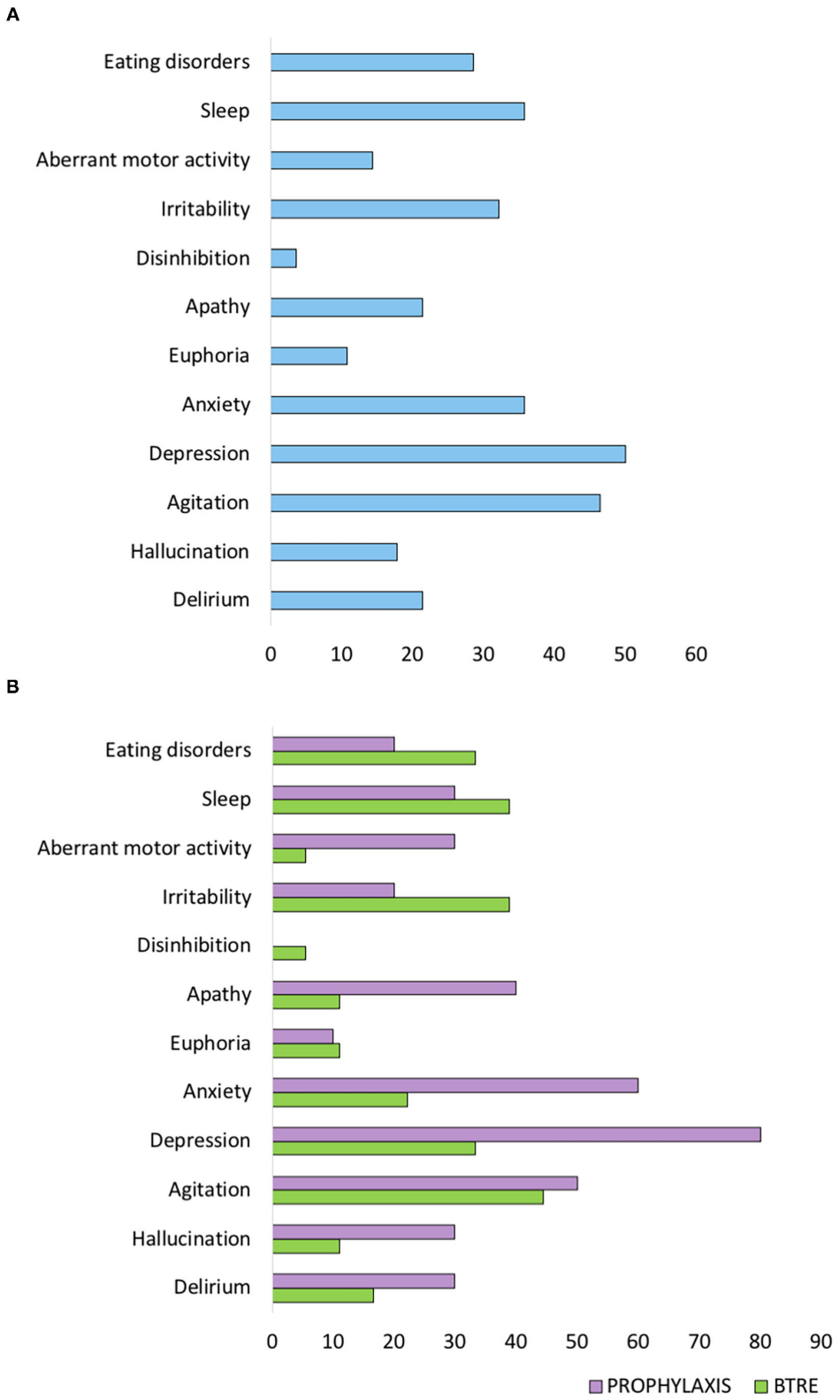

FIGURE 1 | Neuropsychiatric Inventory (NPI-Q) scale score at 12 months follow-up visit. **(A)** NPI-Q sub-items scores of the entire study population. **(B)** NPI-Q sub-items scores of the two subgroups.

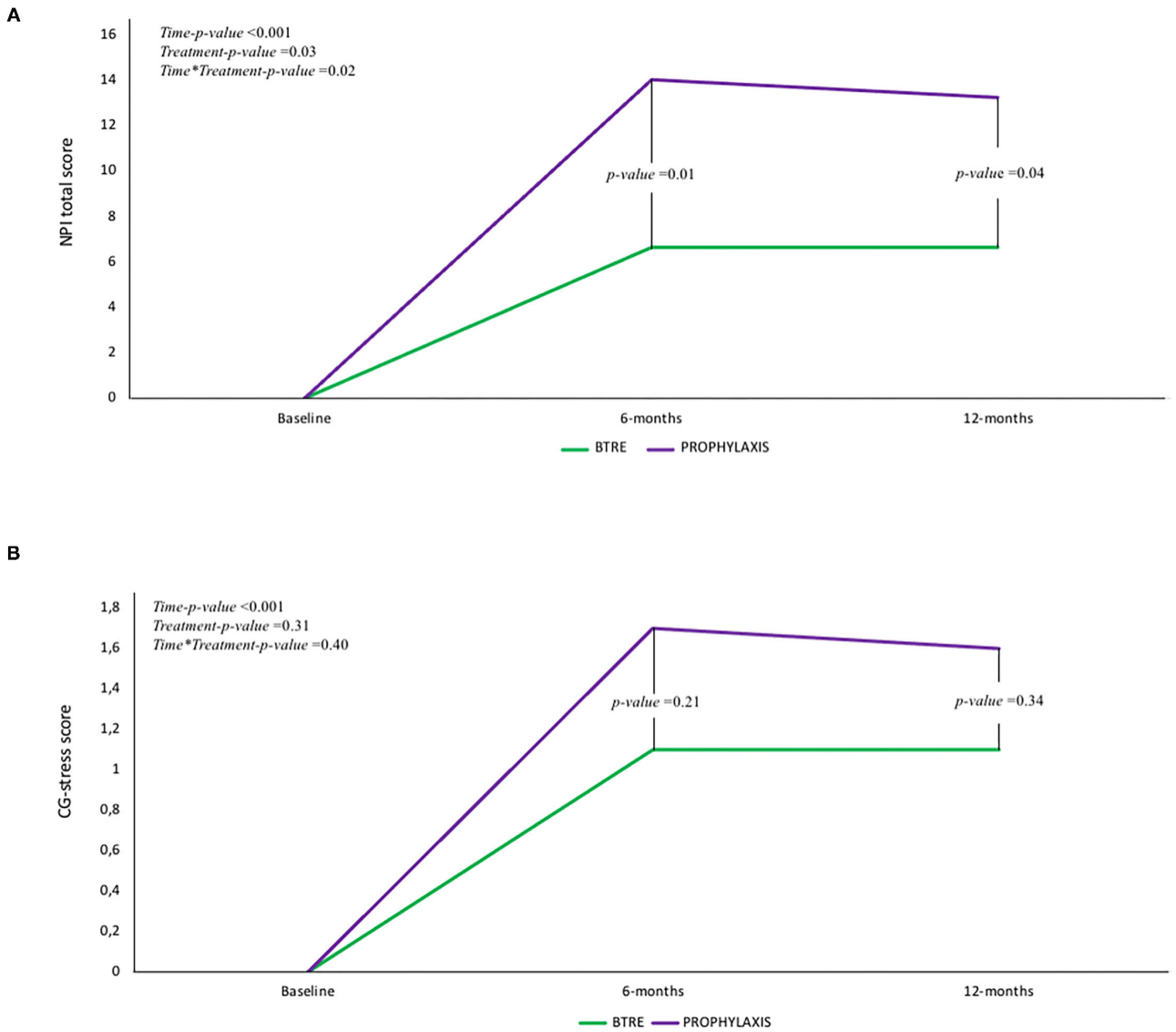

FIGURE 2 | (A) Change in Neuropsychiatric Inventory (NPI-Q) total score in the two subgroups according to time. A multiplicative effect for the interaction between group treatment for time ($p = 0.02$) was observed. **(B)** Change in caregiver distress score (CDS) in the two subgroups according to time. For the CDS only a time-effect was observed whereas no additive or multiplicative effect was found.

of LEV/piracetam with a higher affinity to SV2A, has been associated with a lower incidence of psychiatric SEs than LEV. Moreover, LEV exhibits broad pharmacological effects due to the interaction with various receptors, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors (AMPArs) (12). According to literature, AMPAr Inhibition by LEV is rapid and readily reversible (13). In addition, LEV modulated the presynaptic P/Q-type voltage-dependent calcium channel to reduce glutamate release (13).

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors are highly expressed in glioblastoma and play a pivotal role in mediating the glutamate-related effects in gliomas. Experimental models show that high-grade gliomas release excitotoxic concentrations of glutamate, which has been shown to enhance tumor proliferation and migration (14). Stimulated AMPAr generates the cytoskeletal reorganization of glioma cells and has been shown to improve the detachment of cells from the extracellular matrix and glioma invasion (15).

Recent evidence confirmed that glutamate, the main excitatory neurotransmitter in the central nervous system, is a critical driver for tumor-associated seizures (16). Recent studies comparing patients with or without tumor-associated seizures

demonstrated increased glutamate concentrations in tumors and peritumoral glioma tissues of seizure patients (17). In addition, increased expression of several glutamate receptor subtypes, such as AMPAr, has been shown in the reactive astrocytes of perilesional zones (18). Glutamate can also modulate the onset of psychiatric symptoms. Behavioral changes, agitation, anxiety, psychosis, aggressive behavior, and depression have been described in experimental and clinical settings assessing the use of AMPAr blockers (19). The higher expression of glutamate and increased level of AMPAr in BTRE patients may explain the reduced burden of LEV-related psychiatric SEs in the group. In particular, in BTRE patients, LEV blocks glutamate release and modulates AMPAr activation, thereby helping to halt the neuronal hyperactivation of the epileptic focus.

On the contrary, patients treated with prophylactic therapy with LEV do not exhibit increased glutamate expression or altered neuronal activation. In this context, the blockade of AMPAr may disrupt the brain homeostasis of glutamatergic transmission, thereby leading to the onset of psychiatric symptoms.

The LEV-related mechanism of action is not fully understood. The hypothesis of glutamate-dependent induction of network hyperactivity and the subsequent production of psychiatric symptoms in LEV-treated patients is a possibility. However, neuronal hyperactivity can also be independent of AMPAr overactivation.

According to a recent meta-analysis, ASM prophylaxis does not reduce the incidence of postoperative seizure in seizure-naïve brain tumor patients. On the contrary, ASM prophylaxis is associated with a relatively high rate of dermatological (rash), neurological (ataxia, decreased level of consciousness and aphasia), psychiatric (depression), and hematological (thrombocytopenia, electrolyte imbalance) SEs (up to 17–34%) (20). Supporting this evidence, we have shown that psychiatric SEs of prophylactic therapy, which are generally underestimated, may occur in patients with a brain tumor. In our cohort, the choice of prophylaxis treatment for BTRE was based on decisions of the clinicians shaped by divergent management policies for oncological patients. In particular, most of the PROPHYLAXIS-group patients were evaluated by clinicians with little experience in neuro-oncology and BTRE management. Undoubtedly, brain tumor features should be taken into account to assess the role of LEV in modulating the onset of psychiatric symptoms. Some studies stressed that lesion localization plays a role in psychiatric symptoms onset (21). In particular, neoplastic lesions in the frontal and parietal cortices and paralimbic structures have been generally associated with the occurrence of neuropsychiatric symptoms. In addition, some authors have suggested that the right localization of the lesion is associated with an increased rate of psychiatric symptoms (22). However, in our cohort, lesion sites and lesion lateralization were not different when comparing the two groups for NPI-Q total scores and depression sub-scores. No correlations with either tumor localization or tumor size were found, thereby supporting the assumption of a possible effect of LEV in the onset of psychiatric symptoms unrelated to brain tumor characteristics.

Neuropsychiatric symptoms can negatively affect social environment, such as family members and close friends, and performances of the patients in the activity of daily living. In addition, there are indications that brain tumor patients are at an increased risk for death by suicide even though this risk is lower if compared to patients with other oncological issues (23). Changes in personality and behavior, mood issues, hallucinations, and psychosis are challenging to be recognized in patients with brain tumors and have not been widely explored in literature (24). The use of specific scales and evaluation tools may help clinicians to generate more accurate psychiatric comorbidity evaluations. In this regard, the NPI-Q scale is a valid caregiver-rated measure of psychopathology in people with epilepsy.

The lack of evidence concerning the efficacy and tolerability of antidepressants (25) and antipsychotic treatments, the possible drug-to-drug interaction with CT (26), and the unknown benefits of cognitive-behavioral treatment (CBT) make the management of psychiatric symptoms in patients with brain tumors challenging. In this context, therapies associated with increased risk for suicide or suicide attempt, depression, or panic disorder should be avoided.

LIMITATIONS

The study has several limitations. First of all, given the retrospective observational design of the study, the sample size of the PROPHYLAXIS-group is smaller than the BTRE-group. Hence, caution should be used when interpreting the data as they may not entirely represent brain tumor patients. Studies with larger cohorts are needed. A recent randomized control study in the United Kingdom (27) is set to address this issue and will provide information on the topic. However, our study provides clinicians with data to discuss the risk/benefit ratio of LEV prophylaxis with brain tumor patients.

CONCLUSION

Several studies have demonstrated the efficacy and safety of LEV when used in the context of BTRE and as anti-seizure prophylactic therapy in brain tumor pathology. However, little data are available regarding the neuropsychiatric SEs of LEV intake in patients suffering from brain tumors. Our results support the importance of accurate epileptological evaluations in patients with brain tumors to identify and select who is most likely benefiting more from anti-seizure therapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by G. d'Annunzio University of Chieti-Pescara, Protocol code 2098. 11/06/2020. Protocol Neurodem 26/7/2018, Emend 2/8/2018. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FD: contributed to the conception and design of the study. AR and GE: organized the database. AD: performed the statistical analysis. FD, MO, and SS: wrote the manuscript and supervised all the data. All authors contributed to manuscript revisions, read, and approved the submitted version.

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Validation of the Chinese Version of the Stigma Scale of Epilepsy

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Purpose: This study was carried out to test the validity and reliability of the Chinese version of the Stigma Scale of Epilepsy (SSE), with aim to better understand the public stigmatizing attitudes of epilepsy in China and help elucidate stigma determinants for interventions.

Methods: The SSE was translated into Simplified Chinese Mandarin. In this study, most of the participants were enrolled *via* convenience sampling by randomly distributing questionnaires on the streets and parts of the participants were recruited by an online platform named Wenjuanxing. We assessed the psychometric properties of the SSE in 310 Chinese native-speaker. Cronbach's alpha was tested for reliability. Index of Content Validity (CVI) was calculated. Exploratory and confirmatory analysis were used to explore the factor structure and verify the validity of SSE.

Results: The Cronbach's alpha is 0.936 for the overall scale, and the CVI value is greater than 0.78. The exploratory factor analysis (EFA) extracted SSE six factors: the fear of seizure attacks (factor 1), sympathy for patients with epilepsy (PWEs) (factor 2); difficulties faced by PWEs (factor 3); speculation on PWEs' feeling (factor 4); discrimination against PWEs (factor 5); and knowledge about epilepsy (factor 6). The item 13 was proven to be problematic and has been eliminated. The confirmatory factor analysis (CFA) ensured the great construct validity (χ^2/SD = 1.725, goodness of fit index (GFI) = 0.916, and root mean square error of approximation (RMSEA) = 0.048), convergent validity (the factor loads of each item corresponding to each latent variable >0.6, average variance extracted (AVE) > 0.5, and composite reliability (CR) > 0.7), and discrimination validity (all of the absolute value of correlation coefficient are <0.5,and less than the square root of AVE) of the SSE.

Conclusions: The Chinese version of the SSE scale was a valid and reliable tool to measure epilepsy-associated stigma in the Chinese society.

Keywords: epilepsy, the stigma scale of epilepsy, validation, China, stigma

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INTRODUCTION

Epilepsy is a chronic neurological disease characterized as excessive hyper synchronized discharge of brain neurons (1, 2). Patients with epilepsy (PWEs) not only suffer from the physical problems (such as, fractures and bruising from injuries related to seizures), but also a series of complex psychosocial disorders, such as anxiety, depression, suicidal risk, stigma and discrimination,

exclusion, and overprotection (1, 3–6). Among these psychosocial disorders, stigma is the one with great impacts on the recovery, prognosis, and quality of life among PWEs (7, 8), which is even greater than the adverse reactions of epileptic seizure and antiepileptic drugs (9).

The stigma related to epilepsy prevails globally (10), and it may be much more serious in China than elsewhere. To date, there are more than 9 million PWEs in China with a treatment gap of 63% (10–12). The incidence of stigma among PWEs in urban and rural areas are 71% and 89%, respectively (13). Guo pointed out that the sources of PWEs' stigma in China come from three main aspects: seizure attacks, social misconceptions, and negative attitudes toward epilepsy and negative psychological factors of patients (14). Unlike other chronic diseases, such as diabetes, the onset of seizures is sudden, uncontrollable, and always accompanied with a series of unsightly manifestations, such as sudden falls, limbs twitching, and foaming at the mouth (15), which may be a shock or an unacceptable thing to the witnesses for the first time. These feelings will alienate the witnesses from PWEs, which is a form of stigma. Besides, social misconception about epilepsy may contribute a lot to epilepsy-associated stigma (16). In rural areas of China, it is believed that epilepsy was caused by seeing ghosts, being possessed by devils, and was always thought to be a mental disease rather than neurological disease, with high possibility to be passed on to the next generation (17, 18). About 14% of parents do not want their children to play with children with epilepsy, and 75% of parents do not want their children to marry a PWE (19). Even the medical staffs in basic-level hospitals from southern China, they still showed negative and conservative attitudes toward PWEs (20). For PWEs themselves, they feel that they are physically defective and worry about their future career and social life because of their misperceptions about epilepsy, which will definitely lead to the aggravation of felt stigma (21). Therefore, it is of great importance to make everyone aware of the problems faced by PWEs and fundamentally change misconceptions of people and explore stigma determinants for social interventions in China.

To achieve effective stigma reducing interventions, stigma need to be measured accurately. The Epilepsy Stigma Scale (EES) and the Kilifi Stigma Scale of Epilepsy (KSSE) are the commonly used scales for evaluating self-stigma of PWEs (22, 23). From the perspective of people without epilepsy, the Stigma Scale of Epilepsy (SSE), developed by Brazilian researchers, has been widely applied all over the world, such as Zambia, the Czech Republic, Italy, India, and Korea (24–31). Some studies used "Public Attitudes Toward Epilepsy" scale (PATE) to evaluate the epilepsy-associated knowledge, attitudes, and practices (KAP) among the public (32, 33). But this scale lacks the focus on emotional reaction of public to epilepsy and PWEs. It is known that the PWEs are always accompanied with mood disorder, which would have effect on stigma (34). Furthermore, the public emotional reactions toward epilepsy or seizure attacks may be a source of stigma of PWEs (29). Thus, in our study, we chose the SSE to assess the epilepsy-related stigma and related emotional reaction from the perspective of people without epilepsy. Considering that its high internal consistency and validity has not been confirmed in China, we proposed to investigate the psychometric properties of the SSE and validate the Chinese version of SSE to access the epilepsy-related stigmatization of the public in China.

METHODS

Subjects

Chinese-native speakers were enrolled *via* convenience sampling by randomly distributing questionnaires on the streets of Changsha, China, and parts of the participants were recruited by an online platform named Wenjuanxing. The participants in the study had no history of seizures or epilepsy. No other exclusion criteria were made. Written consents were obtained and all questionnaires were administered anonymously. The sociodemographic characteristics of participants, such as age, gender, marital status, educational levels, medical background, and family history of epilepsy were recorded.

Ethics Statement

Our study has been approved by the Ethics Committee of the Xiangya Hospital of Central South University [No. 201912528]. All the participants were informed about the purpose and significance of our study and that their answers to the scale will be used in our scientific research. All the subjects provided informed consent in writing.

Measurements

The SSE scale is developed and validated by Fernandes (24, 25, 29). The SSE scale is a five-dimensional 24-item scale that measures public stigma toward epilepsy. The first dimension includes one item for the understanding of disease essence. The second dimension consists of four items about the emotions when the people witness a seizure. The third and fourth dimension both have seven items, reflecting the difficulties face by PWEs and the public emotions from the patient's point of view, respectively. The fifth dimension contains 5 items showing the prejudice and discrimination associated with epilepsy. Each item has four response categories with 1 being "agree not at all," 2 being "a little," 3 being "a lot," and 4 being "totally agree." The internal consistency of the SSE for the score showed a general Cronbach's coefficient of 0.88 for the PWEs and 0.81 for people in the community.

Translation of the SSE Into Simplified Mandarin Chinese

To be consistent with rules for the translation of research tools and make the questionnaire acceptable and comprehensible, the original SSE scale was translated into Mandarin Chinese by the two separate and bilingual researchers, who have no medical knowledge and systematic training. Then, the authors modified the translated words because of conservative culture and thinking. A team of clinical neurologists and psychologists checked and determined the better version. Furthermore, the better Chinese version of SSE was translated back into English and compared with the original scale. Modifications are made until the acceptable Chinese version is agreed. After reviewing the logic and typo errors, twenty native Chinese speakers from

different background were asked to complete the draft and point out any ambiguities or difficulties in understanding. All the revisions were contained in the last version of the scale. After that, we invited another twenty native Chinese speakers, and they did not raise any new questions. Therefore, the last version was finalized.

Sample Size

The sample was calculated according to the widely quoted rule of thumb (35), in which 10 or 5 subjects at a minimum are required for every item being analyzed. Not <120 or 240 subjects are required in our research. As Comrey (36) suggested that "a sample size of 100 is poor, 200, fair; 300, good; 500, very good; and 1,000, excellent, we included 300 subjects at least in our study."

Data Analysis

Data were input with excel and analyzed with IBM SPSS Statistics 25 software and AMOS 24 software. Descriptive statistics were used to characterize the subjects and distribution of SSE scores. Categorical variables were expressed as number and percentage.

Reliability

The internal consistency of the scale was assessed by corrected item-total correlations, Cronbach's alpha and Cronbach's Alpha if item removed. The value of corrected item-total correlations should be >0.4. An alpha value of 0.7–0.9 is acceptable, >0.9 is ideal.

Validity

We invited six experts from the psychology, epidemiology, and neurology departments to evaluate the content validity of the SSE. Experts were asked to make a choice on how relevant (or representative) each item was to the corresponding content dimension, and to suggest items that needed to be added or adjusted. In general, the options are 4-point rating: 1 = inappropriate, 2 = relatively inappropriate, 3 = relatively appropriate, and 4 = appropriate. The higher the score, the more appropriate the item. Index of Content Validity (CVI) was calculated to evaluate to the relevance of the item to the corresponding content dimension, and the value of CVI should be not <0.78. Before exploratory factor analysis (EFA), The Kaiser–Meyer–Olkin (KMO) test was applied for sampling adequacy and whether the data met the criteria of principal component analysis (PCA). The KMO value should be >0.6 and the factor loading coefficient of the item on the corresponding factor need to be >0.5. We used the varimax rotation and scree plot for EFA. Eigenvalue >1 was used to identify the number of extracting factors in the scree plot. Confirmatory factor analysis (CFA) was performed to further check the factor structure of the translated Chinese version of SSE. Average variance extracted (AVE) and composite reliability (CR) are commonly used indicators of polymerization validity. In general, AVE is >0.5 and CR value is >0.7 (37), indicating high polymerization validity. The discriminant validity can be tested by comparing the AVE square root with the correlation value. If the AVE square root is greater than the correlation value, the discriminant validity is good. We performed a comparison between the total score of SSE and scores of each factor with medical background and family history of epilepsy using Mann–Whitney test to prove the validity.

TABLE 1 | Demographic characteristic of participants ($n = 310$).

		Number (%)
Sex	Male	179 (57.7)
	Female	131 (42.3)
Age	under 18 years old	7 (2.3)
	18–60 years old	296 (95.4)
	60 years old or above	7 (2.3)
Marital status	Married	126 (40.6)
	Single	178 (57.4)
	Divorced	6 (1.9)
Education level	Primary or under	4 (1.3)
	Middle or High School	106 (34.2)
	College or above	200 (64.5)
Medical background	Yes	65 (21.0)
	No	245 (79.0)
Family history of epilepsy	Yes	10 (3.2)
	No	300 (96.8)

RESULTS

The Chinese SSE

After the standard translation process described above, the finalized Chinese version of the SSE was created (**Appendix 1**). The average time to fill out the scale was about 5 min.

Demographic Data

In total, 310 subjects completed the questionnaire. The ages of the 310 respondents in the study varied between 15 and 74 years, with 57.7% male respondents, 40.6% married, 98.7% having a minimum education of 9 years, 21.0% having medical background, and 3.2% having family history of epilepsy (**Table 1**). **Table 2** depicts the percentage distributions of the responses to each item on the Chinese SSE scale.

Validity

The KMO test and Bartlett's test of sphericity were performed before PCA. The KMO value was 0.913, and Bartlett's test value was 5,226.218 ($p = 0.001$), suggesting that the data are suitable for a factor analysis. Researchers conducted EFA under a condition of undefined factor number. Six factors (eigenvalue >1) were extracted. The cumulative variance contribution rate (%) of six factors was 73.076%. Moreover, the scree plot indicated that the 6-factor structure was suitable for the scale (**Figure 1**). The results of rotated component matrix was shown in **Table 3**. The bold vale of **Table 3** means the factor loading of the item in the corresponding component is >0.5, which indicates the item should be attributed to this component. Based on above theoretical analyses, the interpretation of factors given in **Table 3** was recommended as follows: factor 1 refers to the public's

TABLE 2 | Felt stigma measures using the Stigma Scale of Epilepsy (SSE).

Stigma scale of epilepsy, number (%)	Not at all	A little	A lot	Totally
Question 1: Do you think that people with epilepsy feel able to control their own epilepsy?				
1. Control	190 (61.3)	87 (28.1)	28 (9.0)	5 (1.6)
Question 2: How would you feel when you see an epileptic seizure?				
2. Scared	57 (18.4)	151 (48.7)	50 (16.1)	52 (16.8)
3. Fear	75 (24.2)	129 (41.6)	56 (18.1)	50 (16.1)
4. Sadness	22 (7.1)	82 (26.5)	80 (25.8)	126 (40.6)
5. Pity	15 (4.8)	58 (18.7)	61 (19.7)	176 (56.8)
Question 3: Which difficulties do you think people with epilepsy have in their daily lives?				
6. Relationships	19 (6.1)	117 (37.7)	71 (22.9)	103 (33.2)
7.Work	12 (3.9)	104 (33.5)	74 (23.9)	120 (38.7)
8. School	36 (11.6)	107 (34.5)	73 (23.5)	94 (30.3)
9. Friendships	27 (8.7)	113 (36.5)	72 (23.2)	98 (31.6)
10. Sexual	40 (12.9)	131 (42.3)	73 (23.5)	66 (21.3)
11. Emotional	34 (11.0)	126 (40.6)	81 (26.1)	69 (22.3)
12. Prejudice	22 (7.1)	116 (37.4)	91 (29.4)	81 (26.1)
Question 4: How do you think that people with epilepsy feel?				
13. Worried	15 (4.8)	92 (29.7)	105 (33.9)	98 (31.6)
14. Dependent	31 (10.0)	170 (54.8)	71 (22.9)	38 (12.3)
15. Incapable	42 (13.5)	148 (47.7)	78 (25.2)	42 (13.5)
16. Fearful	25 (8.1)	118 (38.1)	94 (30.3)	73 (23.5)
17. Depressed	22 (7.1)	136 (43.9)	89 (28.7)	63 (20.3)
18. Ashamed	18 (5.8)	134 (43.2)	99 (31.9)	59 (19.0)
19. The same as those without epilepsy	54 (17.4)	147 (47.4)	61 (19.7)	48 (15.5)
Question 5: In your opinion, the prejudice in epilepsy will be related to?				
20. Relationships	33 (10.6)	129 (41.6)	84 (27.1)	64 (20.6)
21. Marriage	26 (8.4)	112 (36.1)	97 (31.3)	75 (24.2)
22. Work	23 (7.4)	120 (38.7)	94 (30.3)	73 (23.5)
23. School	33 (10.6)	124 (40.0)	90 (29.0)	63 (20.3)
24. Family	78 (25.2)	119 (38.4)	72 (23.2)	41 (13.2)

fear of seizure attacks; factor 2 refers to the public's sympathy for PWEs; factor 3 refers to the difficulties faced by PWEs; factor 4 refers to the public's speculation on PWEs' feeling; factor 5 refers to the discrimination against PWEs; and factor 6 refers to the knowledge about epilepsy. However, the varimax rotation indicated that the factor 6 only has one item. Thus, the item 1 was not included in the model and a five-factor structure was extracted. Besides, item 13 had a factor loading (>0.5) both in the factor 3 (difficulties faced by PWEs) and factor 4 (speculation on PWEs' feeling), which means item 13 is not a specifically targeted question to assess the public's speculation on PWEs' feeling. It may also, to some extent, reflect the difficulties faced by PWEs in the Chinese culture. This would bring errors and biases to subsequent analysis, thus. The item 13 was excluded. As for the Q2, although its item-total correlations are relatively low than other questions, we did not exclude it because the Cronbach's α values were close to the total Cronbach's α value no matter which item in Q2 was deleted, as shown in **Table 4**. Based on the aforementioned analyses, the final version of the scale consisted of 5 factors and 22 items.

Content Validity

Content Validity was expressed by the CVI. All the I-CVI are >0.78, and the mean CVI value of all items in the scale was 0.97. CVI value of each dimension is 0.83, 0.96, 0.98, 0.98, and 1.00, respectively.

Construct Validity

The result of the construct validity is shown in **Table 5**, all within the range of acceptance or ideal. The CFA produced the following fit indices: $\chi^2/SD = 1.725$, goodness of fit index (GFI) = 0.916, normed fit index (NFI) = 0.937, comparative fit index (CFI) = 0.972, IFI (incremental fit index) = 0.972, Tucker–Lewis index (TLI) = 0.966, and root mean square error of approximation (RMSEA) = 0.048. These excellent findings for all metrics indicate that the results fitted well with the 5-factor construct of the scale.

Convergent Validity

As shown in the **Table 6**, the factor load of each item corresponding to each latent variable is >0.6,which shows that each item is highly representative of the corresponding latent variable. Besides, the average variance extracted is >0.5, and the composite reliability is >0.7, showing good convergence validity.

Discriminant Validity

As shown in **Table 7**, there was significant correlation among factor 1, factor 2, factor 3, factor 4, and factor 5 ($p < 0.01$). All the absolute values of correlation coefficient are <0.5,and less than the square root of AVE. It does not only show the significant correlation, but also the significant degree of distinction between the five factors.

Effect of Medical Background and Family History of Epilepsy

To evaluate the possible effect of medical background and family history of epilepsy on the level of stigmatization, we performed a comparison using Mann–Whitney test for the sum score and scores of each factor. The results are summarized in **Supplementary Table 1**. It was seen that participants with family history of epilepsy have higher SSE scores than those without family history of epilepsy ($p = 0.007$), as well as three factors out of six factors' scores (factor 2, factor 4, and factor 5). There is statistically no significance of the SSE scores between participants with medical background and participants without ($p = 0.135$), but the scores of factor 1 and factor 2 in participants without medical background are higher than those with medical background ($p < 0.001$ and $p = 0.002$, respectively).

Reliability

The Cronbach's alpha value for the full Chinese Stigma Scale of Epilepsy was 0.936, and above 0.7 for each individual item. Cronbach's alpha was 0.887 for the factor 1, 0.737 for the factor

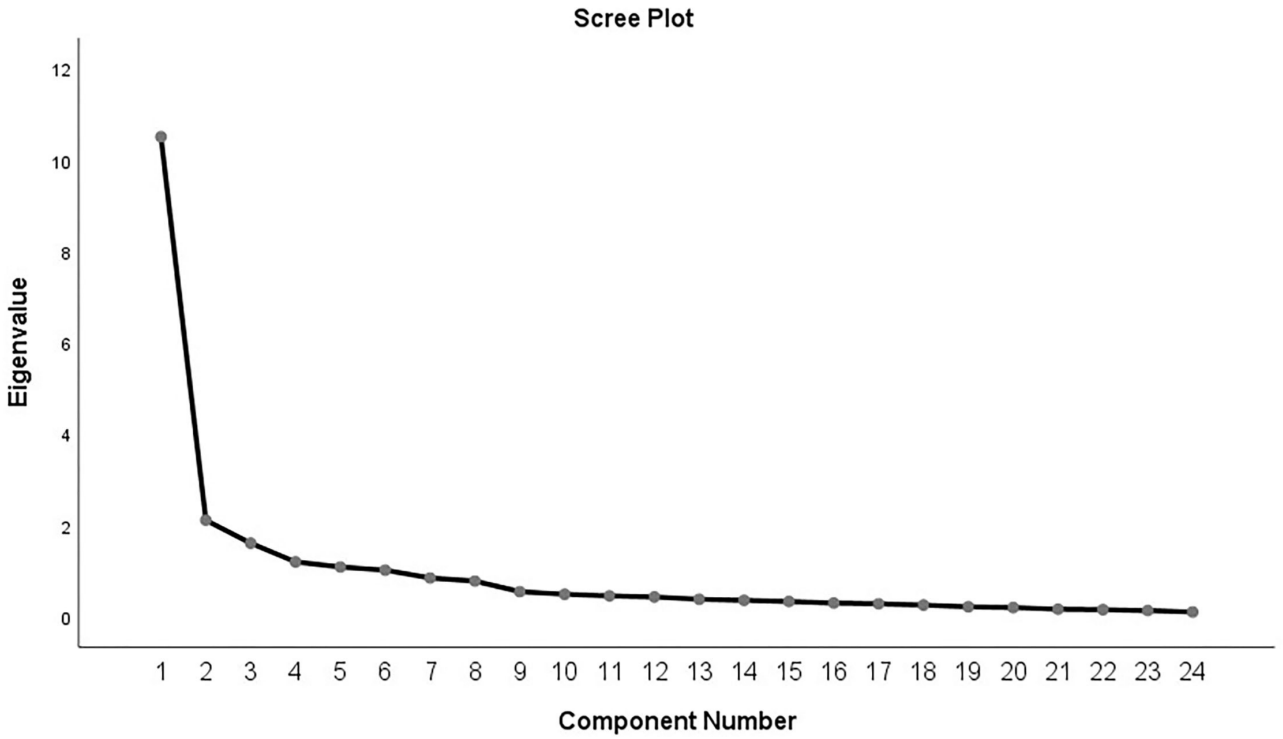

FIGURE 1 | The scree plot of the items related to stigma toward epilepsy in normal people. The scree plot was acquired by principal component analysis (PCA) with correlation matrix.

2, 0.897 for the Factor 3, 0.900 for the factor 4, and 0.920 for the factor 5, as shown in **Table 4**.

DISCUSSION

To validate the Chinese version of the SSE for accessing the epilepsy-related stigmatization of the public and to explore effective stigma reducing interventions, our study translated the SSE into Simplified Mandarin Chinese and qualified the translated scale with psychometric analysis, such as EFA, CFA, and internal consistency analysis. We provided clear evidence for the reliability and validity of the Chinese version of SSE.

Most of the participants included in our study were recruited *via* convenience sampling by randomly distributing questionnaires on the streets. Moreover, a part of the participants was enrolled through an online platform named Wenjuanxing, which enabled a wider coverage of our sample in geographical locations and life backgrounds. Indeed, the demographic data of our study indicated that our respondents had good social and cultural representation. The age of our respondents is mainly 18–60 years (95.4%). Compared with the study form Italy, our male-female ratio was more appropriate, avoiding the effect of excessive positive reactions of women on the results. As for the marital status and educational levels and medical background, there was no difference between the previous study and ours (38, 39). Additionally, most of our participants did not have family history of epilepsy or relatives with epilepsy (3.2%), whose proportion was lower than that of the previous study conducted in other counties (12.4%) (39).

With regard to reliability, the Cronbach's alpha value in our study was 0.936, and the Cronbach's alpha value of each factor of the five latent traits was above 0.7, indicating excellent internal consistency of our Chinese version of the SSE. Content validity is an important step before exploring the structure validity. It refers to the degree of agreement between the content actually measured by a scale and the content to be measured. The SSE was evaluated by experts and calculated CVI value above 0.78 indicated that the scale had good content validity.

For the structure of SSE, previous study has fitted SSE into a model with two latent traits using the exploratory item response theory (IRT) analysis. The first latent trait reflected the difficulties associated with epilepsy, whereas the second one reflected the emotions associated with epilepsy (40). Later, the Czech version was studied by Dana Brabcova et al. which extracted four-factor structure of SSE. The factor 1 and factor 3 were associated with responses of PWEs to epilepsy in their personal life and the effect of epilepsy on their study and work, whereas the factor 2 and factor 4 were associated with the emotional reaction of public to epilepsy, and their emotional perspective about PWEs (31). The Chinese version of SSE structure was a little different from others, we extracted a 6-factor structure of SSE by using the EFA. Factor 1 reflected the scare of respondents, and factor 2 reflected the sympathy of respondents, when they witnessed a seizure attack. The emotional reaction of the public to epilepsy was

TABLE 3 | Rotated component matrix.

	Component					
	1	**2**	**3**	**4**	**5**	**6**
Item 1	−0.042	0.024	0.014	−0.056	0.038	**0.962**
Item 2	**0.925**	0.138	0.036	0.053	0.036	−0.017
Item 3	**0.924**.	0.147	0.101	0.108	0.001	−0.028
Item 4	0.056	**0.872**	0.125	0.095	0.129	−0.04
Item 5	0.314	**0.797**	0.151	0.138	0.052	0.081
Item 6	−0.013	0.144	**0.758**	0.192	0.304	0.014
Item 7	0.02	0.195	**0.806**	0.155	0.248	−0.035
Item 8	0.048	0.042	**0.801**	0.228	0.289	−0.077
Item 9	0.023	0.113	**0.788**	0.23	0.271	−0.084
Item 10	0.077	0.069	**0.741**	0.248	0.191	0.035
Item 11	0.094	0.004	**0.664**	0.303	0.173	0.095
Item 12	0.103	−0.052	**0.611**	0.381	0.174	0.16
Item 13	−0.006	0.203	**0.503**	**0.591**	−0.019	0.002
Item 14	0.107	−0.02	0.294	**0.682**	0.227	0.175
Item 15	0.015	0.043	0.236	**0.72**	0.37	−0.004
Item 16	0.044	0.124	0.286	**0.736**	0.251	−0.069
Item 17	0.072	0.008	0.295	**0.773**	0.252	−0.111
Item 18	0.06	0.084	0.307	**0.808**	0.266	−0.055
Item 19	0.055	0.16	0.066	**0.539**	0.28	−0.041
Item 20	−0.017	0.128	0.304	0.306	**0.699**	0.061
Item 21	0.09	0.083	0.294	0.272	**0.76**	−0.095
Item 22	−0.019	0.077	0.35	0.272	**0.769**	−0.032
Item 23	−0.036	0.038	0.335	0.391	**0.689**	0.096
Item 24	0.089	0.013	0.276	0.427	**0.587**	0.163

TABLE 4 | Reliability results.

	Corrected item-total correlation	**Cronbach's α If item deleted**
Question 1: Do you think that people with epilepsy feel able to control their own epilepsy?		
1. Control	Not included	
Question 2: How would you feel when you see an epileptic seizure?		
2. Scared	0.231	0.939
3. Fear	0.285	0.939
4. Sadness	0.382	0.937
5. Pity	0.341	0.937
Question 3: Which difficulties do you think people with epilepsy have in their daily lives?		
6. Relationships	0.708	0.932
7.Work	0.706	0.932
8. School	0.735	0.931
9. Friendships	0.737	0.931
10. Sexual	0.674	0.932
11. Emotional	0.638	0.933
12. Prejudice	0.636	0.933
Question 4: How do you think that people with epilepsy feel?		
13. Worried	Not included	
14. Dependent	0.65	0.933
15. Incapable	0.704	0.932
16. Fearful	0.698	0.932
17. Depressed	0.709	0.932
18. Ashamed	0.759	0.931
19. The same as those without epilepsy	0.479	0.935
Question 5: In your opinion, the prejudice in epilepsy will be related to?		
20. Relationships	0.672	0.932
21. Marriage	0.693	0.932
22. Work	0.708	0.932
23. School	0.718	0.931
24. Family	0.674	0.932
	Item number	Cronbach's alpha
Factor 1	2	0.887
Factor 2	2	0.737
Factor 3	7	0.920
Factor 4	6	0.897
Factor 5	5	0.900
Total	22	0.936

divided into two aspects, which might be contributed to cultural differences. Essentially, fear and sympathy are two different emotional reactions. Fear refers to a strong depressive emotional experience when people are facing a certain dangerous situation, trying to get rid of it but unable to do anything. Sympathy refers to a caring and understanding emotional response for the suffering and misfortune of others. Specifically, many people in our study said that "I was not scared when I witnessed an epileptic seizure, but I felt sad and pity for him/her." The factor 3 reflected the difficulties faced by PWEs. The factor 4 reflected the thoughts of respondents about how PWEs felt, factor 5 reflected the prejudice associated with epilepsy, and the factor 6 reflected the knowledge of epilepsy. To be honest, the factor structure of Chinese version has been slightly modified from the original version, which might limit its application in other populations.

Items 1 and 13 were proved to be problematic and removed from the model. For item 1, it was the only item of factor 6, and thus incapable of being included in the model to evaluate the validity. Even though the phrase "be able to control their own epilepsy" sounds quite ambiguous when translated into Chinese, about 61.3% of our subjects believed that epilepsy could not be controlled by PWEs themselves or effective treatments. It is the Chinese people's subconscious understanding of epilepsy, thus forming an independent factor. Besides, the item 1 was not suitable for factor structure analysis just for statistical reasons, rather than incapacity of quantifying stigma. In fact, lack of knowledge is one aspect of stigma. People with a more knowledge or a higher education may have a lower score for stigma. In the case of item 13, it was removed for the reason that its factor loading in factor 3 and factor 4 were both higher than 0.5, which meant that item 13 had lower discriminant validity. In fact, the items 1 and 13 were also excluded in the recently validated Zambian and Czech version of the scale. They excluded items 1 and item 13 for their low factor load (31, 40).

We further validated the structural validity, convergent validity, and discriminant validity of the Chinese version of SSE. Structural validity refers to whether the structure of the

TABLE 5 | Goodness of fit index (GFI).

	X^2/df	RMSEA	GFI	NFI	CFI	IFI	TLI
Ideal	≤3.0	≤0.05	≥0.90	≥0.90	≥0.90	≥0.90	≥0.90
Acceptable	≤5.0	≤0.10	≥0.80	≥0.80	≥0.80	≥0.80	≥0.80
	1.725	0.048	0.916	0.937	0.972	0.972	0.966

RMSEA, root mean square error of approximation; GFI, goodness-of-fit index; NFI, normed fit index; CFI, comparative fit index; IFI, incremental fit index; TLI, Tucker–Lewis index.

TABLE 6 | Convergent validity.

			Estimate	AVE	CR
Item 2	<---	Factor 1	0.812	0.8109	0.8947
Item 3	<---	Factor 1	0.981		
Item 4	<---	Factor 2	0.969	0.6513	0.7799
Item 5	<---	Factor 2	0.603		
Item 6	<---	Factor 3	0.796	0.6108	0.9155
Item 7	<---	Factor 3	0.803		
Item 8	<---	Factor 3	0.886		
Item 9	<---	Factor 3	0.893		
Item 10	<---	Factor 3	0.752		
Item 11	<---	Factor 3	0.647		
Item 12	<---	Factor 3	0.656		
Item 15	<---	Factor 4	0.816	0.6142	0.9038
Item 14	<---	Factor 4	0.725		
Item 16	<---	Factor 4	0.837		
Item 17	<---	Factor 4	0.836		
Item 18	<---	Factor 4	0.872		
Item 19	<---	Factor 4	0.578		
Item 21	<---	Factor 5	0.82	0.6721	0.9108
Item 20	<---	Factor 5	0.776		
Item 22	<---	Factor 5	0.877		
Item 23	<---	Factor 5	0.865		
Item 24	<---	Factor 5	0.754		

AVE, average variance extracted; CR, composite reliability.

TABLE 7 | Discriminant validity.

	F1	F2	F3	F4	F5
F1	0.8109				
F2	0.243***	0.6513			
F3	0.133**	0.128***	0.6142		
F4	0.149***	0.119***	0.376***	0.6721	
F5	0.087	0.106**	0.415***	0.423***	0.6108
	0.9005	0.807032	0.781537	0.78370913	0.819817

*Discriminant validity were significant at *p<0.05, **p<0.01, and ***p<0.001.*

scale is consistent with the theoretical assumptions of tabulation. The value of all metrics of the structural validity was excellent, indicating that the 5-factor construct of the scale fitted well. Convergent validity test showed that the item belonging to each factor was highly representative, and the discriminant validity test indicated the factors have a certain correlation, but they had a certain degree of discrimination between each other. Furthermore, we found that participants with medical background scored lower in factor 1 (the fear of seizure attacks) and factor 2 (sympathy for PWEs), which may be related to their deeper understanding of epilepsy. However, participants with family history of epilepsy scored higher on the total score and factor 2 (sympathy for PWEs), factor 3 (difficulties faced by PWEs), and factor 5 (discrimination against PWEs), which is in line with the fact we have observed clinically. Based on the above results, we hold the view that medical background and family history of epilepsy had an effect on the stigma, which is instructive for the application of the scale in the future and provides a theoretical basis for the design and grouping of subsequent studies on epilepsy stigma.

One limitation of the study is that a part of our respondents was recruited by an online platform, by which it may not include people who rarely access to computers or mobile phones, and those less educated people who were incapable of filling the scale online. Meanwhile, since our subjects mainly from Street random sampling and an online platform, we cannot carry out the test-retest reliability test. Besides, our study was conducted in Changsha, urban sampling could lower the participation rate of rural subjects thus affecting the results, as the incidence of stigma among PWEs in rural areas is higher than that of urban areas in China (13). Therefore, further studies with an adequate sample in different regions of China are needed.

Social stigma continues among PWEs. It brings them negative emotions such as anxiety and depression, restricts patients from seeking social support, and greatly affects the quality of life in PWEs. Therefore, it is crucial to formulate an effective public intervention for reducing stigma, starting with development and validation of an accurate Stigma Scale of Epilepsy, which might quantify the extent of stigma. Only when we are aware of the existence of epilepsy-associated stigma and psychosocial burden of PWEs can we have a deeper understanding of it, which may contribute to explore stigma reduction interventions to overcome prejudices, the false cognition, and to create a better social environment for PWEs and their family.

CONCLUSIONS

This study has shown that the Chinese version of the SSE is a valid and reliable measurement instrument.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Xiangya Hospital of Central South University [No. 201912528]. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

YW and KH contributed to the acquisition of data, and the drafting of the manuscript for content and interpretation of data. LF and BX contributed to the study design and revision of manuscript. SW contributed to data analysis.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.796296/full#supplementary-material

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The Mediating Roles of Family Resilience and Social Support in the Relationship Between Illness Severity and Depressive Symptoms Among Primary Caregivers of Children With Epilepsy in China

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Purpose: This study was designed to assess the effects of epilepsy severity, family resilience, and social support on depression in primary caregivers of children with epilepsy (CWE), and to test the mediating roles of family resilience and social support in this relationship.

Method: Two hundred fifty-two caregivers of children with epilepsy were recruited from October 2020 to May 2021. The questionnaire contained sociodemographic characteristics, Epilepsy Severity, Chinese-Family Resilience Assessment Scale (C-FRAS), Social Support Rating Scale (SSRS), Beck Depression Inventory (BDI). Structural equation models were used to evaluate whether family resilience and social support as mediators between epilepsy severity and depression.

Results: In this study, the prevalence of depressive symptoms among primary caregivers of CWE in China was 69.84%. Epilepsy severity was positively associated with depression. Family resilience and social support were negatively correlated with depressive symptoms (both $p < 0.01$). Furthermore, the fitness indices of structural models were satisfactory. The direct effect of epilepsy severity on depression was 0.266 (95% CI 0.064–0.458), this pathway explained 62.88% variance of depression. The indirect effect of family resilience and then social support was 0.069 (95% CI 0.025–0.176), indicating that the serial multiple mediation was significant. The serial mediation pathway explained 16.31% variance of depression.

Conclusions: The high incidence of depression among primary carers of CWE deserves more attention. They should be screened routinely, especially those parents of children with severe epilepsy. Family resilience and social support could be protective factors for caregivers' mental adjustment. Therefore, future psychosocial interventions for enhancing family resilience and social support should be implemented, in order to reduce their depression.

Keywords: children with epilepsy, caregivers, family, resilience, social support, depression

INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders in children, which is characterized by recurrent seizures caused by abnormal brain discharge. Approximately 50–70 million people have epilepsy worldwide (1, 2) and the prevalence of epilepsy among children ranges from 3.9 to 5.1‰ in China (3). Epileptic seizures and its treatment not only have a strong negative impact on the children's physical and psychobehavioral development (4, 5), but also exerts detrimental effects on the whole family. Parents often function as children's main caregivers especially for families of CWE in China, they have to deal with these challenges, as well as face high medical costs, stigma from relatives and friends, limited family social interaction, and negative emotional reactions (6, 7). Growing evidence had shown that parents of CWE had a higher risk of depression (8, 9). As Reilly et al. (8) indicated the prevalence of depression in mothers and fathers was 55 and 33%, compared with 27 and 31% correspondingly in the non-epilepsy-related neuro disability group. In China, the risk of depression was higher in parents of CWE compared with healthy children (23.51 vs. 10.84%, $p < 0.01$) (9). Importantly, this psychological distress has been reported to be linked with an increased risk of depression in children, lower health-related quality of CWE, and decreased family function (10–12). Therefore, it is of vital importance to screen the psychological distress among caregivers of CWE and explore its comprehensive influencing factors for providing interventional strategies.

The theory of multifactorial effects of psychological stress and Walsh's family resilience framework highlights that when families face stressors, various factors (i.e., social support, family resources.) could influence the individual's emotional response and family adaption (13, 14). Illness severity, as a major stressor, may be an influential factor for caregivers' depression. Prior researches had found the degree of disease severity was positively correlated with the parental psychological state in families of children with developmental disorders and ASD (15, 16). Furthermore, raising a child with severe epilepsy was highly related to caregivers' distress and depressive symptoms (17). But the latest study showed that the disease severity of CWE cannot predict parental depression in China (18). The relationship between epilepsy severity and depression is contradictory. Therefore, it is necessary to further explore the relationship and potential mediating mechanisms between disease severity of CWE and caregivers' depression.

To confront the effects of negative events on caregivers' depression, family internal resources and external support are essential factors for them to combat depression (19). First, Family resilience, as one of the most critical family resources, refers to the ability to rebound from adversity and become stronger and more resourceful, which comprises shared family faith systems, patterns of organization, and communication or problem-solving processes (14). Chronic illness as a family stressor is not conducive to the development of family resilience (20, 21). And family resilience has been considered as an important source to maintain family members' mental wellbeing. For example, one study indicated that families with high resilience could reduce the risk for parental depression, which explained 14.9% variance of depressive symptoms (22). Meanwhile, available evidence also reveals that family resilience may mediate the relationship between clinical factors in children and family members' mental health. Suzuki et al. (15) found that the relationship between disease severity and depression among mothers of children with developmental disorders can be mediated by family resilience.

Second, social support has been considered as an important external resource in buffering the influence of stress and promoting physical and mental health (23, 24). Social support refers to emotional, informational, or material support provided by professional or non-professional organizations (25). Raising a child with severe seizures can cause caregivers to alienate with extended families and friends, and receive lower social support (26). These situations are negatively associated with their psychological health (27). As previous studies showed that high levels of social support were related to the improvement of psychological wellbeing among mothers of children with autism spectrum disorders (28) and reduction of depressive symptoms in patients with prostate cancer (29). In other words, a powerful support network can assist parents to cope with difficulties and maintain family members' mental wellbeing. As Carlson et al. (30) found social support mediates the relations between perceived epilepsy severity and mothers' anxiety and depression.

The above studies suggested that family resilience and social support may mediate the relationship between illness severity and caregivers' depression. Nevertheless, to our knowledge, the association of epilepsy severity, family resilience, social support, and depression have not been investigated among parents of CWE in China. Moreover, whether family resilience and social support mediate the association between epilepsy severity and depression remains unexplored. Accordingly, this study was aimed to evaluate the depressive symptoms among primary caregivers of CWE as well as explore the potential effects of family resilience and social support in the relationship between epilepsy severity and caregivers' depression. The theoretical framework was developed based on existing studies, see **Figure 1**. We used data collected from primary caregivers of CWE to test the three hypotheses.

Hypothesis 1: The depressive symptoms among primary caregivers of CWE was common, and higher levels of epilepsy severity increased the risk for parental depression.
Hypothesis 2: When families faced adversities, higher levels of family resilience and social support played a vital role in decreasing the rate of depression among primary caregivers of CWE.
Hypothesis 3: The relationship between epilepsy severity and depression was mediated by family resilience and social support among primary caregivers of CWE.

MATERIALS AND METHODS

Participants

Two hundred fifty-two caregivers of CWE in the neurology ward and neurology outpatient were recruited from a tertiary hospital

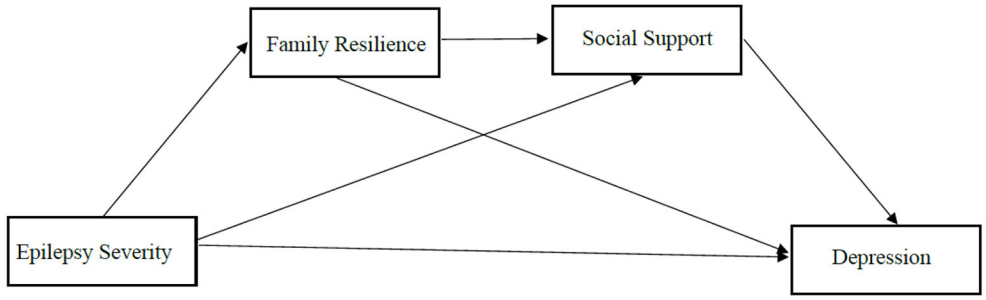

FIGURE 1 | The hypothesized model concerning the relationship between epilepsy severity and depression: family resilience and social support as mediators.

in Guangdong Province. The inclusion criteria for participants were: (1) mothers or fathers of CWE and primary caregiver (Assuming the primary responsibility for caregiving the child, living with and taking care of the child for at least 72 h per week, or at least 12 h per day); (2) having a child aged 0–14 years, and diagnosed with epilepsy by neurologists according to the International League Against Epilepsy (ILAE) criteria (31); (3) aged ≥ 18 years. The exclusion criteria included: (1) the child diagnosed with other complications and (2) principal caregivers were diagnosed with severe medical conditions or cognitive impairment or mental illness. (3) Moreover, families were also excluded if the family experienced traumatic events such as serious natural disasters, accidents, and sudden death of relatives in the past half-year. All parents participated in the study voluntarily and signed the informed consent.

Procedure

Ethical approval was provided by the Medical Ethics Committee of Shenzhen Children's Hospital (No. 2020067), following the Declaration of Helsinki. Data were collected using convenience sampling methods during October 2020 and May 2021. After obtaining written informed consent, all participants were asked to complete questionnaires independently in the neurology wards or neurology outpatient waiting rooms. The questionnaire included four parts: sociodemographic characteristics of children and primary caregivers, family resilience, social support, and depression. The entire survey took about 20–30 min to complete. A total of 280 primary caregivers of CWE were recruited to complete the questionnaire, eighteen caregivers refused to participate, ten participants who filled out questionnaires incompletely were excluded. Thus, 252 (96.18%) participants completed the entire and valid questionnaire.

Instrument

Sociodemographic Characteristics

The self-designed questionnaire was used to collect basic demographic characteristics of CWE and their primary caregivers. The data included patients' gender, age, duration of epilepsy. The information of primary caregivers included their relationship with the child, age, residence, occupation, income per month, education, religion, medical payment. These were mainly collected by medical records and self-report of parents.

Epilepsy Severity

Epilepsy severity was used to measure childhood epilepsy. The total scores of illness severity are 1–9, determined by seizure types (1-3), frequency of seizures (0–3), and the number of anti-seizure medications (ASMs) used (0–3). We assigned a score to the seizure types, 3 for generalized tonic-clonic seizures, 2 for partial seizures, and 1 for the absence of seizures. If the children have weekly or daily seizures, the score is 3, 2 for monthly seizures, 1 for once or twice per year, and 0 for no seizures during the previous year. A score of 0 is assigned when the children have no medication, 1 for single ASMs, 2 for two ASMs, and 3 for three or more ASMs. The three scores are summed, 1–5 is considered low epilepsy severity, and ≥6 is considered high epilepsy severity (32, 33). In this study, the Cronbach's α was 0.605, which was acceptable. These data were collected from the medical records.

Chinese-Family Resilience Assessment Scale

The Chinese-Family Resilience Assessment Scale (C-FRAS) was used to evaluate the resilience levels of families (34). The 44-item scale includes four dimensions: family communication and problem solving (FCPS), utilizing social and economic resources (USR), maintaining a positive outlook (MPO), and the ability to make meaning of adversity (AMMA). It uses a Likert four-point scale from strongly disagree to strongly agree (1–4), with a total score of 44–176. Higher scores indicate higher degrees of family resilience. The Cronbach's α of C-FRAS was 0.960, and the four subscales Cronbach's α range from 0.70 to 0.97 (34). In this study, the Cronbach's α was 0.958, 0.946, 0.888, 0.884, and 0.807 for C-FRAS, FCPS, USR, MPO, and AMMA.

Social Support Rating Scale

Social Support Rating Scale (SSRS) (35) was used to measure the degree of support received from friends, relatives, and healthcare providers. The 10-item self-rated scale contains three subscales: objective support, subjective support, and support utilization. Among them, the scores for items 5, 6, and 7 are based on the number of choices, and other items are scored on four-point scale. The higher scores indicate higher levels of social support. The Cronbach's α was 0.707 for SSRS in the present study.

Beck Depression Inventory

The Beck Depression Inventory (BDI) was used to detect the severity of depressive symptoms within the past week (36).

BDI has 21 items, each item is scored from 0 to 3 based on self-assessment severity, which total scores ranging from 0 to 63. Higher scores reflect the increasing severity of depressive symptoms. Scores of 5–13 were considered mild depression, scores of 14–20 showed moderate depressive symptoms, and scores equal or above 21 indicated severe depressive symptoms. In this study, the Cronbach's α of this scale was 0.849.

Statistical Analysis

EpiData 3.1 was used to input the data and IBM SPSS Statistics (version 25.0, IBM Corp, Armonk, NY, USA) was used to perform statistical analysis. Two-sided p-value < 0.05 was statistically significant. The demographic characteristics and four main variables (epilepsy severity, family resilience, social support, and depression) were analyzed descriptively. Continuous data were described as means ± standard deviation (SD) or median (interquartile range Q1–Q3) according to whether the data follows a normal distribution. Categorical data are described using frequencies and percentages. Pearson correlations were used to explore the relations among these variables. Principal caregiver, monthly family income, occupation, medical expenses payment were included as control variables.

Structural Equation Modeling (SEM) was used to examine the mediating effect of family resilience and social support. The maximum likelihood (ML) procedure was used given the variables were normally distributed, which was inferred by skewness (±3) and kurtosis (±8). For latent variables (i.e., epilepsy severity, family resilience, social support), we used the domain-representative approach to get items parcels. And random assignment approach to get items parcels for depression in Excel (37).Chi-square/degrees of freedom (χ^2/df), Comparative Fit Index (CFI), Tucker-Lewis index (TLI) and Incremental Fit Index (IFI), Root Mean Square Error of Approximation (RMSEA) were used to evaluate the fit of the model. Ninety-five percentage bootstrap confidence interval (CI) was used to estimate the significance of the indirect effect. The mediation effect was significant if the 95% CI did not contain 0. SEM was running in AMOS 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic Characteristics and Four Variables

Among 252 parents of children with epilepsy, 201 (79.80%) were mothers, accounting for a high proportion, and 51 (20.20%) were fathers, the average age was (35.41 ± 5.06) years, with a range of 23 to 48 years. Children with epilepsy had a mean age of (5.83 ± 3.87) years, ranging from 0 to 14 years, with the median disease duration being 24 months (IQR 10–48). The prevalence of depression was 69.84%, including mild, moderate, and severe depression. As shown in **Table 1**.

In **Table 2**, the average score of depression was (10.96 ± 9.25), and epilepsy severity was (5.55 ± 2.07), 141(55.95%) of children were low epilepsy severity, 111 (44.05%) of children were high epilepsy severity. The average score of family resilience was (134.96 ± 16.65), family communication and problem solving was rated highest, while utilizing social and economic resources received the lowest score. The average score of social support was (38.69 ± 6.04), with the domain of objective support received the highest scores, followed by subjective support, and utilization of support was the lowest.

TABLE 1 | Descriptive statistics for sociodemographic characteristics and depression ($N = 252$).

Variable	Response	*N* (%)
Child gender	Male	144 (57.1)
	Female	108 (42.9)
Age of children	≤3	88 (34.9)
(years old)	3–6	56 (22.2)
	7–14	108 (42.9)
Principal caregiver	Mother	201 (79.8)
	Father	51 (20.2)
Residence	Countryside	48 (19.0)
	Suburban	27 (10.7)
	City	177 (70.2)
Occupation	Employed	152 (60.3)
	Unemployed	100 (39.7)
Religion	Yes	26 (10.3)
	No	226 (89.7)
Monthly family income	<5,000	27 (10.7)
(Yuan)	5,000–10,000	70 (27.8)
	10,000–15,000	53 (21.0)
	>15,000	102 (40.5)
Education	High school or below	92 (36.5)
	Undergraduate	150 (59.5)
	Graduate or above	10 (4.0)
Medical expenses payment	Urban basic medical insurance	145 (57.5)
	New rural cooperative medical insurance	57 (22.6)
	Self-paying and others	50(19.8)
Depression	Mild	92(36.5)
	Moderate	45(17.8)
	Severe	39(15.5)

Correlations Between Epilepsy Severity, Family Resilience, Social Support, and Depression

The correlation analysis results were summarized in **Table 2**, which showed significant correlations among these variables. Epilepsy severity was negatively correlated with family resilience ($r = -0.247$, $p < 0.01$) and social support ($r = -0.221$, $p < 0.01$). According to the effect size criteria of Cohen (23), these effects were weak. Epilepsy severity was positively related to depression ($r = 0.374$, $p < 0.01$). Family resilience and social support were negatively correlated with depression ($r = -0.385$, $r = -0.404$, respectively, $p < 0.01$), with a moderate effect size. These bivariate correlations suggest that the following mediation analysis can be performed.

TABLE 2 | Description statistics and correlations among the study variables ($N = 252$).

	Number of items	Mean ± SD	1	2	3	4	5	6	7	8	9	10	11
1. Epilepsy severity	9	5.55 ± 2.07	1										
2. C-FRAS	44	134.96 ± 16.65	−0.247**	1									
3. FCPS	27	85.70 ± 11.12	−0.227**	0.967**	1								
4. USR	8	21.73 ± 3.50	−0.217**	0.713**	0.561**	1							
5. MPO	6	18.23 ± 3.03	−0.210**	0.831**	0.732**	0.519**	1						
6. AMMA	3	9.30 ± 1.25	−0.148*	0.714**	0.634**	0.442**	0.676**	1					
7. Social support	10	38.69 ± 6.04	−0.221**	0.477**	0.440**	0.418**	0.384**	0.336**	1				
8. OS	4	21.73 ± 3.94	−0.078	0.254**	0.258**	0.156*	0.198**	0.167**	0.658**	1			
9. SS	3	10.18 ± 2.50	−0.252**	0.468**	0.420**	0.438**	0.394**	0.314**	0.852**	0.254**	1		
10. US	3	6.78 ± 1.68	−0.085	0.237**	0.211**	0.240**	0.161*	0.220**	0.614**	0.281**	0.335**	1	
11. Depression	21	10.96 ± 9.25	0.374**	−0.385**	−0.373**	−0.290**	−0.296**	−0.284**	−0.404**	−0.199**	−0.377**	−0.268**	1

$^{**}p < 0.01$; $^{*}p < 0.05$.

C-FRAS, Chinese-Family Resilience Assessment Scale; FCPS, Family Communication and Problem Solving; USR, Utilizing Social and economic Resources; MPO, Maintaining a Positive Outlook; AMMA, Ability to Make Meaning of Adversity; OS, Objective Support; SS, Subjective Support; US, Utilization of Support; SD, standard deviation.

Validation of Structural Model

We used SEM to test the model, with epilepsy severity as an independent variable, family resilience and social support as the mediating variables, and caregivers' depression as the dependent variable. SEM results demonstrated that the structural model had a good fit to the data (38), with $\chi^2/df = 1.801$, CFI = 0.933, IFI = 0.934, TLI = 0.919, RMSEA = 0.056.

Mediating Effects of Family Resilience and Social Support in the Relationship Between Epilepsy Severity and Depression

As presented in **Figure 2**, the standardized coefficient of epilepsy severity on family resilience was $\beta = -0.298$, $p < 0.01$, and family resilience on depression was $\beta = -0.078$, $p > 0.05$, and the indirect effect of this pathway was 0.023. The 95% CI for indirect effect from epilepsy severity to depression *via* family resilience was −0.042 to 0.094, the 95% CI included zero, indicating the indirect effect of this pathway was not statistically significant.

The standardized coefficient of epilepsy severity on social support was $\beta = -0.166$, $p > 0.05$, and social support on depression was $\beta = -0.390$, $p < 0.01$. The indirect effect of this pathway was 0.065, 95% CI (−0.006, 0.220), which indicated the indirect effect of social support was also not statistically significant.

The standardized coefficient of family resilience on social support was $\beta = 0.593$, $p < 0.001$, the serial mediation effect from epilepsy severity to depression through family resilience and then social support was 0.069, 95% CI (0.025, 0.176). We concluded that there was a significant serial mediation effect. In addition, the direct effect of epilepsy severity on depression was 0.266, 95% CI (0.064, 0.458), $p < 0.05$, indicating the existence of a direct effect.

The total indirect effect of these three pathways was 0.157, 95% CI (0.073, 0.319), which explained the 37.12% variance of depression. Of which, the serial mediation pathway explained 16.31% variance of depression, and the direct effect pathway explained 62.88% variance of depression. As shown in **Table 3**.

DISCUSSION

In this study, we developed a multiple-mediation model between epilepsy severity and caregivers' depression to investigate the protective roles of family resilience and social support against negative effects on caregivers' psychological adjustment. Our study confirmed that depressive symptoms was common among parents of CWE in China. And epilepsy severity was positively correlated with depressive symptoms (supporting hypothesis 1). Meanwhile, it also corroborated that family resilience and social support could reduce the risk for depression (supporting hypothesis 2). Importantly, there was a serial mediation pathway between severity and depression through family resilience and then social support (partly supporting hypothesis 3).

In the present study, the prevalence of depressive symptoms was 69.84%. A recent cross-sectional research conducted among 308 caregivers of children with epilepsy found that the proportion of depression accounts for 65.60% (18), which was consistent with our reported incidence of depression. In other studies, the prevalence of depressive symptoms ranged from 23.5 to 55% (8, 9). A possible explanation for this discrepancy is the difference in instruments. In addition, the higher incidence of depressive symptoms in the current study may attribute to the mean age of CWE in this study is (5.83 ± 3.87) years and the median disease duration is 24 months, indicating earlier onset in children with epilepsy. As shown in previous studies, early-onset epilepsy was often associated with intractable seizures, developmental delay, and a high risk for epileptic encephalopathy (39), which inevitably had a detrimental effect on parental mental health (8). Meanwhile, the high incidence of depression could be related to the fact that limiting the study to parents of CWE rather than other relatives. Prior studies indicated that parents are more likely to experience psychological burden and parenting stress, which will increase the risk for depression (6, 40). Our study

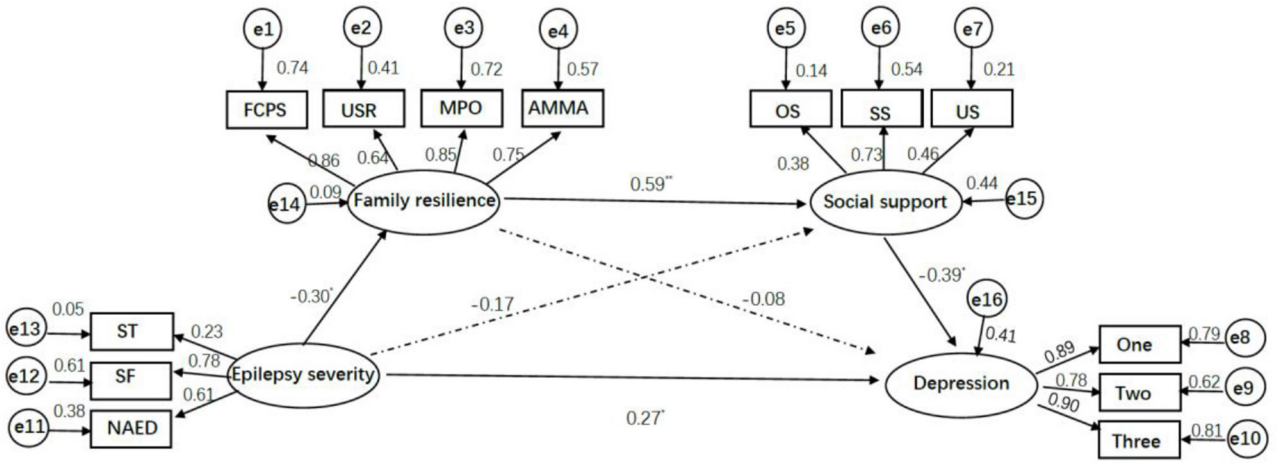

FIGURE 2 | Structural equation model of epilepsy severity, family resilience, social support, and depression. *$p < 0.01$, ** $p < 0.001$. FCPS, USR, MPO, AMMA, four parcels of family resilience; FCPS, Family Communication, and Problem Solving; USR, Utilizing Social and economic Resources; MPO, Maintaining a Positive Outlook; AMMA, Ability to Make Meaning of Adversity; ST, SF, NASM, three parcels of epilepsy severity; ST, Seizure Type; SF, Seizures Frequency; NASM, number of anti-seizure medications; OS, SS, US, three parcels of social support; OS, objective support; SS, subjective support; US, utilization of support; One, Two, Three, three parcels of depression using random assignment approach.

TABLE 3 | The model path diagram, total indirect effect, total effect analysis of the four concepts.

				Bootstrap 95%CI		
Path	**Effect size**	**S.E.**	***P***	**Lower**	**Upper**	**Effect proportion (%)**
Epilepsy severity -> Family resilience->Depression	0.023	0.034	0.379	−0.042	0.094	5.44%
Epilepsy severity->Social support->Depression	0.065	0.055	0.070	−0.006	0.220	15.37%
Epilepsy severity->Family resilience->Social support ->Depression	0.069	0.035	0.001	0.025	0.176	16.31%
Epilepsy severity->Depression	0.266	0.100	0.010	0.064	0.458	62.88%
Total indirect effect	0.157	0.061	0.001	0.073	0.319	37.12%
Total effect	0.423	0.084	< 0.001	0.252	0.585	

further supports that all parents of CWE should be screened for depression (8).

In terms of the relationship between epilepsy severity and caregivers' depression, Phillips et al. (41) demonstrated that caregivers of children who gained seizure freedom had fewer depressive symptoms compared with caregivers of children with consistent seizures. This could be attributed to that parent of children with severe epilepsy experience more physical, psychological, and economic burdens (26). However, a Danish study assessing the incidence of psychopathology in parents of children with high-severity epilepsy reported that seizure-related factors were not related to caregivers' mental distress (17). In the present study, we demonstrated that disease severity was positively correlated with caregivers' depression, that is caregivers of children with low-severity epilepsy have fewer depressive disorders. A possible explanation for this difference is that the evaluation of key aspects of epilepsy severity varied among studies. Conducting qualitative research may be helpful to elucidate the nature of the relations between epilepsy severity and parental depression.

Inconsistent with our expectations, family resilience and social support were not independently mediated the relationship between illness severity and depression. While the serial mediation of family resilience and then social support was found among primary caregivers of CWE in the present study. These results further validated the theory of multifactorial effects of psychological stress and Walsh's family resilience framework. As Jiang et al. (13) indicated psychological stress response is actually a system of multiple factors interacting with each other, which ultimately affects the individuals' mental health. This may partly explain why family resilience and social support cannot independently mediate the relationship between illness severity and depression.

In addition, our finding differs from prior studies, which found family resilience and social support as independent mediators among mothers of children with developmental disorders in Japan (15), and mothers of children with epilepsy in the USA (30). The possible reason for this difference is that children with epilepsy affect caregivers' mental adaptation beyond the effects of family resilience and social support alone. For example, due to social misconceptions and negative attitudes, epilepsy is regarded as a kind of mental illness in China, the families often experience severe stigma, especially in rural areas (42). This is considered as the greatest handicap for people

with epilepsy rather than the disability caused by recurrent seizures, causing families tremendous psychological burden (43–45). Furthermore, there are still no respite care services for CWE in China, caring for CWE is regarded as parents' priority. They have to give up social activities to take care of their children, and the effects on their mental health outweigh the severity of epilepsy (46). Finally, families of children with epilepsy have difficulty developing supportive and sharing parent-child relationships (47), and they are more prone to experience marital disharmony than caregivers of children without epilepsy (48). These crises could weaken the ability of families to recover from the difficulties. External support is essential for maintaining the mental health of family members.

Noteworthily, the serial mediation pathway between epilepsy severity and depression through family resilience and then social support was found among primary caregivers of CWE in the present study. In other words, family with children of low-severity epilepsy can maintain higher levels of resilience than others, which promote the mobilization of social resources. Therefore, the primary caregivers would experience lower depression. This is possibly due to that families have a positive outlook toward crises, a flexible family organization model, open and clear communication, which enables them better take advantage of social support (49, 50). Meanwhile, family resilience and social support could positively predict the individuals' psychological resilience, which further contributes to maintaining individuals' mental health in the face of stressful events (51). The serial mediation analysis provides another comprehensive evidence that epilepsy severity impacts parents' psychological adjustment through family resilience and social support. Family resilience and social support are modifiable factors that can be assessed at the initial medical visit. By identifying the needs of the primary caregivers and providing proper support for the whole family to improve the parental mental wellbeing.

Based on these findings, health professions can provide interventions in the effort to minimize parental depressive symptoms by identifying multiple factors. For example, Puka et al. found that online mindfulness-based intervention programs can significantly improve the CWE's and parents' mental wellbeing. This program includes mindful awareness, social-emotional learning skills, and positive psychology (52). In addition, interventions aimed to enhance family resilience include family narrative co-construction, systemic family therapy (foster shared family beliefs, problem-solving skills, coping strategies, fostering hope, and communication) (49, 53). Health professionals can also assist families to explore available social resources to further establish family-community-society support networks.

There exists three limitations. First, our study enrolled participants from a single center in China, the representativeness of samples is limited. In other words, the external validity of our results may be limited by the difference in the characteristics of caregivers from different regions. Multi-center, larger samples studies should be conducted in the future. Second, due to the cross-sectional design of the study, we could not infer the causality relations and dynamic changes over time among variables. Cohort studies can be conducted in the future to explore the mediate effect of these variables at different stages. Third, we measured family resilience only through one caregiver of the children with epilepsy, which could not fully reflect family functions. Therefore, it is recommended that assess family resilience from the perspective of children with epilepsy and other family members in the future.

CONCLUSION

To our knowledge, this is the first study to explore the complex interactions between epilepsy severity, social support, family resilience, and mental condition among parents of CWE in China. We found that the incidence of depression among primary caregivers of CWE reached 69.84%, and epilepsy severity was positively correlated with caregivers' depression. Importantly, our study confirmed the serial mediation effects of family resilience and social support in the relationship between epilepsy severity and depression. This finding may be helpful in determining treatment strategies, where families living with children of high-severity epilepsy are more likely to benefit from interventions designed to strengthen family resilience and social support. This may reduce the negative impact of epilepsy severity on caregivers' mental health.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of Shenzhen Children's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WW and ZX designed the study. RY, JZ, HC, and JY were involved in data collection. WW and QS analyzed the data. WW wrote the original draft. JL and ZX provided a critical review of the original draft. All authors read and approved the content of the manuscript.

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The Relationship Between Depression and Anxiety Symptoms of Adult PWE and Caregivers in a Tertiary Center

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Background: Although several studies have emphasized the association between epilepsy and psychiatric disorders, fewer have investigated the impact of epilepsy on caregivers' emotional status, mainly in adult people with epilepsy (PWE). Here we investigated depressive symptoms, suicidal ideation, and anxiety symptoms in a large group of adult PWE and their caregivers.

Methods: We analyzed symptoms of depression [with the Beck Depression Inventory-II (BDI-II)], suicidal ideation (with BDI-II item 9), and anxiety symptoms (with the Beck Anxiety Inventory) in a large group of adult PWE [$N = 548$ (60% women; median age 41)] and caregivers [$N = 191$ (72% women; median age 47)] from a Brazilian tertiary center, considering sociodemographic and clinical aspects. We also applied the Liverpool Adverse Events Profile to assess anti-seizure drugs adverse events.

Results: While the presence ($p = 0.026$) (and intensity, $p = 0.007$) of depressive symptoms and suicidal ideation ($p = 0.02$) were higher in PWE compared to caregivers, the proportion of clinical anxiety symptoms ($p = 0.32$) (and the intensity, $p = 0.13$) was similar in both groups. Although the rates of suicidal ideation were higher in focal epilepsy (20%), both generalized genetic epilepsy and caregivers also presented elevated frequencies (11%) of suicidal ideation. The analyses of 120 patient-caregiver dyads revealed that the intensity of depressive symptoms in PWE (but not anxiety) correlated with the intensity of depressive ($r = 0.35$; $p < 0.001$) and anxiety ($r = 0.25$; $p = 0.01$) symptoms in their caregivers. In the multivariate analyses of PWE, focal epilepsy (compared to GGE) was associated with clinical depressive symptoms (odds ratio, OR 2.1) and suicidal ideation (OR 3.2), while recurrent seizures (compared to the seizure-free group) were associated with suicidal ideation (OR 2.6) and anxiety symptoms (OR 2.1). Also, caregivers with anxiety symptoms were 8 times more likely to exhibit depressive symptoms, and those with depressive symptoms were 8 times more likely to present anxiety symptoms.

Conclusion: Our study suggests that specific attention for the caregivers' mental health is as essential as PWE. There is an urgent need for more studies involving caregivers to identify their emotional distress and provide adequate treatment.

Keywords: epilepsy, caregivers, depression, anxiety, suicidality

INTRODUCTION

The impact of epilepsies extends beyond recurrent seizures and their consequences, such as falls, accidents, and fractures (1). Epilepsies are highly associated with cognitive dysfunction (2), mood disorders, a higher risk of suicidal ideation and other psychiatric abnormalities (3, 4). The multifactorial characteristic of the poor quality of life in people with epilepsy (PWE) yields a great challenge to be addressed by physicians, health professionals, and caregivers (4).

While several studies have investigated cognitive dysfunction and psychiatric abnormalities in PWE, less attention has been directed to the impact of epilepsy on the emotional status of relatives and caregivers (5, 6). The caregivers of PWE are involved with support strategies, such as medication management, frequent visits to health care centers and help with accidents related to seizures. This intense demand may lead these individuals to chronic stress and emotional coping difficulties (6).

Many studies have evaluated caregivers' emotional distress of other chronic diseases (7–9); however, fewer have investigated depressive and anxiety symptoms in caregivers of PWE (especially in adults). We hypothesized that the unpredictability of seizures and elevated risk of accidents (and sudden death) affect PWE's mental health, their families and caregivers (10). Several studies evaluated the burden on family caregivers of children with epilepsy. Parental emotional distress is a well-known condition in this context, as those patients may demand chronic and intensive care (11, 12). Although the caregivers of the pediatric population have been evaluated in epileptology, the emotional status of caregivers of adult PWE is still poorly understood. We believe this is of extreme importance, especially in developing countries such as Brazil, in which adult PWE have a high frequency of psychiatric manifestations (13). Therefore, we aimed to investigate the occurrence of depression symptoms, suicidal ideation, and anxiety symptoms in a large group of PWE and caregivers and analyze demographic and clinical aspects associated with these symptoms.

We tested the following hypotheses:

1. Caregivers may present depressive and anxiety symptoms as the adult PWE they follow.
2. The severities of depression and anxiety symptoms are positively correlated between PWE and their related caregivers.
3. The pattern of seizure control may affect the severity of depressive and anxiety symptoms of their caregivers.

MATERIALS AND METHODS

Subjects Selection

We evaluated 739 consecutive subjects between 2016 and 2017 (548 non-institutionalized PWE and 191 caregivers) currently followed at our outpatient epilepsy clinic (Tertiary hospital at the University of Campinas, UNICAMP, São Paulo, Brazil) with interviews and questionnaires to investigate depression, suicidal ideation, and anxiety symptoms.

We divided patients into focal epilepsy [417 subjects, (252 women), median age 43, range 18–83 years], genetic generalized epilepsy [GGE = 74, (48 women), median age 33, range 18–60 years], and unknown epilepsy [UE = 57 subjects, (27 women), median age 38, range 18–65 years].

We included a large sample of PWE caregivers [191 subjects, (137 women), median age 47, range 18–82]. The group of caregivers included relatives (genetically related and unrelated) and non-relatives who live in the same environment as the patients. These caregivers were in close contact with their respective patients and were responsible for helping them with medications, consultations, seizures, and daily life problems. Among those 191 caregivers, we obtained paired data from 120 dyads (PWE and their respective caregivers) collected on the same day of consultation. None of the caregivers were private health professionals, and only two patients presented mild developmental delays.

Clinical and Sociodemographic Data

Patients and caregivers were assessed on the day of the medical appointment. Clinical and sociodemographic data were collected during the interview and from medical charts. Clinical data included epilepsy type (focal, genetic generalized epilepsy, and unknown epilepsy), seizure control (recurrent seizures, fluctuating, and seizure-free) (14), anti-seizure drugs (ASD), depression and anxiety symptoms, and suicidal ideation. We also collected age, gender, employment status, marital status, and years of education. The local Ethics Committee approved this study, and all subjects signed a consent form to participate (Research Ethical Committee Number: 06816819.5.0000.5404).

Psychiatric Symptoms and Anti-seizure Drugs Assessment and Instruments

We addressed the volunteers who accepted to participate in the study to an appropriate place to fill out self-administered scales (average duration of 30 min) under the supervision of undergraduate students, trained and previously monitored by a psychologist (M.H.N.). All participants were informed that

non-participation would not influence the treatment of their respective patients.

To assess symptoms of depression, we applied the Beck Depression Inventory-II (BDI-II), a self-assessment scale used for screening and severity quantification of depressive symptoms (15). The BDI-II cut-offs for the Brazilian population were applied (0–13: subclinical depression, 14–19: mild depression, 20–28: moderate depression, and 29–63: severe depression), wherein PWE and caregivers with scores higher than 14 (16) were classified with clinical depressive symptoms. We used item nine of the BDI-II to evaluate suicidal ideation. A score equal to or >1 was set for the presence of suicidal ideation, based on studies that suggested this classification for assessing long-term vulnerability for suicide (17). We used the Beck Anxiety Inventory (BAI), a self-report scale to screen anxiety symptoms (18). Although the minimum cut-off for clinical anxiety is 11 (0–10: subclinical anxiety, 11–19: mild anxiety, 20–30: moderate anxiety, and 31–63: severe anxiety), we set the clinical anxiety scores as ≥14 to prevent false positives and provide a more balanced sensitivity and specificity. Accordingly, PWE and caregivers with scores higher than 14 were considered significant for clinical anxiety symptoms.

PWE also answered the Liverpool Adverse Events Profile (LAEP), an epilepsy-specific self-administered questionnaire with 19 items. The LAEP has a Likert scale with global scores ranging from 19 to 76. Scores ≥ 46 were considered significant for adverse events (19).

Statistical Analysis

We used the Statistical Package for the Social Sciences—SPSS22 (Armonk, NY, USA) to perform statistical analysis. Categorical variables, expressed in percentages, were analyzed with the Chi-square test (*post-hoc* analyses with Bonferroni adjustment were applied for group comparisons) (20). The Kolmogorov-Smirnov test was performed to evaluate data distribution. Kruskal-Wallis tests were applied to compare continuous variables with non-normal distribution. Correlations between continuous non-normal distributed variables were assessed with Spearman tests. We also performed logistic regression models with clinical and sociodemographic variables to investigate factors associated with depressive, suicidal ideation, and anxiety symptoms. The significance level for the analyses was set at $p < 0.05$.

RESULTS

Demographic and Clinical Data (PWE and Caregivers)

As showed in **Table 1**, PWE were younger than caregivers ($p < 0.001$) and presented higher rates of unemployment ($p = 0.001$) and non-married subjects ($p < 0.001$). We found a higher proportion ($p = 0.004$) of women in the caregiver's groups than PWE. Years of education were similar between the two groups ($p = 0.9$). While the proportion of depression symptoms ($p = 0.026$), the intensity of depressive symptoms ($p = 0.007$) and suicidal ideation frequency ($p = 0.02$) were higher in PWE compared to caregivers, the proportion of clinical anxiety ($p = 0.32$) and the intensity of anxiety symptoms ($p = 0.13$) were similar in both groups. We observed a similar proportion of concurrent clinical depression and anxiety in both groups ($p = 0.23$), with comparable intensity.

Caregivers' Analyses

Most caregivers with depressive symptoms were women (87% in the subgroup with clinical depression symptoms vs. 65% with non-clinical symptoms, $p < 0.01$). Similarly, most caregivers with anxiety symptoms were women (86% in the subgroup with clinical anxiety symptoms vs. 65% with non-clinical symptoms, $p < 0.01$). Considering the caregivers with combined anxiety and depressive symptoms, we observed that the majority were women ($p = 0.002$) and presented familiar antecedents of psychiatric disorders (39% in the subgroup with combined symptoms vs. 15% in the subgroup without combined symptoms, $p < 0.01$).

We obtained paired data from a subset of 120 patient caregivers' dyads, collected on the same consultation day. From this group of caregivers, 87 individuals were genetically related to PWE (first or second-degree relatives), and 33 were genetically unrelated. Symptoms of depression tended to be more frequent in genetically related (28%) than in genetically unrelated (23%) caregivers, although without statistical significance ($p = 0.75$). However, the presence of anxiety symptoms was similar in genetically related (29%) and unrelated caregivers (31%) ($p = 1$). We observed that the intensity of depressive symptoms in PWE (but not anxiety) correlated with the intensity of depressive ($r = 0.35$; $p < 0.001$) and anxiety ($r = 0.25$; $p = 0.01$) symptoms in their caregivers. While we identified higher LAEP scores in the PWE of caregivers with symptoms of depression ($p = 0.026$) and those with concurrent anxiety and depression ($p = 0.038$), neither the type of epilepsy nor the seizure control impacted their correspondent caregivers' frequency of anxiety and depression symptoms (**Supplementary Table 1**).

Depression, Suicidal Ideation, and Anxiety Symptoms [PWE (Groups) and Caregivers] According to Epilepsy Types

As showed in **Supplementary Table 2**, PWE with GGE were younger ($p < 0.001$) than those with focal epilepsy and caregivers. Furthermore, the *post-hoc* analyses (with Bonferroni correction) showed a higher frequency of non-married subjects in the GGE group ($p < 0.001$) and married subjects among caregivers ($p < 0.001$). In addition, we observed increased unemployment rates among patients with focal epilepsy ($p < 0.001$) and equivalent years of education across the three groups ($p = 0.1$).

The presence ($p = 0.026$) and the severity ($p = 0.018$) of depressive symptoms was higher in the focal epilepsy group (51% with temporal lobe epilepsy) than the caregivers. Subjects with focal epilepsy presented more suicidal ideation than the GGE and caregivers' groups ($p = 0.006$). However, the three groups presented similar frequency ($p = 0.56$) and intensity ($p = 0.3$) of anxiety symptoms. We observed an equivalent proportion (∼25%) of subjects with concurrent clinical depression and anxiety symptoms in the three groups ($p = 0.38$). In addition, the frequency ($p = 0.8$) and the intensity ($p = 0.37$) of ASD adverse events were equivalents between patients with FE and GGE.

TABLE 1 | Sociodemographic characteristics and clinical data (PWE and caregivers).

	PWE *N* = 548 Median (range) or *N* (%)	Caregivers *N* = 191 Median (range) or *N* (%)	*p*-value
Median age	41 (18–83)	47 (18–82)	<0.001
Gender			
Women	327 (60%)	137 (72%)	0.004
Men	221 (40%)	54 (28%)	
Employment status			
Unemployment	337 (62%)	92 (48%)	0.002
Employment	211 (38%)	99 (52%)	
Marital status			
Married	228 (42%)	111 (58%)	<0.001
Non-married	320 (58%)	80 (42%)	
Years of education	11 (0–18)	10 (0–18)	0.9
Clinical depression			
N	497	174	
Yes	207 (42%)	55 (32%)	0.026
No	290 (58%)	119 (68%)	
BDI-II score	11 (0–57)	7 (0–56)	0.007
Suicidal ideation			
N	534	186	
Yes	99 (19%)	20 (11%)	0.02
No	435 (81%)	166 (89%)	
Clinical anxiety			
N	492	168	
Yes	184 (37%)	55 (33%)	0.32
No	308 (63%)	113 (67%)	
BAI score	9 (0–58)	7 (0–51)	0.13
Concurrent clinical depression and anxiety			
N	457	160	
Yes	124 (27%)	35 (22%)	0.23
BDI-II score	25 (14–57)	24 (14–56)	0.65
BAI score	25 (14–56)	29 (15–51)	0.56

PWE, people with epilepsy; BDI-II, beck depression inventory-II; BAI, beck anxiety inventory; p, p-value for pearson χ^2-test of association between categorical variables and for Mann-Whitney test of comparison of medians for quantitative variables.

The distributions of depressive, suicidal ideation, and anxiety clinical symptoms among the three groups according to epilepsy types are shown in **Figure 1**.

Depressive Symptoms, Suicidal Ideation, Anxiety Symptoms, and ASD Adverse Events in PWE According to the Seizure Control

PWE were classified according to their seizure-control pattern as recurrent seizures, fluctuating, and seizure-free. The pairwise comparisons revealed that the recurrent-seizures group included a higher proportion of subjects with depression symptoms (compared to the seizure-free group; $p < 0.01$) and with suicidal ideation (compared to the fluctuating and seizure-free groups; $p < 0.001$). Moreover, the group with recurrent seizures also presented increased severity of depressive [compared to both fluctuating ($p = 0.03$) and seizure-free groups ($p < 0.001$)] and anxiety symptoms [compared to the seizure-free group ($p < 0.001$)]. We also observed more frequent ASD adverse events in the recurrent-seizures group (34%) when compared to the seizure-free (16%; $p < 0.001$). The severity of ASD adverse events (LAEP score) was higher in the recurrent-seizures group compared to the seizure-free group ($p < 0.001$; **Supplementary Table 3**).

The distributions of depressive, suicidal ideation, and anxiety clinical symptoms among the three groups according to the seizure control are shown in **Figure 2**.

Factors Associated With Depressive, Suicidal Ideation, and Anxiety Symptoms in Adult PWE

We applied logistic regression to identify predictive factors associated with depressive, suicidal ideation, and anxiety symptoms in PWE. The predictor variables were the types of epilepsy (focal and GGE), sex, education, employment status, seizure control, and presence of depressive or anxiety

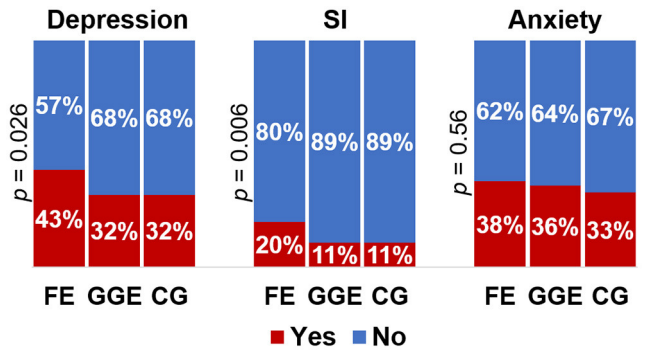

FIGURE 1 | Distribution of depressive symptoms, suicidal ideation and anxiety clinical symptoms according to epilepsy type and caregivers. Depression, clinical depression symptoms; SI, suicidal ideation; Anxiety, clinical anxiety symptoms; FE, focal epilepsy; GGE, genetic generalized epilepsy; CG, caregiver; *p*, *p*-value for Pearson χ^2-test of association between categorical variables.

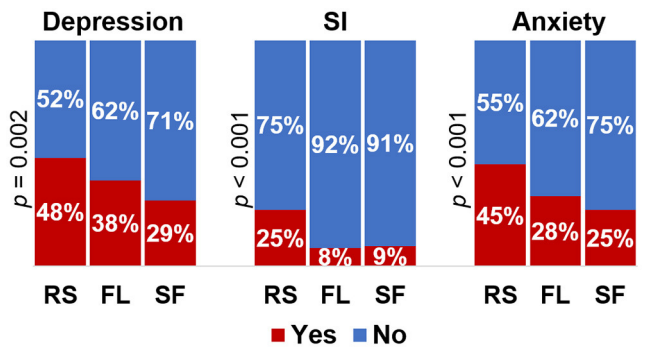

FIGURE 2 | Proportions of depressive symptoms, suicidal ideation and anxiety clinical symptoms according to seizure control. Depression, clinical depression symptoms; SI, suicidal ideation; Anxiety, clinical anxiety symptoms; RS, recurrent seizures; FL, fluctuating; SF, seizure-free; *p*, *p*-value for pearson χ^2-test of association between categorical variables.

symptoms (when appropriate). For depressive symptoms, the entire model explained between 24.2% (Cox and Snell R^2) and 32.6% (Nagelkerke R^2) of the variance, with an accurate overall prediction of 75.5% of the cases; it yielded an accurate prediction of 64.5% of the PWE with clinical depression. Anxiety symptoms and the type of epilepsy made a unique contribution to the model. The strongest predictor of depression symptoms was the presence of anxiety symptoms (odds ratio, OR 8) when controlled for other variables in the model. The second predictor of depressive symptoms was focal epilepsy with an OR of 2.1 (when controlled for the other variables included). Women with epilepsy were 1.7 folds more likely to present depressive symptoms than men (**Supplementary Table 4**).

Our model to assess predictors of suicidal ideation explained between 15.7 and 25.4% of the variance in suicidal ideation. Overall, it correctly classified the outcome for 81%; however, only 15.6% of the predictions for the PWE with suicidal ideation were accurate. After controlling for the variables in the model, the significant predictors were clinical anxiety symptoms (OR 5.23), focal epilepsy (OR 3.16, compared to GGE), and recurrent seizures (OR 2.57, compared to the seizure-free group). The increase of 1 year of age associated with a decrease in the odds of presenting suicidal ideation by a factor of 0.98 (**Supplementary Table 5**).

The model with predictors for anxiety symptoms accounted for between 26.1 and 35.6% of the variance in anxiety symptoms, with overall correct discrimination of the outcome for 76.6% (it accurately predicted 67.5% of the PWE with clinical anxiety). The strongest predictor of anxiety was the presence of depressive symptoms (OR 8) when controlled for other variables in the model. Recurrent seizures yielded an OR of 2.1 (compared to the seizure-free group), and women presented anxiety symptoms twice as much as men when controlled for other variables (**Supplementary Table 6**).

We also investigated predictors for comorbid anxiety and depression with a model that included the adverse effects (**Supplementary Table 7**). The model explained between 32 and 47% of the variance in the combination of anxiety and depression symptoms, with correct identification of the outcome in 85.4% (it precisely identified 72.6% of individuals with comorbid symptoms). After controlling for the variables in the model, the presence of adverse effects resulted in an OR of 19.8, while women were approximately twice more likely to present comorbid symptoms than men.

Factors Associated With Depressive and Anxiety Symptoms in Caregivers of Adult PWE

We used logistic regression to identify predictor variables related to depressive, suicidal ideation, and anxiety symptoms in caregivers of adult PWE. The models included age, sex, education, marital status, and the presence of depressive or anxiety symptoms (when appropriate) as predictor variables. The model for depressive symptoms correctly discriminated the outcome for 75.5% of the cases (it accurately predicted 65.8% of the caregivers with clinical depression and 82% of those without). It explained between 22 (Cox and Snell R^2) and 30% (Nagelkerke R^2) of the variance in the depression of caregivers. The strongest predictor of presenting depression symptoms was clinical anxiety, with an OR of 8; women were 1.6 times more likely to have depression symptoms (compared to men) after controlling for the other variables in the equation (**Supplementary Table 8**).

Although the whole model with predictors of suicidal ideation was significant (chi-square = 56.7, df = 5, $p < 0.001$) and yielded an overall prediction of 81.5%, it was unable to accurately predict suicidal ideation in the group of caregivers, on the contrary, it successfully predicted the absence of suicidal ideation in 100%. Nevertheless, the strongest predictor for suicidal ideation was the presence of anxiety symptoms (OR 5.9), after controlling for the variables in the model. The coefficients showed that an increase of 1 year of age associated with a decrease in the odds of suicidal ideation by a factor of 0.98.

The model with predictors of anxiety symptoms accounted for between 24.5 and 33% of the anxiety variance and correctly classified the outcome for 75.9% of the cases. It accurately predicted the presence of anxiety symptoms in 68.4%. The coefficients revealed that the strongest predictor was the presence of depression symptoms with an OR of 8.4 after controlling for the other variables in the model. It also showed that women were twice more likely to present symptoms of depression compared to men; the non-married individuals were 1.7 times more likely to present depression than those who were married (**Supplementary Table 9**).

DISCUSSION

The examination of a large group of patients and caregivers (739 subjects) revealed frequent depressive and anxiety symptoms in both groups. The intensity of depressive symptoms was higher in PWE, mainly in focal epilepsy and recurrent seizures. However, the occurrence and intensity of anxiety symptoms were similar in caregivers and all groups of PWE. Depressive and anxiety symptoms were similarly observed in genetically related and genetically unrelated caregivers, although depressive symptoms tended to be more frequent in genetically related caregivers. The severity of depression in PWE was associated with both anxiety and depression symptoms in their respective caregivers. Unfortunately, suicidal ideation was also identified in both groups, though higher in PWE.

The occurrence of depressive and anxiety symptoms in PWE concurs with previous studies that consistently reported rates of depressive disorders in ∼35–44% of PWE (21, 22) of anxiety in nearly 20–40% (23, 24). A correlation between epilepsy outcomes and psychiatric disorders has been previously demonstrated (25, 26). Thus, our results reinforce the hypothesis of common underlying neurobiological mechanisms between these entities (27), as higher frequency and severity of depressive and anxiety symptoms were associated with recurrent seizures. However, the occurrence of these symptoms in caregivers of adult PWE has not been extensively investigated (28), compared to studies performed with caregivers of other chronic diseases such as cancer, Alzheimer's disease, and other neurological disorders (7–9).

Some studies have shown higher parental anxiety and depression levels in children and adolescents with epilepsy (11, 12). Nevertheless, in adults with epilepsy, fewer studies investigated the presence of anxiety, depression (and suicidal ideation) in caregivers (28, 29). In contrast, several studies of caregivers of PWE demonstrated their poor quality of life (12, 30, 31) and increased burden (32). As both anxiety (33) and depression (34) are associated with quality of life, we speculated that the emotional distress identified in the caregivers might be associated with their poor quality of life.

Higher levels of depression (29%) have been described in caregivers of palliative cancer patients (35) and dementia (32%) (8). In our sample, depressive symptoms affected 32% of PWE caregivers, similar to the 33.6% observed in a recent Chinese study with 131 dyads (29). Compared to other diseases, some differences are noteworthy, especially considering the lifetime condition for PWE (especially those with pharmacoresistant seizures), compared to shorter periods of sickness for patients with dementia and cancer. Unfortunately, the impact of epilepsy on family and caregivers has been under-evaluated and mostly neglected (5), compared to several studies performed to recognize and understand both the emotional status and quality of life of caregivers in other chronic medical conditions. These studies have allowed the development of different strategies (36, 37) to improve their emotional status.

The suicidal ideation frequency of 19% in PWE of our sample was higher than the 12.1% prevalence found in a cross-sectional study with 139 patients at North American epilepsy centers (38). A recent meta-analysis of 24 studies showed a pooled suicidal ideation prevalence of 23.2% in PWE (39). Although suicidal ideation was more frequent in PWE (mainly in those with focal epilepsy), it was surprising that the rates (11%) were similar for GGE and caregivers. This proportion is considerably high, compared to rates of suicidal thoughts (0.67%) in the seven days prior to the evaluation of 15,105 Brazilian participants (civil-servants) (40); our observed rate of 11% is closer to the percentage identified by the authors in the subgroup with major depressive disorder (7.7%) (40). This finding is surprising and emphasizes the need for further investigation. In our subjects, the presence of clinical anxiety symptoms was a common critical predictor of suicidal ideation in both PWE and caregivers, which is similar to the results of studies that suggested anxiety as a risk factor for suicidal thoughts (41). As few studies investigated depressive and anxiety symptoms in caregivers of adult PWE, the frequency of suicidal ideation and its predictors also remain poorly recognized and understood in this population.

We identified a similar proportion of anxiety symptoms in caregivers and PWE. Although high levels of anxiety have been repeatedly reported in PWE, the examination of caregivers has received less attention. Interestingly, we observed a similar proportion of symptomatic caregivers (33%) compared to the 31.3% identified in a recent Chinese study (29). One previous study from 1992 examined 44 families and revealed severe anxiety levels in 36.4% of primary caregivers of adult drug-resistant epilepsy (28). Our study's proportion of caregivers with anxiety symptoms was similar to that identified in caregivers of palliative cancer patients (31.2%) (35). This finding, along with the depression rates, raises a concern about the impact of epilepsy on family members and caregivers.

The dyads' analyses showed similar proportions of symptoms of anxiety and depression in caregivers genetically related and unrelated, suggesting the presence of a strong negative environmental impact on caregivers' psychological status. It is essential to highlight that the instruments we used do not allow for diagnosing major depressive disorder (MDD), which may have a bi-directional biological relationship with epilepsy (3, 38). Further studies are necessary to investigate a difference in MDD frequency between caregivers who are genetically related and unrelated to PWE.

Interestingly, the severity of depressive symptoms in PWE is associated with the intensity of anxiety and depressive symptoms in their paired caregivers. These data suggest that the negative

impact of epilepsy on caregivers is not negligible and certainly deserves more attention. Although these relationships have been poorly investigated in epilepsy, they have been well recognized in cancer (42) and MDD (43). We observed similar correlations (range 0.25–0.35) to those reported for cancer patient-family caregiver dyads in a Chinese study with 641 dyads (range 0.25–0.32) (44). In 2018, one study reported depressive symptoms in 28.5% of caregivers of 165 people with MDD diagnosis. Multivariate analysis showed that the severity of depressive symptoms in patients with MDD is associated with the severity of depressive symptoms of their caregivers (43).

We observed a similar frequency of concurrent depressive and anxiety symptoms in caregivers (22%) and PWE (27%). This simultaneous finding has been reported in PWE (45) and associated with worse seizure control (46) and reduced quality of life (26). We also have observed this mixed phenomenon in both GGE (25) and mesial temporal lobe epilepsy (47), mainly associated with recurrent seizures. Despite the negative impact on the quality of life, this co-occurrence has not been deeply investigated in caregivers of PWE. Unfortunately, the caregivers of PWE have not received proper attention (5) while facing the lifetime issues of dealing with a chronic, unpredictable disease of their patients. So far, we do not know the best approach to improving their psychological well-being, as dealing with a lifetime condition poses an additional challenge compared to other illnesses. While great effort has been directed to highlight the importance of the treatment of the psychiatric comorbidities of PWE (48) as part of a global approach, our results alert to the need to equal attention to be directed to the caregivers as their emotional distress appears to be equivalent to the PWE and the caregivers of cancer patients. Further studies are required to understand the specific needs of caregivers of PWE, including pharmacological intervention, when necessary. It is also possible that a multidisciplinary treatment for both patients and caregivers, including counseling and support groups, would improve their emotional impairment and quality of life.

Concurrent Depressive and Anxiety Symptoms in PWE

Our results showed a relationship between depressive and anxiety symptoms in PWE. Those with depressive symptoms were eight times more likely to have anxiety symptoms, and those with anxiety were eight times more likely to have depressive symptoms. As previously reported, this mixture of symptoms is associated with poor seizure control (48). We recently showed that patients with mesial temporal lobe epilepsy with concurrent mood and anxiety disorders were ∼4 times more likely to have recurrent seizures than subjects without psychiatric disorders (47). We also observed severe disruption in the functional MRI brain connectivity of GGE patients with mixed anxiety and depressive symptoms (25). The negative impact of this combination on brain function, quality of life (49), and seizure control (48) reinforce the need for better therapies, including pharmacological and non-pharmacological approaches.

Anxiety, Depressive Symptoms, and Suicidal Ideation in PWE: Relationship With Epilepsy Type and Seizure Control

As previously described, patients with FE (mostly temporal lobe epilepsy) presented more severe depressive symptoms (50) compared to other patients and caregivers. According to our model, patients with FE were two times more likely to present depressive symptoms in comparison to GGE; however, seizure control did not influence the presence of depressive symptoms in this model. Our results differ from a community-based study (with 440 PWE), in which depressive symptoms were equally distributed among different epilepsy types (22). Such discrepancy may be related to our tertiary hospital-based patients and the fact that only 23% of our group with focal epilepsy was free of seizures, while in that study, 56% of all patients were free of seizures for 2 years. This finding reinforces the idea of a bidirectional relationship between temporal lobe epilepsy and depression, as detailed in previous studies (46, 48). On the contrary, anxiety symptoms were similarly observed among the FE, GGE, and caregivers, with equivalent severity. Unlike depression symptoms, subjects with recurrent seizures were two times more likely to present anxiety symptoms, following a previous study that showed an association between anxiety and poorer seizure control (51).

Similar to the analyses of South-Korean patients (74 in the suicide group; 222 patients in the non-suicide group) (52), our multivariate analyses showed the presence of anxiety, frequent seizures, and focal epilepsy associated with the occurrence of suicidal ideation. Suicidal ideation in PWE is complex and multifactorial, including the bidirectional relationship with psychiatric symptoms, exposure to specific anti-seizure drugs, and type of epilepsy syndrome. Some studies have shown an association between suicidal thoughts and increased seizures (53). Unlike what is observed in the general population, we speculate that in epilepsy (with the expected decreasing frequency of seizures over the years) the lower incidence of suicidal ideation at an older age could be related to the strengthening of coping strategies. These approaches are probably developed and consolidated over their lifetime with the restraints of stigma and social and professional limitations (54), added to the clinical aspects of epilepsy that directly impact the patients' quality of life.

CONCLUSION

The novelty of our results is mainly associated with the identification of high rates of anxiety, depression and suicidal ideation not only in PWE but also in caregivers. Our findings indicate that specific attention for the emotional health of caregivers is as essential as for PWE. Further studies involving PWE caregivers are required to understand the particular needs and the best approaches, considering the lifetime characteristic of epilepsy for most of the patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Hospital de Clinicas (Unicamp) Research Ethics Committee (CAAE Number: 06816819.5.0000.5404), the research participants were recruited at the Epilepsy Outpatient Clinic of the Hospital de Clínicas of UNICAMP. All subjects included in the sample signed the Informed Consent Form. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RJ: designed the study, performed statistical analysis, and wrote the paper. MN: recruited and evaluated subjects, designed the study, performed statistical analysis, and wrote the paper. MM-S: recruited and evaluated subjects, designed the study, and contributed to the discussion session. MA: recruited and evaluated subjects and contributed to the discussion session. SJ and HPe: recruited and evaluated subjects. HPi: supported the statistical analysis. FC: designed the study, contributed to the discussion session, and wrote the paper. CY: recruited and evaluated patients, designed the study, performed statistical analysis, contributed to the discussion session, and wrote the paper. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.766009/full#supplementary-material

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REVIEW
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Assessment of Anxiety in Patients With Epilepsy: A Literature Review

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Objective: Approximately 20% of people with epilepsy (PWE) suffer from anxiety. These fears are quite diverse and may manifest periictally or interictally, be part of the seizure's semiology, or an expression of reactive psychological distress from seizures themselves. Our review addresses the question of what screening tools are used in clinical care and epileptological research to capture the complexity of epilepsy-specific anxieties.

Method: On 2021/11/11, we entered a search string in PubMed that covered our research interest as completely as possible. We also screened the bibliographies of our findings and followed PubMed's recommendations. From the assessments we found in the included studies, we extracted domains that represent the range of manifestations of anxiety, in order to compare the tools and to discuss to what extent they are suitable for assessing epilepsy-specific anxieties.

Results: We screened 1,621 abstracts. In total, we identified 24 different anxiety assessments. In addition to the psychiatric assessments in use, we found 7 tools that were designed to assess epilepsy-specific anxieties. The latter focus on different aspects of epilepsy-specific anxieties. In some cases, the conceptual frameworks are not sufficiently transparent or divergent.

Conclusion: Because a diagnosis of epilepsy can result in, or seizures may appear as, anxiety, it is important to better understand this psychological burden and address it therapeutically, if necessary. There is a need for screening tools that integrate specific points of a variety of assessments, so as to cover the broad range of epilepsy-specific fears. None of the assessments we found meets this integrative perspective. At the same time, the appropriate design of such a required tool presupposes a conceptual framework of what should be considered as epilepsy-specific anxiety.

Keywords: (epilepsy-specific) anxiety, (epilepsy-specific) fear, psychiatric comorbidity, assessment, epilepsy, questionnaire

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INTRODUCTION

People with epilepsy (PWE) suffer from anxiety more frequently than the general population and patients affected by other chronic diseases (1). The recognition of the association of psychiatric issues and distress with epilepsy has a long history (2), and the need for assessing psychiatric comorbidities for an adequate therapy has received increasing awareness (3). Whereas psychiatric

disorders and depression in particular are considered as relevant comorbidities (4), anxiety has been under-researched so far. Recent studies, however, suggest that in people with epilepsy, anxiety is at least as frequent as depression and dysphoria (5). In recent years the different forms of anxiety in PWE and their pathophysiological and clinical appearance have been debated. These do not only differ in their temporal relation to seizures, but also in terms of their subjective quality and behavioral consequences (5, 6). Thus, anxiety does not appear to be a uniform comorbidity of epilepsy but rather encompass a spectrum of manifestations. This spectrum also represents different pathogenetic mechanisms, including preictal prodromes possibly indicative of proictal alterations in excitability, direct neurobiological mechanisms related to the involvement of brain structures involved in emotional perception and regulation, early ictal anxiety reflecting a loss of control, and interictal anxiety, e.g., in expectation of further seizures, and social stigma manifesting as phobic behavior (7, 8).

Available screening tools have been discussed [e.g., (9, 10)]. Presently, in both epileptological research and clinical care of PWE, a number of questionnaires with different aims have been used, including scales that explicitly or implicitly address the multiple aspects of anxiety, e.g., assessments of quality of life (11–13), social functioning (14), health locus of control (15), or psychological flexibility (16).

In this paper, we have limited our analysis solely to those instruments that are explicitly dedicated to the task of assessing (epilepsy-specific) anxiety in adults. We analyze how anxiety has been assessed in patients with epilepsy to date, which aspects are covered by standardized self-report questionnaires for the general population or instruments specifically developed for people with epilepsy. We also wished to investigate if there are aspects which have been reported qualitatively, but may not have been sufficiently included in standardized assessments so far. For this purpose, a standardized literature search was carried out to identify studies performing an assessment of anxiety in people with epilepsy. Inventories are described and compared concerning their coverage of different conceptual aspects of anxiety. Results are analyzed and discussed with regard to the appropriateness and completeness of assessment of types of anxiety by the respective questionnaires.

METHOD

To represent the state of research on the topic comprehensively, we entered the following search terms into PubMed/Medline:

> epilepsy OR seizure AND (anxiety OR ictal fear OR "psychiatric comorbidity")
> NOT covid NOT "adverse effects" NOT "side effects"

We selected "humans" as an additional filter, excluded studies for people under 18 years old, and only searched for studies with an available abstract.

This strategy was chosen to obtain broad overview of anxiety research in human epileptology. To ensure coverage of the complexity of anxiety's phenomenology, we entered inclusively "ictal fear" (without quotation marks, so that "fear" is respected as a search term on its own) and "psychiatric comorbidity" in addition to the term "anxiety."

We did not specifically assess the question to which extent Covid-19 might be associated with anxiety in patients with epilepsy; neither did we wish to study "adverse effects" or "side effects" of medical treatment that might trigger anxieties. Nevertheless, publications were considered insofar as they also discussed issues of medical treatment as epilepsy-specific anxiety (see below).

The search was entered on November 11, 2021, and resulted in 1621 findings. No language limits were selected. Abstracts were screened for relevance, and we checked which screening tools were applied. Both studies applying general anxiety screening tools, as well as studies that designed assessments for epilepsy-specific anxieties, were included, as were papers that discussed forms of anxiety in PWE conceptually (not listed in **Figure 1**). We also considered the literature lists of screened articles and suggestions for similar articles on PubMed/Medline.

Selection of Domains

We compared the questionnaires and extracted different domains for the purpose of comparison. Here, we had in mind the main anxiety forms classified by ICD-10 and DSM-5 and the corresponding symptomatology, and the epilepsy-specific forms of anxiety that are discussed in epileptological research. Such domains have been used, e.g., in the Hamilton Anxiety Rating Scale that subsumes the mentioned symptomatology under concise attributes (17), and are further elaborated here and complemented with domains essential to the coverage of epilepsy-specific phenomena.

An analysis of the questionnaires with regard to conceptual categories covered resulted in the following domains:

1. Anxious mood and worries as symptoms that occur in generalized anxiety disorder.
2. Emotional expressions of anxiety (or its opposite), like feelings of tension, irritability, fatigability, restlessness, or weakness.
3. Fear of concrete things, situations, people, including reactive avoidance behavior, reflecting specific phobias, such as social phobia or agoraphobia.
4. Extreme anxiety and panic representing the acute distress as it appears in panic disorders.
5. Somatic symptoms, including muscular and sensory, cardiovascular, gastrointestinal, respiratory, genitourinary symptoms and sleep-related problems.
6. Autonomic symptoms such as blushing or sweating.
7. Cognitive and mental symptoms like compulsive thoughts or hypervigilance.
8. Specific and reactive behavior as a domain represents the behavioral consequences for an individual suffering from anxiety, e.g., having trouble to relax due to inner tension or compulsive thoughts.
9. Specific fears related to anti-epileptic medication (AEM) and its side-effects.
10. Other manifestations of anxiety.

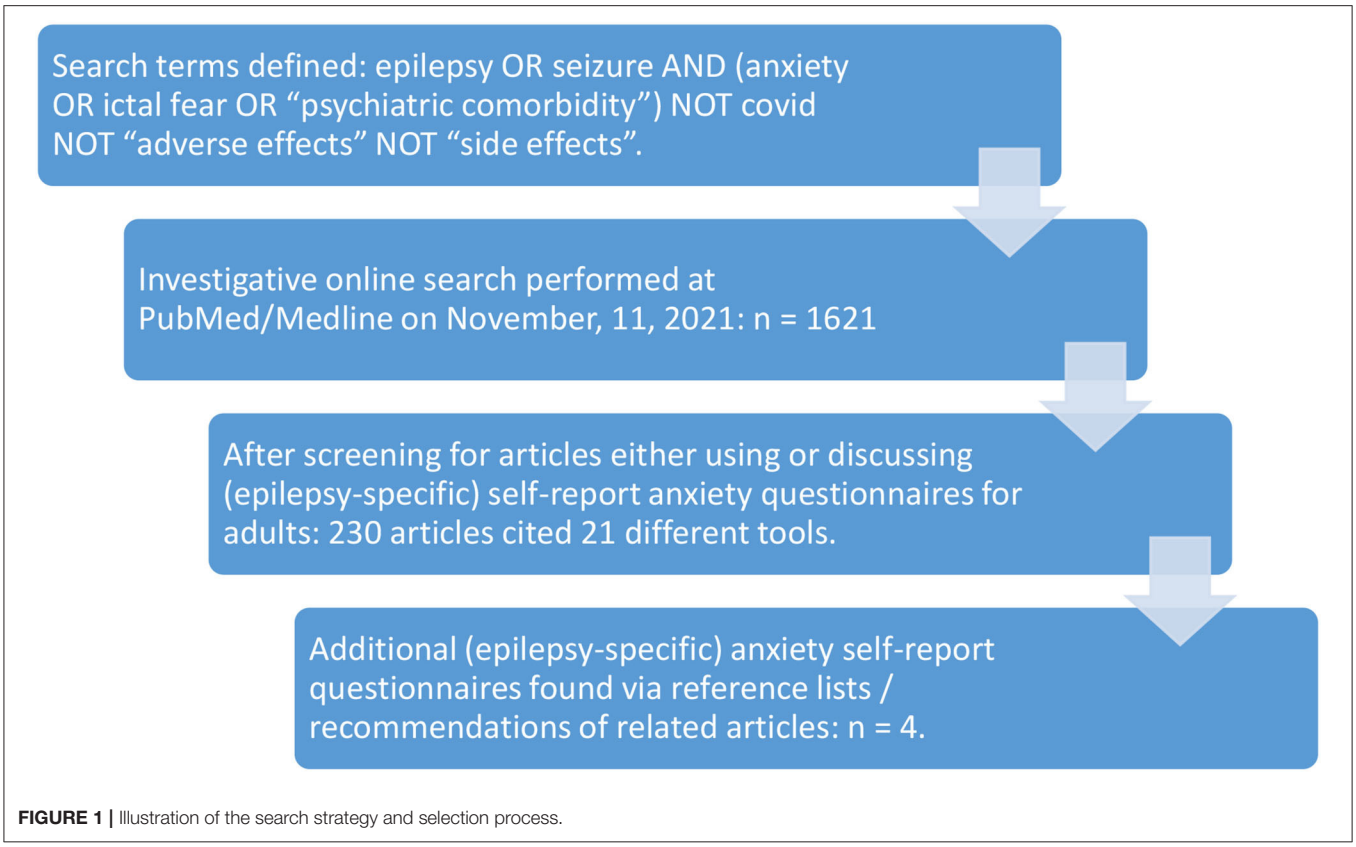

FIGURE 1 | Illustration of the search strategy and selection process.

RESULTS

We identified a total of 21 different self-report questionnaires used for adult PWE in both research and clinical care. **Figure 2** shows that the search strategy resulted in common psychiatric questionnaires on anxiety, but also in questionnaires focusing focusing on specific topics like, for example, the Death Anxiety Questionnaire by Otoom et al. (18) or inventories of Interictal Dysphoric Disorder.

We identified four further questionnaires by reading the reference lists of relevant publications and following the recommendation lists at PubMed. Except the Social Phobia Inventory (19), these are methodologically quite different attempts to capture epilepsy-specific anxiety: Bhalla-Gharagozli Fear in Epilepsy Questionnaire (20), Disease-related Fear Scale (21), Fear of Seizures Scale (modified version) (22). **Table 1** gives an overview of the questionnaires discussed in our review.

Not all of the assessments found could be included in the structure of our review. We found older studies using questionnaires on anxiety in the context of epileptology research and care that are no longer in use today, including the Morbid Anxiety Inventory (23). Furthermore, one study combined items from the General Health Questionnaire 5 and the Crown-Crisp Experiential Index to assess anxiety (24). Burton and Labar (25) compiled their own questionnaire to assess the emotional status after right vs. left lobectomy, with 1 item including anxiety ("Feeling nervous and anxious"). Finally, we found a study in (26), in which the Emotional Thermometer-7 is in use, a visual analog scale, for associating anxiety and quality of life in PWE.

Identified Questionnaires Applied in the Assessment of Anxiety in People With Epilepsy

In the following section, questionnaires covering aspects of anxiety in their assessment are discussed. We arranged our findings systematically in three main categories: comprehensive assessment of anxiety (covering anxiety symptoms in general), focused assessment of anxiety (covering specific types of anxiety), and assessment of epilepsy-specific forms of anxiety.

Comprehensive Assessment of Anxiety

Beck Anxiety Inventory

The BAI consists of 21 questions. The items are one-word descriptions of symptoms considered to address subjective feelings ("nervous", "unsteady", "shaky/unsteady", "scared", "faint/lightheaded"). Specific fears of dying and of losing control are covered by 2 items. Two items belong to the extreme anxiety/panic domain ("fear of worst happening", "terrified or afraid"). Eight items focus on somatic expressions of anxiety: 2 muscular, 4 sensory, 1 cardiovascular, 1 gastrointestinal, 2 respiratory. Three items ask for autonomic symptoms. Finally, 1 item addresses the behavioral level ("unable to relax").

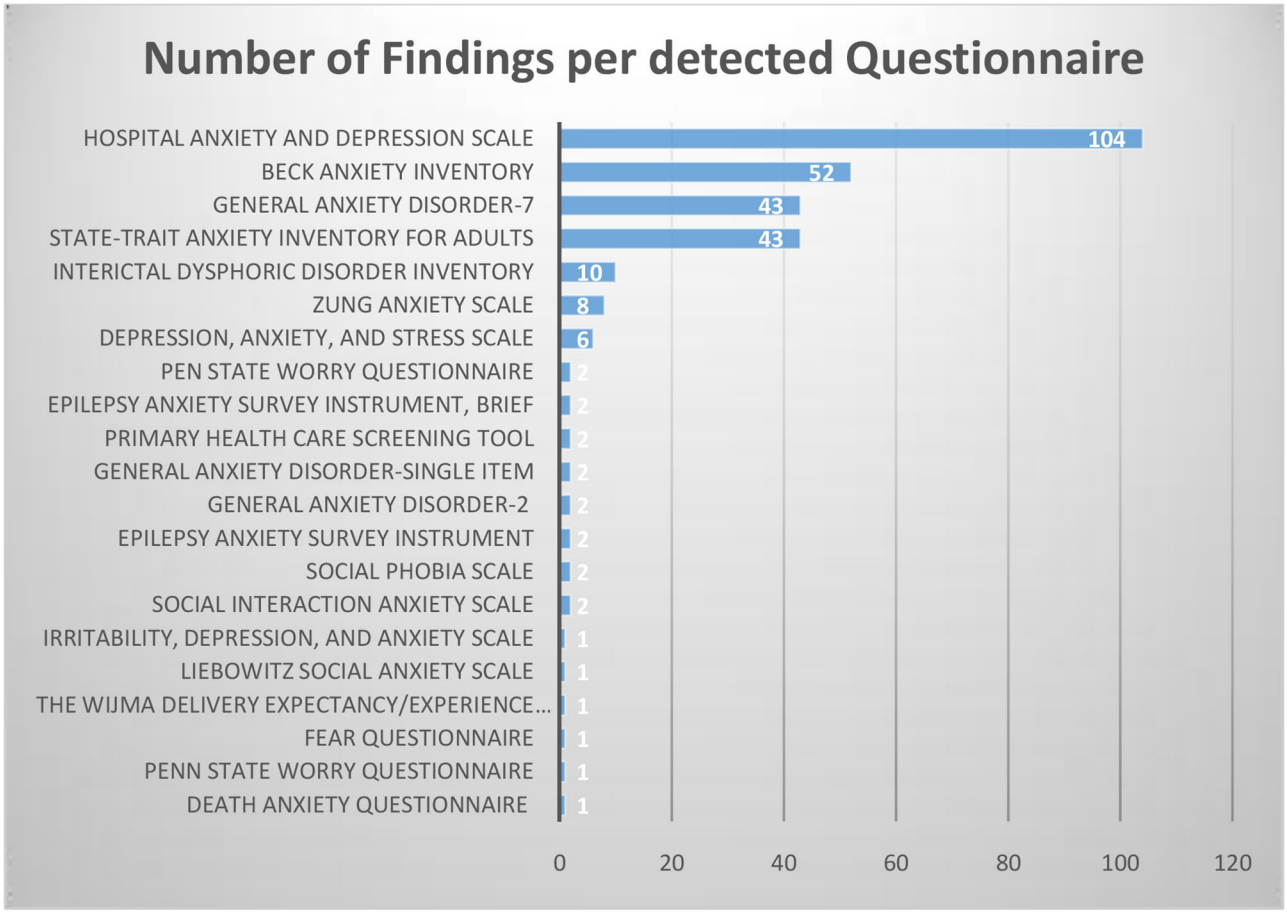

FIGURE 2 | Number of detections per questionnaire.

Thus, the BAI is a screening tool covering symptoms especially related to generalized anxiety disorders and panic attacks. Out of the epilepsy-specific fears, it covers ictal and interictal panic disorders well and interictal GAD. Other anxiety forms, such as anticipatory anxiety disorder or epileptic social phobia, are not covered.

Depression, Anxiety, and Stress Scale

The DASS-21 consists of a total of 21 items, 7 on depression, 7 on anxiety, and 7 on stress. The 7 explicit anxiety items cover anxious mood, social phobias and panic experience, somatic muscular (hand tremor), cardiovascular (palpitations), respiratory (shortness of breath) and autonomic (dry mouth) symptoms.

The DASS-21 is focused on somatic and autonomic symptoms, as they typically occur during panic attacks. Additionally, 3 of 7 stress items ("I found it hard to wind down", "I found it difficult to relax", "I felt that I was using a lot of nervous energy") address stress symptoms associated with a spectrum of anxiety forms. From the wide range of inter- and periictal fears occurring in PWE, the fear (and stress) items are mainly limited to panic experience and specific phobias including somatic expressions, i.e., epileptic social phobia, ictal fear, and panic disorder. Other epilepsy-specific fears, such as anticipatory anxiety or fears related to medication, are not included.

Fear Questionnaire

The FQ consists of three sections. The first section consists of 17 items. The patient is asked to indicate on a scale from 0 ("would not avoid it") to 8 ("always avoid it") which situations he would avoid as they cause him anxiety or unpleasant feelings. The first item must be written down by the patient as his individual "main phobia," which he wishes to be treated. In this section, fears of concrete things, situations and people are assessed, which are also relevant in PWE. For example, the fear of "Hospitals," "Injections or minor surgery," "Going alone far from home," "Thought of injury or illness," and "Large open spaces" are relevant fears in PWE.

In the second section, the patient is asked to indicate the present state of his actual phobic symptoms on a scale from 0 ("no phobias present") to 8 ("very severely disturbing/disabling").

The third section again consists of 6 items directly asking about psychological problems on the emotional level: 1. "miserable or depressed"; 2. "irritable or angry"; 3. "tense or

TABLE 1 | Summarizes the questionnaires in alphabetic order and categorizes them according to basic features: Number of items, survey period, survey scale, time taken to administer, domains covered.

Name of assessment/ questionnaire	Items	Time taken to administer (minutes)	Survey Period	Survey Scale	Domains assessed	Validation for PWE reported	Reliability for PWE reported	specific for PWE	Comments
Beck anxiety inventory (BAI)	21	5	Past month	4-point Likert scale	Emotional expression; fear of things, situations, people; extreme anxiety/panic; somatic symptoms; autonomic symptoms; specific/reactive behavior	No	No	No	Puts focus on somatic (sensory and muscular) and autonomic anxiety expressions
Bhalla-gharagozli fear in epilepsy questionnaire (BG-FEQ)	6	2	Not specified	Dichotomous: yes/no	Fear of things, situations, people; somatic symptoms; AEDs	Yes	Yes (the alpha coefficeint was 92,8)	Yes	Epilepsy-specific items, focuses on epilepsy's and medication's consequences with unique items
Depression, anxiety, and stress scale (DASS-21)	21 (7)	9 (3)	Last week	4-point Likert scale	Anxious mood/worries; fear of things, situations, people; extreme anxiety/panic; somatic symptoms; autonomic symptoms	No	No	No	Focus on somatic and autonomic symptoms
Death anxiety questionnaire (DEAQ)	20	10	Not specified	5-point Likert scale	Fear of things, situations, people; others	No	No	Yes	Epilepsy-specific items considering death anxiety in PWE
Disease-related fear scale (D-RFS)	30	10	Not specified	4-point Likert scale	Anxious mood/worries; fear of things, situations, people; somatic symptoms; AEDs; others	Yes	Yes (cronbach alpha:.921); test-retest: no value provided)	Yes	Epilepsy-specific items covering fears of seizure consequences and fear of disease's long-term consequences
Epilepsy anxiety survey instrument (EASI)	18	10	Past 2 weeks	4-point Likert scale	Anxious mood/worries; emotional expression; fear of things, situations, people; extreme anxiety/panic; cognitive/mental impairment; specific/reactive behavior	Yes	Yes (cronbach alpha:.94; test-retest: 0.77) (p <.000,5)	Yes	Epilepsy-specific items covering mainly interictal forms of anxiety
Epilepsy anxiety survey instrument, brief (brEASI)	8	5	Past 2 weeks	4-point Likert scale	Anxious mood/worries; emotional expression; fear of things, situations, people; extreme anxiety/panic; cognitive/mental impairment; specific/reactive behavior	Yes	Yes (cronbach alpha:.94; test-retest: 0.79) (p < 0.0005)	Yes	Epilepsy-specific items covering mainly interictal forms of anxiety
Fear questionnaire (FQ)	24	15	Not specified	Mixed (see description)	Emotional expression; fear of things, situations, people; cognitive/mental impairment	No	No	No	Valuable tool for assessing especially specific phobias and their intensity
Fear of seizure scale (FSS)	15	10	Not specified	8-point Likert scale	Emotional expression; fear of things, situations, people; cognitive/mental impairment specific/reactive behavior; AEM; others	No	No	Yes	Older screening tool for assessing the fear of seizures construct
General anxiety disorder 7 (GAD-7)	7	5	Past 2 weeks	4-point Likert scale	Anxious mood/worries; emotional expression; fear of things, situations, people; specific/reactive behavior	Yes	Yes	No	Short and concise tool to screen for (interictal) GAD
General anxiety disorder 2 (GAD-2)	2	12	Past 2 weeks	4-point Likert scale	Anxious mood/worries; emotional expression	No	No	No	Value for clinical or academic use questionable
General anxiety disorder single item (GAD-SI)	1	1	Past 2 weeks	4-point Likert scale	Specific/reactive behavior	No	No	No	Value for clinical or academic use questionable

(Continued)

TABLE 1 | Continued

Name of assessment/ questionnaire	Items	Time taken to administer (minutes)	Survey Period	Survey Scale	Domains assessed	Validation for PWE reported	Reliability for PWE reported	specific for PWE	Comments
Hospital anxiety and depression scale (HADS-A)	7	5	Past week	4-point Likert scale	Anxious mood/worries; emotional expression; extreme anxiety/panic; somatic symptoms; specific/reactive behavior	Yes	Yes	No	Short and concise questionnaire whose items cover a wide range of anxiety's phenomenology
Irritability, depression, and anxiety scale (IDA)	18 (5)	10 (5)	Not specified	4-point Likert scale	Anxious mood/worries; emotional expression; autonomic symptoms; somatic symptoms; specific/reactive behavior	No	No	No	Valuable tool for assessing overlapping symptoms with specific relevance in PWE
Interictal dysphoric disorder Inventory (IDDI)	19 (6)	15 (5)	Not specified	Mixed (see description)	Anxious mood/worries; extreme anxiety/panic	Open	Open	Open	Epilepsy-specific questionnaire, focuses on timely association to the ictus
Liebowitz social anxiety scale (LSAS)	24	15	Past week	4-point Likert scale	Fear of things, situations, people	No	No	No	Valuable tool for assessing (epileptic) social phobia plus resulting avoidance behavior; items limited to this form of anxiety only
Penn state worry questionnaire (PSWQ)	16	10	Not specified	5-point Likert scale	Anxious mood/worries; fear of things, situations, people; cognitive/mental impairment; specific/reactive behavior	No	No	No	valuable tool for assessing a central symptom of (epileptic) generalized anxiety disorder
Primary health care screening tool (PHCST)	10 (5)	5	Past month	4-point Likert scale	Anxious mood/worries; emotional expression; somatic symptoms; cognitive/mental impairment	Yes	Yes (cronbach alpha: 0.57)	Questionable	Tool for assessing general symptoms of anxiety and depression in PWE
Social interaction anxiety scale (SIAS)	20	10	Not specified	5-point Likert scale	Anxious mood/worries; emotional expression; fear of things, situations, people; cognitive/mental impairment; specific/reactive behavior	No	No	No	Valuable tool for assessing (epileptic) social phobia, items limited to this form of anxiety only
Social phobia inventory (SPIN)	17	10	Past week	5-point Likert scale	Fear of things, situations, people; somatic symptoms; autonomic symptoms	No	No	No	Valuable tool for assessing (epileptic) social phobia, items limited to this form of anxiety only
Social phobia scale (SPS)	20	10	Not specified	5-point Likert scale	Anxious mood/worries; fear of things, situations, people; extreme anxiety/panic; somatic symptoms; autonomic symptoms; cognitive/mental impairment; specific/reactive behavior	No	No	No	Valuable tool for assessing (epileptic) social phobia; items limited to this form of anxiety only
State-trait anxiety inventory for adults (STAI-S)	20	10	Present moment	4-point Likert scale	Anxious mood/worries; emotional expression; cognitive/mental impairment; specific/reactive behavior	Yes	Yes	No	Important screening-tool to assess state-anxiety, not of special value for PWE
State-trait anxiety inventory for adults (STAI-T)	20	10	In general	4-point Likert scale	Anxious mood/worries; emotional expression; cognitive/mental impairment	Yes	Yes	No	Important screening-tool to assess trate-anxiety, not of special value for PWE
Wijma delivery expactancy/experience questionnaire (W-DEQ A & B)	33	15	Before (A) and after (B) birth	6-point Likert scale	Emotional expression; fear of things, situations, people; somatic symptoms; cognitive/mental impairment; specific/reactive behavior	No	No	No	Valuable tool for assessing fear of childbirth (of specific relevance in PWE)
Zung anxiety scale (ZAS)	20	10	Past few days	4-point Likert scale	Anxious mood/worries; emotional expression; somatic symptoms; autonomic symptoms	No	No	No	Valuable screening-tool that covers many anxiety domains

The table shows which publications on anxiety assessments report validity and reliability in epilepsy patients. If reported, statistics are provided (for references see description in our results). A short evaluation can be found in the comments section.

panicky". Item 4 asks for disturbing thoughts, item 5 for depersonalization experiences, and, finally, item 6 asks for "other feelings" and can be answered individually. Again, these items are to be measured in intensity on a scale from 0 ("hardly at all") to 8 ("very severely troublesome").

Hospital Anxiety and Depression Scale

The HADS is a questionnaire with 14 items, 7 addressing depression, 7 anxiety. The 7 anxiety items cover anxious mood (worrying thoughts), anxious feelings (tense and frightening feelings), panic (sudden feelings of panic), somatic anxiety symptoms ("butterflies" in the stomach) and reactive behavior (sit at ease/relax vs. restlessness).

The 7 items cover a wide range of manifestations of anxiety relevant to PWE, like interictal GAD and panic disorder. There is no explicit reference to seizures, as in all anxiety questionnaires that were not designed for PWE. Thus, crucial epilepsy-specific forms of anxiety remain unconsidered.

The HADS is discussed as a valid and reliable screening tool in PWE (27). For its methodological evaluation in Temporal Lobe Epilepsy patients, see Zingano (28).

Irritability, Depression, and Anxiety Scale

The IDA consists of 18 items. 5 items ask about anxiety, 5 about depression, 4 items about outward directed irritability, and 4 items about inward directed irritability. The 5 anxiety items cover 4 of our domains, including anxious mood and worries, emotional expression of fear, somatic symptoms, and specific or reactive behavior. As only 5 items ask explicitly for anxiety, not all anxiety domains can be covered. In addition to anxiety, the IDA also covers symptoms of irritability and depression, which play a crucial role in PWE.

State-Trait Anxiety Inventory for Adults

The STAI is a self-evaluation scale with 20 items probing for state and trait anxiety. The state-anxiety items ask about acute anxiety at the present moment, while the trait-anxiety items ask about how the respondent feels in general.

The state-anxiety items focus on the current feeling dimension. Thus, they ask partly about positive and partly about negative feelings. A total of 15 items ask about the following states with the antecedent phrase "I feel": nervous, steady, calm, secure, strained, at ease, upset, satisfied, frightened, comfortable, content, pleasant, indecisive, confused, self-confident. Another 5 items have the description "I am" (tense, relaxed, presently worrying over possible misfortunes, jittery, worried) as a prefix. Some of these emotion categories overlap with our seventh domain (cognitive symptoms) (confused, indecisive, self-confident).

The state-anxiety items, on the other hand, have only 8 items with the prefix "I feel" (pleasant, nervous and restless, satisfied with myself, like a failure, rested, that difficulties are piling up so that I cannot overcome them, secure, inadequate). The 12 remaining items ask about general and more persisting personality traits and beliefs (e.g., "I take disappointments so keenly that I can't put them out of my mind," "I get into a state of tension or turmoil as I think over my recent concerns and interests").

The STAI is not designed to capture different forms of anxiety. Rather, it is designed to distinguish whether anxiety is a persistent personality trait or a transient emotional experience. This question is also relevant with regard to epilepsy-specific anxieties.

The STAI is discussed as a valid and reliable tool for the use in PWE (29).

Zung Anxiety Scale

The ZAS is a questionnaire with 20 items on anxiety that addresses acute anxiety. The ZAS covers a wide range of anxiety expressions, from basic anxious mood, anxious feelings, muscular and sensory-somatic, gastrointestinal, cardiovascular, respiratory, genitourinary, autonomic symptoms, and sleep problems.

Although the symptoms are clearly associated with anxiety and cover several categories, it does not allow to differentiate specific types of anxiety. However, the variety of somatic anxiety symptoms and responses have particular relevance in PWE, for example, anxiety during prodromal or early ictal phases typical for some types of TLE.

Focused Assessment of Anxiety

Generalized Anxiety Disorder-7

GAD-7 is a 7-item self-report questionnaire. The instrument is used to survey Generalized Anxiety Disorder and is the only questionnaire that has been validated in several languages for the use in PWE (see discussion). This international standardization may be one reason why the ILAE promotes it as a screening tool. One item falls into the domain of anxious mood and worry, 2 items address anxious feelings, 1 item addresses compulsive thoughts, and finally 3 items fall into the category of specific reactive behaviors (trouble relaxing, restlessness, becoming annoyed/irritable).

GAD-7 can be used for the identification of (interictal) GAD in PWE. However, other interictal and periictal aspects of anxiety are not covered by this assessment.

General Anxiety Disorder-2 and General Anxiety Disorder-Single Item

The GAD-2 is an ultra-short screening tool designed to detect GAD as a distillation of the GAD-7 with 2 items remaining. The 2 remaining items "Not being able to stop or control worrying" and "feeling nervous, anxious or on edge" are shortened to a single item in the GAD-SI: "Trouble Relaxing." These short and ultra-short screening tools for use in PWE are discussed by Micoulaud-Franchi et al. (12) and Munger Clary et al. (30). Obviously 2 items cannot cover the entire spectrum of anxieties relevant for PWE.

Liebowitz Social Anxiety Scale

The LSAS is a questionnaire designed to assess the severity of social phobias. The items describe concrete situations that are expressions of social phobias, such as "telephoning in public," "going to a party," "working while being observed," or "meeting strangers." At the same time, the extent to which these specific fears result in avoidance behavior is assessed. The LSAS is specific to social phobias and the avoidance behavior that may result

from them. Other fears that are equally relevant to PWE are not covered by this questionnaire.

Penn State Worry Questionnaire

The PSWQ consists of 16 items. The focus are worries in different facets and contexts. These worries are a crucial symptom of Generalized Anxiety Disorder. In addition to general unspecific worries, sorrows related to projects or tasks are also covered by some items. Furthermore, an obsessive character of the worries, which can manifest itself as a bothering uncontrollable cognition, is also covered.

The PSWQ is particularly useful for assessing generalized anxiety disorder, from which PWE may also suffer. In addition, epilepsy-related worries can bother PWE in many different regards, for example, disease-related memory deterioration, side effects of AEMs, or performing daily routines like shopping or going to work. Other forms of anxiety that may play a significant role in the lives of PWE, such as panic or social phobias, are not assessed by the PSWQ.

Social Interaction Anxiety Scale

The SIAS consists of 20 items. It focuses on social anxiety, in particular on its expression in social interactions. It asks about the respondent's psychological and physical wellbeing when socializing with strangers, making eye contact, talking to authority figures, or attractive persons of the opposite sex.

The SIAS is designed to assess the extent to which social anxiety manifests itself in interactions and makes them more difficult. These aspects also play a role in PWE [see also (31)]. Detecting them can be important in some cases, such as when targeting them through cognitive behavioral therapies. However, this questionnaire does not cover a variety of other epilepsy-typical fears.

Social Phobia Inventory

The SPIN consists of 17 items and is designed to assess social phobia. It addresses in detail situations in which social anxiety may arise (dealing with authority figures, parties, strangers, embarrassment in front of others, public speaking, etc.) and the resulting avoidance behavior. In addition, somatic and autonomic reactions that arise during social interactions are assessed, such as heart palpitations, blushing, and sweating.

SPIN is designed for the assessment of social phobia, which is of importance also for PWE. However, other epilepsy-specific fears, such as periictal fears, are not considered.

Social Phobia Scale

The SPS consists of 20 items. The focus is on fears that arise in social contexts. It covers many fear expressions, from anxious mood to fears caused by situations in interactions with people, to panic expressions. Somatic and autonomic symptoms are also addressed, as are mental aspects and finally reactive behaviors.

The SPS places a focus on social phobias, while also including somatic and autonomic responses. Social phobias may be epilepsy-specific; nevertheless, other epilepsy-specific, inter- and periictal fears are not addressed.

The Wijma Delivery Expectancy Questionnaire—Version A and B

The W-DEQ is a questionnaire designed to assess fear of childbirth. Version A asks about expectations of labor and birth, and version B asks about how labor and birth actually went. The items in the two versions are identical in content. For clarity, we discuss here only version A. The 33 items are divided into 6 categories. It asks first about the expected outcome as a whole (with "fantastic" and "frightful" as items), second, it asks generally about feelings during labor and delivery (with, for example, "lonely," "afraid," "desolate," "tense," "glad," "abandoned," "relaxed" as items), third, it asks for expected feelings during labor and birth (with, for example, "panic," "hopelessness," and "pain" as items), fourth, it asks what is expected to happen during labor and birth (e.g., "I will totally lose control over my body"), fifth, it addresses the feelings at the very moment of delivery (with e.g., "natural" or "dangerous" as items), and finally sixth, it is asked whether negative thoughts have determined the past concerning labor and birth (like the death of the child).

These items refer to a very specific fear, which makes integration into our domains rather tricky. However, fears as emotional expressions, fear of things and situations, extreme panic, somatic symptoms, cognitive and mental impairment, and specific behavior are covered by the items.

Fear of childbirth may be of great importance to PWE for several reasons. It may be directed more broadly to the inheritance of the disorder or to a negative impact of anti-seizure medication on the child, but also to the possibility of experiencing a seizure during delivery.

Assessment of Epilepsy-Specific Forms of Anxiety

Bhalla-Gharagozli Fear in Epilepsy Questionnaire

Gharagozli et al. (20) discuss fears related to epilepsy and further the psychometric properties of the BG-FEQ. The authors identify 6 epilepsy-specific fears: fear of brain tumor, of premature death, of more frequent/severe seizures over time, fear of suffocation, fear of addiction to medication and fear of adverse effects of long-term intake of anti-seizure medication (AEMs).

The BQ-FEQ addresses two epilepsy-specific fear aspects not covered by other assessments, the fear of addiction and the fear of a brain tumor. However, it is not completely clear on the basis of which methodological considerations the items were selected.

Death Anxiety Questionnaire

The DEAQ was developed in a study by Otoom et al. (18). The authors hypothesize that death anxiety plays a particular role in PWE. Twelve items can be most easily assigned to specific fears: dying because of epilepsy, the thought of bereaved relatives after one's own death, fear when medication runs out, fear when the death of other PWE is reported, fear of a painful, sudden, lonely death or death during sleep, fear due to an epilepsy surgery procedure, fear of visiting other PWE in the hospital, sitting beside a dying person, attending a funeral or a corpse washing, or simply the fear of hearing about death. Difficult to assign are

the items, "I wish that death was a curable disease" and "I wish that people would not use the word 'death'."

The authors state that the above items were assembled from previous studies and adapted for PWE. The validation of the tested items is considered, referring to a Master's thesis discussing death anxiety in cardiac patients, yet not clarified. In the authors opinion, the internal consistency was high (alpha = 0.94) [cf. (18), p. 143].

Inquiring about fears of death as reported by PWE is relevant. For some items, however, it remains open what is specifically meant by fear of death. A theoretical discussion of what subjective character this fear can take, and on the basis of which beliefs it is generated is needed. Due to its specification on death anxiety, the DEAQ does not assess other epilepsy-specific forms of anxiety, such as an epileptic panic attack or epileptic social phobia.

Disease-Related Fear Scale

Shamsalinia et al. (21) designed and psychometrically evaluated a disease-related fear scale for PWE. Thirty items are included, divided into fear of the consequences of seizures and fear of long-term damage from the disease. Two items capture a basic anxious mood, a total of 20 items capture concrete fears: the fear of having a seizure during flirting/sex, that the family will lose faith in the cure of the disease, being injured during a seizure, social discrimination, worsening of the disease, brain damage, or even fear of compassion. In addition, 3 somatic fear expressions are assessed: fear of choking, of incontinence during a seizure, and fear of seizures due to insomnia. Five items refer to antiepileptic medication, and 1 item refers to the inheritance of the disease to one's own children.

The authors consider the D-RFS a valid and reliable assessment for PWE [(21), p. 5].

The assessment emerged from interviews with PWE and covers individual medical histories and the individual complexity and heterogeneity of epilepsy-specific fears. The authors themselves point out that the study should be replicated in other cultural contexts. The interviews from which the items were generated were conducted with 14 PWE, a relatively small sample. A larger population in a different cultural context may alter the composition of items.

Epilepsy Anxiety Survey Instrument and Brief Epilepsy Anxiety Survey Instrument

The EASI claims to be the first epilepsy-specific validated anxiety screening tool (32). It consists of 18 (long version) or 8 items (brief version). In 9 (EASI) and 6 (brEASI) items, respectively, the reference to epilepsy is not mentioned. In 2 (EASI), respectively, 1 (brEASI) item, the reference to seizures is explicitly excluded ("getting terrified out of the blue, unrelated to my seizures' and 'sudden feeling of panic, unrelated to my seizures"). The methodological reasoning behind this is that periictal fears are part of epilepsy. The authors do not consider these to be fears, as they are pathophysiologically determined as being part of a seizure.

The EASI asks about basic anxious mood, 1 item independent of epilepsy, 1 item related to epilepsy in terms of fear of the next seizure, and the impact on the social environment. A total of 6 items address specific fears and phobias with avoidance behavior. Three items address panic fears. Four items address cognitive and mental aspects of anxiety. Finally, 3 items assess behavioral manifestations.

In the brEASI, all categories of EASI are covered, with a reduced number of items per category.

The items of the EASI were distilled from interviews with PWE and expert opinions. The experts were asked to what extent common anxiety screening tool items (from BAI, GAD-7, and HADS) could be confounded by "aspects of epilepsy, seizures, or AEDs" (p. 2070). However, open questions remain as to which anxiety entities are considered as epilepsy-specific. Also, the methodological premise of separating a possible anxiety semiology of a seizure from epilepsy-specific anxiety necessarily leads to gaps in assessing clinically relevant forms of anxiety in PWE—especially periictal manifestations.

Fear of Seizures Scale

The FSS was originally designed by Mittan (33) and revised by Goldstein et al. (22). We only discuss the latter version (the items are the same). It consists of 15 items. It is designed to assess epilepsy-specific fears, namely fear of seizures. Answering patients are first asked about their acute fears, that are addressed by the items, and second about the probability, a respective seizure-related event might happen to them. Thus, the items mainly presume effects and consequences of seizures (e.g., emotional disorders, brain damage, death, a shorten life-span, mental deterioration, tongue swallowing, suffocation), their exacerbation (e.g., more medication needed) and their preconditions (e.g., brain tumors), including reactive avoidance behavior (e.g., physical exertion or exposure to flashing light/loud noise).

The items point to crucial domains of concrete epilepsy-specific fears that are related to seizures. Other symptoms of common psychiatric anxieties, which also play a central role in PWE, such as generalized anxiety disorders or social phobia, are not assessed.

Interictal Dysphoric Disorder Inventory

The IDDI covers 8 main symptoms, which are grouped into 3 main categories: labile depressive symptoms (depressed mood, anergia, pain, and insomnia), labile affective symptoms (fear, anxiety), and supposedly 'specific' symptoms (paroxysmal irritability and euphoric moods) [(34), p. 82]. In the appendix, 6 questions assess the temporal relationship of symptoms, the frequency and duration of dysphoric symptoms, and their relationship to seizures and AEDs. It asks whether dysphoria (only) emerges in the context of seizures, and if so, in what temporal sequence seizures and dysphoria occur, and how long each lasts.

Two main items on "Fear/Panic" ("Do you experience feelings of fear or feel panicky from time to time?") and "Anxiety" ("Do you have frequent worries, feelings of oppression, agitation, or anxiety from time to time?") require a dichotomous ("yes" or "no") response.

Even if the disease entity IDD has been questioned, and it is also unclear whether this syndrome can be identified as

epilepsy-specific [e.g., (35, 36)], all symptoms assessed can have relevance for PWE. The IDDI specifically addresses the time of occurrence of anxiety symptoms in relation to a seizure. The 2 main anxiety items cover important epilepsy-specific anxiety experiences, such as an panic attack or interictal GAD; others, however, are missing, as they are not considered to be component of the construct of IDD.

Primary Health Care Screening Tool

The PHCST consists of 10 items for assessment of depression and anxiety in PWE. According to the authors (37, 38) explanation, 4 items exclusively refer to anxiety ("thinking about too many things or thinking too much", "feeling anxious", "difficulty in concentrating" (in our opinion this item represents a typical depressive symptom, but we follow the authors conception), "experience of increased heartbeat for the past 1 month"), 1 item refers simultaneously to anxiety and depression ("disturbed sleep"). The anxiety items play a significant role in PWE. They cover some typical expressions of anxiety in general. More specific forms of anxiety are not covered by this tool.

The reliability and validity of the tool is discussed in the respective original paper (37).

Figure 3 summarizes our results in one illustration. The domains can be distinguished by different colors, which allows to compare the focus and range of the different assessments. The height of the column corresponds to the number of items; colors represent different domains, and the distribution of colors in relation to others represents the balance between domains addressed.

DISCUSSION

The results show that a variety of questionnaires is in use to assess anxiety in PWE for different purposes. We want to highlight two main aspects. First, epileptological research is interested to better understand the spectrum of forms of anxiety in PWE, and its manifestation in, and interrelation to, different types of epilepsy and demographic data. Questionnaires are used to advance research in understanding the relationship between the prevalence of specific fears in PWE and the mechanisms involved in their genesis as well as the correspondence to specific types of epilepsy.

Second, practitioners are interested in supporting their patients with best available care, anxiety being a debilitating experience with negative impact on the quality of life. Questionnaires are then of interest to detect the occurrence of anxiety and to include this knowledge in the treatment. A better theoretical understanding of the epilepsy-specific forms will likely lead to better health care, and vice versa. We identified:

- Questionnaires designed to capture anxieties comprehensively or with regard to specific forms of anxiety, yet, without addressing epilepsy-specific aspects.
- epilepsy-specific questionnaires that target aspects which are presumed to be specific forms of anxiety in PWE and aim to map them accordingly.

The usefulness of the identified assessments in PWE critically depends on the conceptualized epilepsy-specific forms of anxiety (39), which we will briefly discuss in the following. An official standardized classification of epilepsy-specific fears is not yet available. It is still an open question if psychiatric comorbidities should be considered in the classification of epileptic disorders (40).

Forms of Anxiety in PWE

A temporal distinction is made between periictal (preictal, ictal, and postictal) and interictal fears (5, 6, 41). Hingray et al. (5) and Ertan et al. (6) also formulate open questions for assessing these entities.

Periictal anxieties mainly include early ictal-aware perception of fear ("fear auras" according to the old terminology (42) and "ictal fears," "subjective ictal anxiety," or "ictal panic" of temporal lobe epilepsy with involvement of the amygdala and other limbic structures (43). They can be misdiagnosed as panic attacks due to their similar clinical appearance (44). These neurobiological forms of fears have no particular nomenclature. Postictal anxiety can arise from phases with impaired awareness with retrograde amnesia of the patient's ictal behavior.

Interictal fears (5) include the "anticipatory anxiety of epileptic seizures." This form of anxiety describes a strong fear directed at the expected occurrence of further seizures. "Seizure phobia" is a particularly disturbing form of this anticipatory anxiety, which is accompanied by intensified thoughts and avoidance behaviors regarding certain circumstances, places, situations where seizures have already occurred or might occur. "Epileptic social phobia" means the intense fear of being watched by others during a seizure. This phobia may also refer to particular aspects of the seizure type, including loss of consciousness, motor phenomena, postural instability or autonomic signs with highly stigmatizing potential like drooling or enuresis. A resulting avoidance of social interactions is a particularly debilitating aspect, as it may persist over time and render the patient prone to loneliness and social isolation. "Epileptic panic disorder" is according to (5) a specific panic disorder that occurs in association with agoraphobia, an entity that is not described by other researchers, as far as we know. In our opinion this supposedly interictal form of anxiety could be an expression of ictal fear, thus, could be a part of the seizure semiology. The term "fear of seizures" (45) is quite extensive and refers to fears that follow from assumed preconditions or consequences of seizures, but also to the fear of losing control during a seizure or the unpredictability of the next seizure (anticipatory anxiety, see above).

Last but not least, iatrogenic anxieties play a role for different therapeutic approaches. Thus, they may be related to anticipated or experienced adverse effects of medication (5, 7), and a fear of non-adherence and its possible consequences in terms of seizure exacerbation. Treatment-related anxiety is a matter, particularly when brain surgery is offered to control seizures. A possible transient increase in anxiety or *de novo* anxiety is reported after surgical interventions (46).

These entities provide some orientation, but are neither strictly defined nor a sufficient or exhaustive reflection of

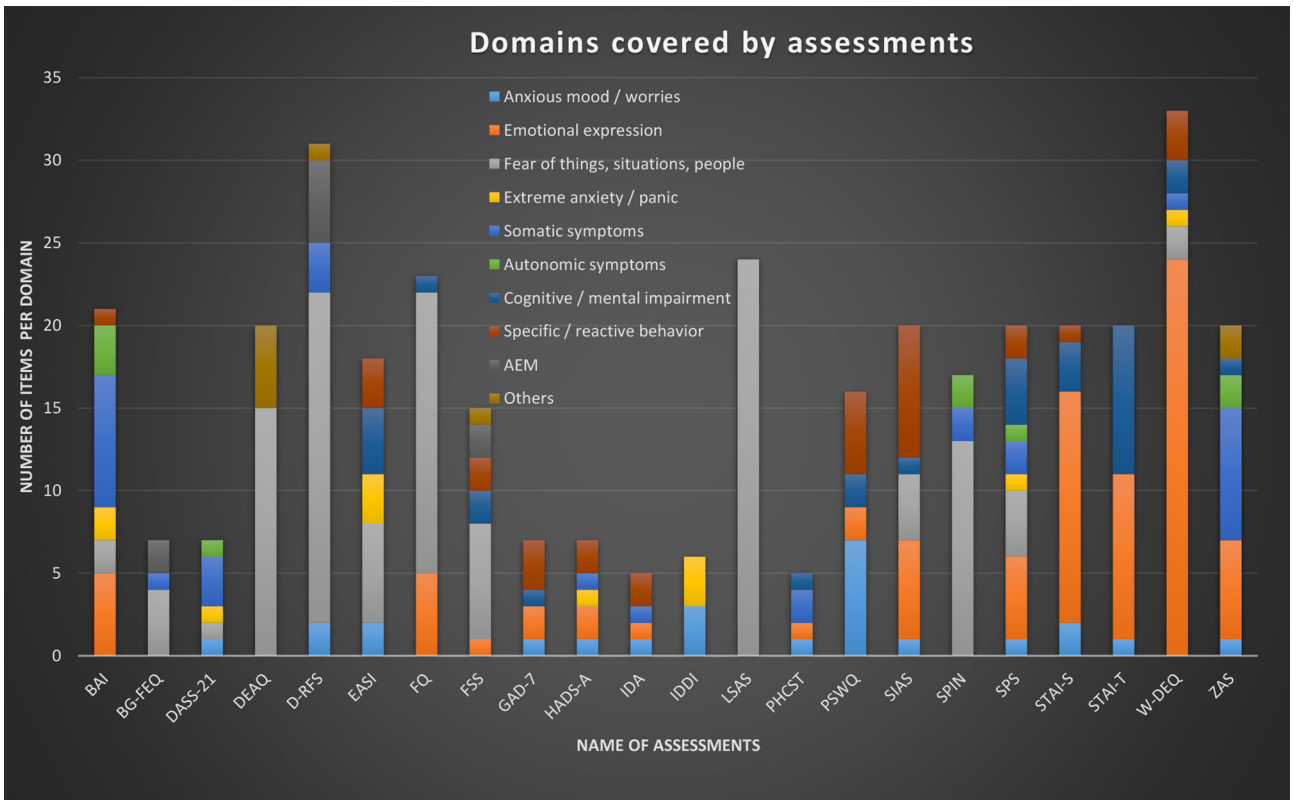

FIGURE 3 | Summary of our findings illustrating and comparing 22 different self-report questionnaires that are in use for the assessment of anxiety in PWE. It illustrates the number of items per questionnaire and their allocation to the domains we have extracted. We have not included the short versions of GAD-7 and EASI (GAD-2, GAD-SI, and brEASI) in this illustration.

epilepsy-specific fears, which are described and experienced as individually as the personal disease histories.

Assessments for Epilepsy-Specific Forms of Anxiety

Our search identified seven epilepsy-specific assessments targeting anxiety.

The BQ-FEQ consists of six items that query epilepsy-specific fears. It is the only questionnaire addressing fear of addiction to the prescribed antiepileptic medication. Addressing this phenomenon and actively discussing it with patients may be of relevance for the establishment of a trustful atmosphere and therapeutic adherence. The five other items are nearly identical with the items in the FSS (see below).

The DEAQ by Otoom et al. (18) strives for a more accurate understanding of fear of death in PWE. The authors do not explicitly delve into which death anxieties should be considered. Thus, real seizure-related risks of dying during the course of a seizure due to a fall, in status epilepticus, or as a result of autonomic dysfunction in SUDEP can fuel death fears. However, some patients also describe ictal fear as something like a subjective premonition or experience of death that does not refer to seizure-related risks but is rather a particular ictal experience. Further, items are somewhat heterogeneous as they also address fear of a surgical procedure or of medication running out. Some items seem to be suited to special cultural contexts. The item of the fear of corpse washing, for example, is only meaningfully assessed in a context where this practice still has relevance.

The D-RFS consists of 30 items that were derived deductively from the literature and inductively from patient interviews. This addresses and captures a particularly comprehensive range of issues. In particular, fear of both the immediate consequences of seizures and of long-term sequelae are captured. The range of fears thus covered is very specific, with most items relating to public space or social interactions. The D-RFS items refer to social, peer, and family support, sexual intimacy, stigma, and discrimination, but also more subtle and irrational fears, such as social isolation due to the contagiousness of the disease or the fear of being harassed by the pity of the social environment. In contrast, other epilepsy-specific fears of a subjective nature, including anxiety as part of the seizure semiology, are not included in this assessment.

The EASI and its abbreviated version emerged from patient interviews and expert opinions. Experts were asked to what extent items of common psychiatric anxiety assessments could be confounded by genuinely epileptic symptomatology. That is, the authors did not consider anxiety that is part of seizure semiology as epilepsy-specific anxiety. This is an *a priori* methodological

decision distinguishing this approach from other assessments, but it leads to gaps in assessing periictal forms of anxiety which patients experience and report as anxiety. Neglecting or excluding this subjective experience as such, just because the underlying pathophysiology is epileptic, is certainly debatable.

The EASI scores particularly well with respect to interictal fears, which are comprehensively covered by the items. The EASI is the only epilepsy-specific assessment that limits the survey period, referring to the past 2 weeks only. This decision has the advantage of being able to assess recent experiences that make a recall bias unlikely. On the other hand, it is possible that potentially existing interictal fears are not captured because the period considered is too short. The International League Against Epilepsy's homepage offers a free download of the EASI/brEASI as an alternative tool to the GAD-7 for assessing comorbid and interictal anxieties in PWE.

The FSS is an older instrument to assess epilepsy-specific fears of seizures that include subjective, often unfounded attitudes or expectations concerning seizures. They are frequently experienced by PWE and might subconsciously alter cognitive or behavioral attitudes. It is important to address them early after the first diagnosis of epilepsy since it may be reassuring for PWE to have them reflected in medical knowledge and facts. Further, they may have a negative influence on emotional and behavioral adjustment.

The IDDI assumes a specific syndrome, which also includes anxiety symptoms. The time course of dysphoric mood plays a crucial role. A particular advantage of this questionnaire is that it does not only categorize the presence of experienced pain, insomnia, anxiety and panic, etc., but additionally captures the intensity of these experiences and also the impact on the quality of life in a semi-quantitative manner. The appendix also allows for further differentiation, including, for example, the temporal relation to seizures. Of note, some researchers doubt that interictal dysphoric disorder is a distinct diagnosis and specific to PWE (for references see description in our results).

The PHCSTs obviously screens for symptoms of anxiety and depression. But as a matter of fact, the items are not specific for PWE, but assess typical anxiety and depression symptoms that can be found in the general population, too.

From these descriptions, it becomes evident that these tools vary in their theoretical and practical usefulness. The BQ-FEQ, D-RFS and the DEAQ, FSS, and the IDDI analyze the spectrum of anxiety in PWE. The EASI/brEASI is the most practical tool to assess interictal anxiety in PWE. High scores in any of the mentioned tools may trigger considerations of therapeutical consequences. Many epilepsy-specific anxieties can be eased by just naming and addressing them in a protected environment with the physician. For a discussion of pharmacological and (underresearched) psychotherapeutical treatment of anxiety in PWE see (5, 47).

Common Psychiatric Anxiety Assessments

The common psychiatric anxiety assessments found in our literature search differ significantly. The STAI's questions whether state- or trait-anxiety is present are also relevant for anxiety in PWE. An important question in this context is whether patients with an anxious personality would benefit from other therapies than patients whose fears turn out to be related more closely to epilepsy. Studies are furthermore needed to investigate to which degree anxiety traits reflect the chronic course of the disease. Questionnaires such as the SIAS, SPIN, SPS, LSAS, or GAD-7 specifically ask about defined psychiatric disease entities that have a counterpart in PWE. However, they are inappropriate for generating a picture of the many different forms that anxiety can take in PWE. Shortening the GAD-7 to GAD-2 or GAD-SI again results in a highly incomplete coverage of manifestations of anxiety in PWE.

The use of the GAD-7 as a screening tool for comorbid anxiety in PWE has been promoted by the International League Against Epilepsy. A free version can be downloaded at the ILAE's homepage. It has been validated for the use in PWE and is available in different translations: Chinese (48), French (49), Indonesian (50), Korean (51), Russian (52). The availability in multiple languages allows to perform cross-cultural comparisons in different populations. Of note, the cutoff of the GAD-7 is lower in PWE compared to the general population [for different interpretations, see (53)]. In general, different cutoff points may serve to draw attention to specific comorbidities and address these, rather than to establish the diagnosis of a disorder of its own as is a typical use in the general population, which may favorably use a higher cutoff score.

The W-DEQ asks for fear of childbirth, which often is relevant in PWE. The PSWQ asks for milder but nonetheless disturbing forms of anxiety, including compulsive thoughts. The FQ addresses mainly specific phobias and leaves space for differentiation therein, insofar as the patient can state his individual main phobia. The ZAS and BAI questionnaires are remarkable in that they include a range of sensory, muscular-somatic, and autonomic symptoms. Of note, some infrequently applied questionnaires such as the DASS-21 or IDA cover a wide range of the domains we have differentiated and ask for symptoms relevant to PWE, including irritability, stress, and depression.

Overall, it is clear that the forms of anxiety that PWE may suffer are particular forms of anxiety insofar as they are related to experiencing seizures. These fears are at most, if at all, only indirectly captured by general anxiety assessments.

LIMITATIONS

The present review's results are restricted by the applied search string. A broader search, not excluding terms such as "covid" or "adverse effects" would have resulted in a larger count of initial hits, and perhaps further relevant questionnaires would have emerged. However, such a strategy would also have resulted in a much larger number of abstracts to screen, which would have been beyond the scope of our resources. Another restriction is the limitation to self-report questionnaires only due to the same reasons. Fiest et al. (10) discuss other forms of assessments beyond self-report questionnaires, such as semi-structured interviews. Another limitation of our narrative review is that we did not discuss the methodological robustness of the

different assessments. In contrast, Wang et al. (54) provide a systematic review regarding validated anxiety questionnaires for PWE. But they do not mention any tool for epilepsy-specific anxieties. In contrast, our narrative review covers a larger number of questionnaires that are actually used in epileptological research and clinical practice. Further, it discusses and compares for the first time seven questionnaires that take on the task of assessing epilepsy-specific forms of anxiety.

CONCLUSION

The psychological burden of a diagnosis of and living with epilepsy is pronounced and complex. While affective disorders have received more in-depth attention in epileptology, anxiety—despite its high prevalence—has received relatively little attention.

Often patients initially feel overwhelmed and left alone with the diagnosis of epilepsy. Early consideration of the psychological distress that a patient goes through may help to alleviate this burden, either by simply addressing it directly or, if necessary, through appropriate therapeutic measures. A routine assessment of epilepsy-specific fears with appropriate instruments may be helpful in this context.

Overall, the spectrum of symptoms and signs of anxiety in PWE identified in this review is noteworthy and reflects the multitude of phenomenological aspects of anxiety present in PWE. On the other hand, none of the questionnaires reported here covers all relevant epilepsy-specific fears. Instead, the assessments are focused on particular aspects and domains. There is still a lack of validated screening tools that cover the wide range of anxiety's phenomenology in PWE. This calls for future developments of more comprehensive assessment strategies covering the variety of epilepsy-related anxieties, which can be used to screen for and thoroughly assess issues relevant to the heterogeneous population of PWE.

AUTHOR CONTRIBUTIONS

RR performed the literature research, evaluated the literature, and wrote the manuscript. AS-B designed the study, participated in writing, and the discussion of results. BM assisted with the literature search, performed corrections of the manuscript, and discussed results. All authors contributed to the article and approved the submitted version.

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The Degree Centrality and Functional Connectivity in Patients With Temporal Lobe Epilepsy Presenting as Ictal Panic: A Resting State fMRI Study

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Objectives: Ictal panic (IP) can be observed occasionally in patients with temporal lobe epilepsy (TLE). Such descriptions can be found in previous studies, but the mechanism is still not clear and often confused with panic attacks in patients with panic disorder (PD). We try to use imaging methods (resting-state functional magnetic resonance imaging, rs-fMRI) to study the mechanism of this psychiatric comorbidity in patients with TLE.

Methods: Forty right-onset TLE patients were observed, including 28 patients with TLE but without IP and 12 patients with TLEIP along with 30 gender-age matched healthy controls were included. We collected clinical/physiological/neuropsychological and rs-fMRI data. Degree centrality (DC) and functional connectivity (FC) were calculated. For the DC and FC values, analysis of covariance (ANCOVA) was used to find different areas and *t*-tests were used to compare differences between the TLEIP, TLE without IP, and healthy control(HC)groups. The relationship between brain abnormalities and patient characteristics was explored by correlation analyses.

Results: No significant differences in gender and age were found among the three groups, and no significant differences in education level, Montreal Cognitive Assessment (MOCA), Hamilton Depressive Scale (HAMD), Hamilton Anxiety Scale (HAMA), and epilepsy duration (years) between the TLEIP and TLE without IP groups. In addition to fear, other symptoms were observed, including nausea, palpitations, rising epigastric sensation, and dyspnea. There was no correlation between the duration of IP and HAMA. Moreover, all IP durations were <2 min. Compared to the HCs and TLE without IP group, the DC value of the TLEIP group in the left middle temporal gyrus (LMTG) was significantly increased. Compared to the HCs, FC could be found between the LMTG and left inferior temporal gyrus (LITG) in the TLEIP group. In addition, there was FC between the LMTG and cerebellum in the TLEIP group. The difference in the magnitude of FC between the TLEIP vs. HC group was greater than the difference between the TLE vs. HC group.

Conclusions: This study describes brain abnormalities in patients with TLEIP. These results will help to preliminarily understand the mechanism of ictal panic and abnormal functional connection in patients with TLE, and further explore the neuroimaging mechanism of ictal panic in patients with TLE.

Keywords: degree centrality (DC), functional connectivity (FC), TLE, ictal panic, rs-fMRI, middle temporal gyrus (MTG)

INTRODUCTION

Fear is a very distinct and recognized emotion caused by exposure to real or imagined threats (1, 2). The fear response represents a quick repertoire of visceromotor, neuroendocrine, and behavioral mechanisms to the aversive stimuli (3–5). The limbic system is well-recognized as a network of brain structures coordinating such responses (5, 6). The mainstream view is that there are fear circuits in the brain. First, the sensory information for assessing danger is transmitted to the amygdala through the anterior thalamus (7, 8), and when the amygdala perceives the threat, it is immediately activated, triggering a number of different pathways. When the amygdala sends information to the parabrachial nucleus, it can cause shortness of breath (9). If the amygdala sends out information to the lateral hypothalamus, sympathetic nerve activity can be enhanced (10). If the amygdala transmits information to the locus coeruleus, it can cause the secretion and increase of norepinephrine, increase in heart rate and blood pressure, and participate in the fear behavior response (11). If the amygdala transmits information to the paraventricular nucleus axis of the hypothalamus, the secretion of adrenocortical hormone can be increased (12). If the amygdala transmits information to the periaqueductal gray area of the midbrain, it can trigger additional behavioral reactions including defensive behavior and post-escape freezing, which may be related to panic attack symptoms (13–15). But these pathways are not complete. The wider fear network also comprises the prefrontal cortex, anterior cingulate, hippocampus, amygdala, and hypothalamus to learn, store, and evoke fear responses (1). In predisposed individuals exposed to acute or chronic stress, limbic network remodeling may result in the development of psychiatric disorders such as post-traumatic stress disorder, anxiety, and mood disorders (16–18).

Temporal lobe epilepsy (TLE) is a partial form of epilepsy that originates in one or several of the anatomic locations of the temporal lobe, and which can spread through a network of neuronal interconnections to adjacent brain tissue (19). Occasionally, before patients develop secondary generalized tonic-clonic seizure or complex partial seizure, patients with simple partial seizures of temporal lobe origin present with ictal panic which is sometimes treated as panic attacks, a symptom of panic disorder (PD) (20–25). This notion has been supported by some TLE patient studies describing panic disorder during the ictal stage (26–30). Although some studies have focused on the differential diagnosis of TLE with ictal panic and panic attacks, the local brain function mechanisms of TLE with ictal panic are still unclear (31, 32).

Resting-state functional magnetic resonance imaging (rs-fMRI) is now widely used in studies of the human brain. It is an advantageous tool that allows the mapping of regional interactions in the subject's brain when explicit cognitive tasks are not being performed (33, 34). Local dynamics and network functions of the brain can be described by rs-fMRI data, such as degree centrality (DC) and functional connectivity (FC) (35–37).

Degree centrality is proposed to map the degree of functional connectivity inherent in the brain in order to reflect the stability of cortical network structure at the voxel level. FC is the mechanism for the coordination of activity between different neural assemblies in order to achieve a complex cognitive task or perceptual process (38). The two indicators have now been widely used to study the functional modulation of many neuropsychiatric disorders including TLE (39, 40).

Degree centrality describes the importance of individual voxels in the whole brain and can help find areas with abnormal connections with other brain regions. FC can further find the abnormal connection. In this study, we employed an rs-fMRI to explore the brain-functional abnormalities in patients with right-onset TLEIP from different perspectives. Compared to control subjects, we sought to determine whether patients with TLEIP have specific brain-functional abnormalities by using the DC metrics and whether they have abnormal FC. Further, we sought to determine whether these abnormalities were associated with the clinical/physiological/neuropsychological characteristic scores of these patients.

MATERIALS AND METHODS

Participants

All participants were recruited from the epilepsy clinic of the First Affiliated Hospital of Guangxi Medical University. This study was approved by the hospital's Medical Research Ethics Committee. Written informed consent was provided by all participants. Forty patients with TLE were diagnosed by two neuropsychologists according to clinical characteristics, EEGs, and imaging examination. Patients were divided into two groups, TLEIP and TLE without IP groups. In order to reduce the impact on the results, we selected patients with epileptogenic focus on the right as the research subjects.

The inclusion criteria for the TLEIP group involved: (1) Patients with epilepsy who satisfy any two or more of the following conditions: a. The epileptogenic focus was located in the right temporal lobe. b. MRI showed unilateral or bilateral hippocampal atrophy/sclerosis, or other abnormalities in the unilateral or bilateral temporal lobe. c. EEG examination revealed

that epileptic discharges originated from the right temporal lobe; (2) Mini-mental state examination (MMSE) scores more than 24, right-handed, 18–50 years, and; (3) TLE history with ictal panic, as a precursor of seizures or as a symptom of seizures.

The following exclusion criteria were used in the TLEIP group: (1) Structural MRI showed other brain structural lesions besides hippocampal atrophy or hippocampal sclerosis; (2) A diagnosis of severe mental or neurological diseases except for ictal panic history; (3) People with alcohol abuse or drug abuse (41), and; (4) Patients who were unable to satisfactorily cooperate and complete all experimental procedures.

The inclusion criteria for the TLE without IP group involved: (1) Patients with epilepsy who satisfy any two or more of the following conditions: a. The epileptogenic focus was located in the right temporal lobe. b. MRI showed unilateral or bilateral hippocampal atrophy/sclerosis, or other abnormalities in the unilateral or bilateral temporal lobe. c. EEG examination revealed that epileptic discharges originated from the right temporal lobe; (2) MMSE scores more than 24, right-handed, 18–50 years, and; (3) TLE history without ictal panic.

The following exclusion criteria were used in the TLE without IP group: (1) Structural MRI showed other brain structural lesions besides hippocampal atrophy or hippocampal sclerosis; (2) A diagnosis of severe mental or neurological diseases; (3) People with alcohol or drug abuse (41), and; (4) Patients who were unable to satisfactorily cooperate and complete all experimental procedures.

Thirty right-handed healthy controls (HCs) without a history of mental or neurological diseases were enlisted from the community. Gender, age, and MMSE scores were matched with those of patients.

MRI Data Acquisition

MRI data were acquired using an Achieva 3.0-T MRI scanner with a 12-channel head coil (Philips, Amsterdam, The Netherlands). Prior to scanning, each subject was asked to rest for 20 min. During MRI scanning, subjects were instructed to close their eyes, remain conscious, and avoid active thinking. Foam padding was utilized for noise mitigation and to limit head movements. For each subject, resting-state functional imaging was obtained using the echo-planar image (EPI) technique with the following parameters: repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, 31 slices and 180 volumes, slice thickness = 5 mm, slice gap = 1 mm, voxel size = 3.44 × 3.44 × 6.00 mm, field of view = 220 × 220 mm, flip angle = 90°, scanning time = 360 s.

Data Preprocessing

Image preprocessing was performed using the Resting-State fMRI Data Analysis Toolkit plus V1.24 (RESTplus V1.24) toolbox (http://restfmri.net/forum/restplus) based on SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), including (1) removing the first 10 time points to make the longitudinal magnetization reach steady state and to let the participant adapt to the scanning environment; (2) slice-timing to correct the differences in image acquisition time between slices; (3) head motion correction; (4) spatial normalization to the Montreal Neurological Institute (MNI) space *via* the deformation fields derived from tissue segmentation of structural images (resampling voxel size = 3 mm × 3 mm × 3 mm); (5) spatial smoothing with an isotropic Gaussian kernel with a full width at half maximum (FWHM) of 6 mm; (6) removing linear trend of the time course; (7) regressing out the head motion effects (using Friston 24 parameter) from the fMRI data, and; (8) band-pass filtering (0.01–0.08 Hz). No participants were excluded from further analysis due to large head motion (more than 3.0 mm of maximal translation in any direction of x, y, or z or 3.0° of maximal rotation throughout the course of scanning)(DC omits step 5).

DC Calculation

In an undirected graph, degree centrality measures the degree to which one node in the network is associated with all other nodes. For an undirected graph with g nodes, the degree centrality of node i is the total number of direct connections between i and other g-1 nodes, which is represented by a matrix as follows:

$$C_D(N_i) = \sum_{J=1}^{g} x_{ij} \left(i \neq j\right)$$

TABLE 1 | Comparison of clinical data and neuropsychological scores among the three groups.

	TLEIP (*N* = 12)	TLE without IP (*N* = 28)	HCs (*N* = 30)	Value
Gender(M/F)	2/10	5/23	5/25	0.963[a]
Education (years);	11.933 ± 2.604	15 (9.75, 16)	17 (16, 17)	H = 24.468 ($P < 0.001$)[b]
TLEIP vs. TLE				U = 138.000 ($P > 0.05$)[c]
MOCA total score;	27.5 (25.25, 28)	27 (25, 29)	29 (28, 30)	H = 10.619 ($P < 0.05$)[b]
TLEIP vs. TLE				U = 160.000 ($P > 0.05$)[c]
HAMA scores;	5.58 ± 5.035	2.5 (1, 7.7)	0 (0, 2)	H = 18.733 ($P < 0.001$)[b]
TLEIP vs. TLE				U = 140.500 ($P > 0.05$)[c]
HAMD scores;	11.167 ± 7.826	6.607 ± 6.232	1 (0, 3)	H = 27.474 ($P < 0.001$)[b]
TLEIP vs. TLE				t = 1.963 ($P > 0.05$)[d]
Age(years)	29 (25, 30)	30 ± 7.369	25 (23, 30)	H = 2.381 ($P > 0.05$)[b]
Epilepsy duration(years)	14.167 ± 5.638	6 (4, 16)		U = 94.500 ($P > 0.05$)[c]

Values are mean ± SD.

N, number; MOCA, Montreal cognitive assessment; F, female; M, male; HAMD, Hamilton depressive Scale; HAMA, Hamilton anxiety rating scale.

[a] *Pearson Chi-square tests.*

[b] *Kruskal-Wallis nonparametric multiple sample test.*

[c] *Mann-Whitney U test (two-tailed).*

[d] *Two-sample t-test.*

Where $C_D(N_i)$ represents the degree centrality of node i, $\sum_{J=1}^{g} x_{ij}$ is used to calculate the number of direct connections between node i and other j(g-1) nodes (i $\neq$ j, excluding the connection between i and itself; that is, the value of the main diagonal can be ignored). The calculation of $C_D(N_i)$ is simply to sum the cell values of the corresponding row or column of node i in the network matrix (because undirected relationships form a symmetric data matrix,

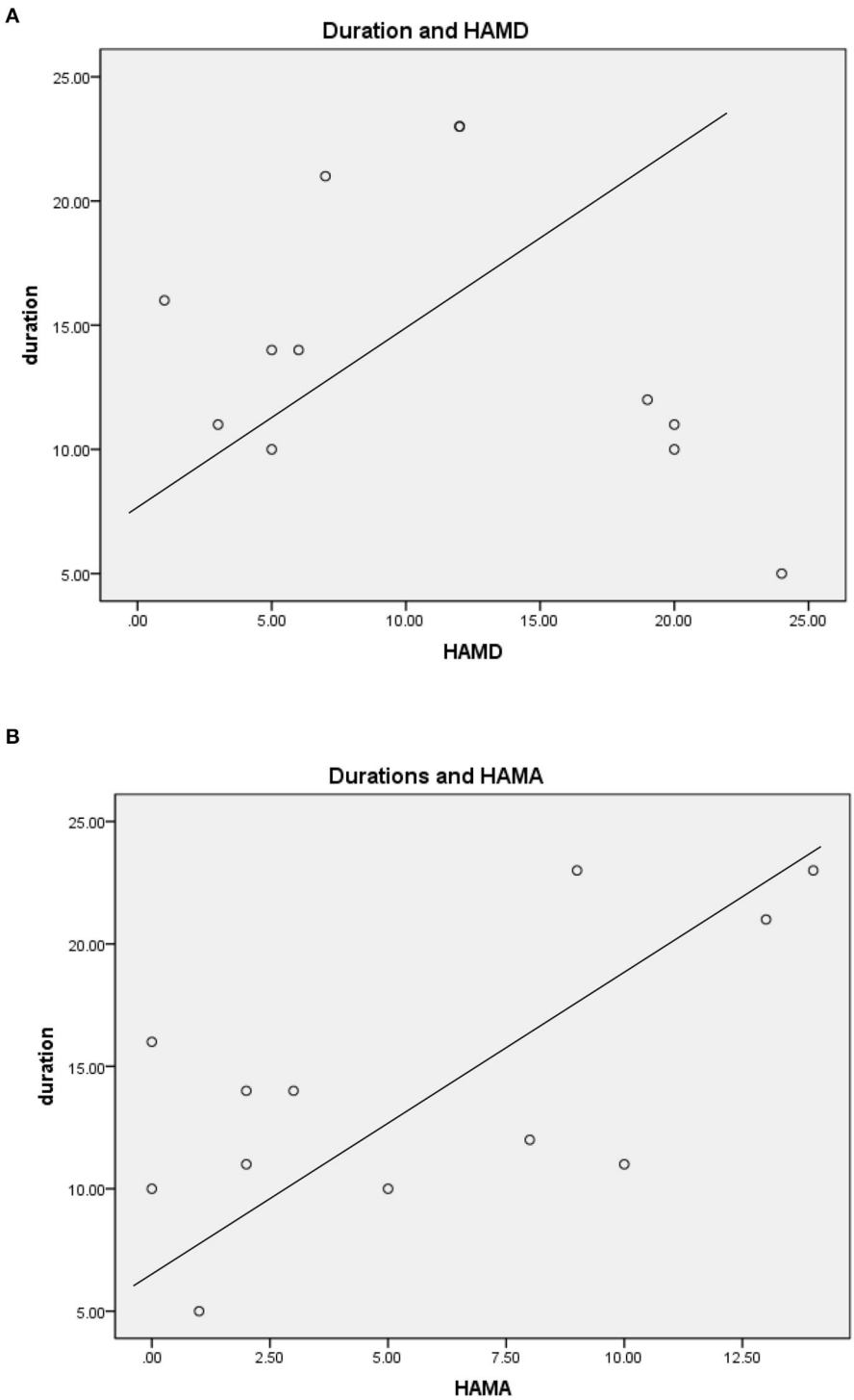

FIGURE 1 | (A) Durations of IP symptom and HAMD scores. **(B)** Durations of IP symptom and HAMA scores.

cells with the same rows and columns have the same values) (42).

DC and FC Analyses

First, in the DC analysis, the processed data of three groups were analyzed by one-way analysis of covariance (ANCOVA) to find the significant difference regions among groups (GRF correction, one-tailed, voxel level $P < 0.0005$, cluster level $P < 0.025$). Second, (if found) the difference region was made to be a mask and the mask was used to conduct two-sample *t*-tests between each two of the three groups, with the results corrected by GRF (two-tailed, voxel level $P < 0.001$, cluster level $P < 0.05$). Gender, age, and education level were applied as covariates to minimize their potential effects on the analysis.

In the FC analysis, first, through the comparison of DC values, the region with a significant difference between TLEIP and the other two groups is regarded as a region of interest (ROI). In order to explore the difference between TLEIP and TLE without IP, the main parts of the fear circuit: amygdala, hippocampus, parahippocampal gyrus, and thalamus are also taken as ROIs, then voxel-wise FC was performed on the whole brain to calculate the FC between the ROIs and the whole brain. Second, the processed data of the three groups were analyzed by one-way ANCOVA to find the significant difference regions among groups (GRF correction, one-tailed, voxel level $P < 0.0005$, cluster level $P < 0.025$). Third, (if found) the difference region was made to be a mask and the mask was used to conduct two-sample *t*-tests between each two of the three groups, with the results corrected by GRF (two-tailed, voxel level $P < 0.001$, cluster level $P < 0.05$). Gender, age, and education level were applied as covariates to minimize their potential effects on the analysis.

Statistical Analysis

The clinical/physiological/neuropsychological variables were analyzed using the Statistical Package for the Social Sciences 21.0 (SPSS) (SPSS Inc., Chicago, IL, United States). First, the Shapiro-Wilk test was conducted to determine whether the quantitative data conformed to a normal distribution. Second, if data conformed to a normal distribution, the data of the three groups were statistically analyzed by one-way ANCOVA test, and the data of the two groups were statistically analyzed by an independent *t*-test. For data with a non-normal distribution, the data of the three groups were examined by Kruskal-Wallis nonparametric multiple sample test, and the data of the two groups were examined by the Mann-Whitney U test. Gender differences were tested with the Chi-Square *t*-test.

RESULTS

Demographics, Clinical, and Neuropsychological Characteristics

There were no significant differences in gender and age among the TLEIP, TLE without IP, and HC groups. There were no significant differences in education level, MOCA, HAMD,

TABLE 3 | The degree centrality (DC) differences between the TLEIP group, TLE without IP group, and healthy control (HC) group.

Groups	Regions	MNI coordinates	Cluster voxels	T value (peak voxels)
DC				
TLEIP vs. HCs	Middle temporal gyrus_L	(−61, −47,3)	47	4.3149
TLEIP vs. TLE without IP	Middle temporal gyrus_L	(−61, −47,6)	43	4.3360
TLE vs. HCs	Negative finding			

TABLE 2 | Temporal lobe epileptic ictal panic (TLEIP) characteristics.

Patients	Age(years)	HAMD	Durations of IP symptom (years)	HAMA scores	Seizures type	Symptom	Durations of IP (minutes)
1	46	20	10	0	CP	Fear, nausea	<1
2	45	12	23	9	CP to G	Fear, palpitations, rising epigastric sensation	1–2
3	29	7	21	13	CP to G	Fear	1–2
4	29	1	16	0	SP to G	Fear	<1
5	28	20	11	10	CP	Fear	<1
6	29	5	10	5	SP to G	Fear	<1
7	22	5	14	2	CP to G	Fear	1-2
8	25	24	5	1	CP to G	Fear, palpitations	<1
9	30	3	11	2	SP	Fear	<1
10	23	12	23	14	SP	Fear, dyspnea, palpitations	<1
11	25	19	12	8	CP	Fear	<1
12	30	6	14	3	SP	Fear	<1

HAMD, Hamilton depressive Scale; CP, complex-partial seizure; SP, simple-partial seizure; G, generalized seizure; HAMA, Hamilton anxiety rating scale.

HAMA, and epilepsy duration (years) between the TLEIP and TLE without IP groups (**Table 1**).

For TLEIP patients, in addition to fear, other symptoms were also observed, including nausea, palpitations, rising epigastric sensation, and dyspnea (43). There were no correlations between duration of IP symptoms and HAMD scores, and there were no correlations between duration of IP symptoms and HAMA scores (Pearson correlation, two-tailed, $p = 0.659$, **Figure 1**). Moreover, the duration of all IPs were <2 min, and most were <1 min (**Table 2**).

DC and FC Results

Compared to the HC and TLE without IP groups, the DC value of the TLEIP group in the left middle temporal gyrus (LMTG) was significantly increased (GRF correction, two-tailed, voxel level $P < 0.001$, cluster level $P < 0.05$) (**Table 3** and **Figure 2**).

Compared to the HC group, we found that there was FC between the LMTG and left inferior temporal gyrus (LITG) in the TLEIP group, we also found that there were FCs between the LMTG and cerebellum in the TLEIP group. Although compared to the HC group, we found that there was FC between the LMTG and LITG in the TLE without IP group, the area of LITG in the TLEIP vs. HC group was larger than those in the TLE without IP group vs. HC group. In addition, the difference in the magnitude of FC between the TLEIP vs. HC group was greater than the difference between the TLE without IP vs. HC group. (GRF correction, two-tailed, voxel level $P < 0.001$, cluster level $P < 0.05$) (**Figure 3**).

DISCUSSION

In this study, we found that there were no significant differences in HAMA scores between the TLEIP and TLE without IP groups, and there was no significant correlation between the duration of IP symptoms and HAMA scores in the TLEIP group. Therefore, we speculate that there is no correlation between IP and anxiety in patients with TLEIP, which is different from previous studies describing the relationship between anxiety and panic (24, 26, 31, 44). In addition, the duration of IP in patients with TLEIP is different from patients with PD, and the duration of IP in patients with TLEIP is shorter, which is consistent with the observations in a previous study (31). We also found that compared with the HC group, the total MOCA score of the TLE without IP and TLEIP groups was lower, which may be because the education years of the TLE without IP and TLEIP groups were significantly lower than the HCs.

Degree centrality reflects the role and status of voxels in the brain network and represents the most local and directly quantifiable centrality measure. In this study, we found the LMTG exhibited increased DC, which indicated increased importance of this region in the brain of patients with TLEIP. The LMTG was involved in several functions, including semantic processing, sentence understanding, word generation, action observation, complex sound processing, logical reasoning, and dynamic facial expression recognition (45–52). Generalized social anxiety disorder (GSAD) is one of the most common anxiety disorders and mainly involves a notable fear and avoidance of most social or performance situations. Yuan et al. found that the DC value of the LMTG in patients with GSAD before group cognitive behavior therapy (GCBT) is increased than the DC value of the LMTG in patients with GSAD after GCBT. This may suggest the role of LMTG in the disease with fear comorbidity (53). Zhao and colleagues found that fearful faces evoked greater activity in the LMTG (54). Moreover, by using functional MRI, Takano et al. (55) investigated common and distinct neural responses to experiences of positive- and threat-awe, elicited by watching awe-inspiring videos, and found that both awe experiences deactivated the LMTG in contrast to the control conditions (positive-awe vs. amusement; threat-awe vs. fear), which meant the fear experience activated the LMTG. Geng et al. (56) found that high trait anxious individuals showed significantly increased activation in the middle temporal gyrus (MTG) during anticipation of an uncertain threat compared to the certain condition. Additionally, a recent meta-analytic work (57) found that the LMTG was activated when fear stimulation was given to adults with childhood trauma. Thus, we speculate that the increased DC in the LMTG may indicate increased FC with the fear circuit, and may explain the panic attack of some patients with TLEIP when stimulated by the external environment, such as harsh sounds and scary pictures.

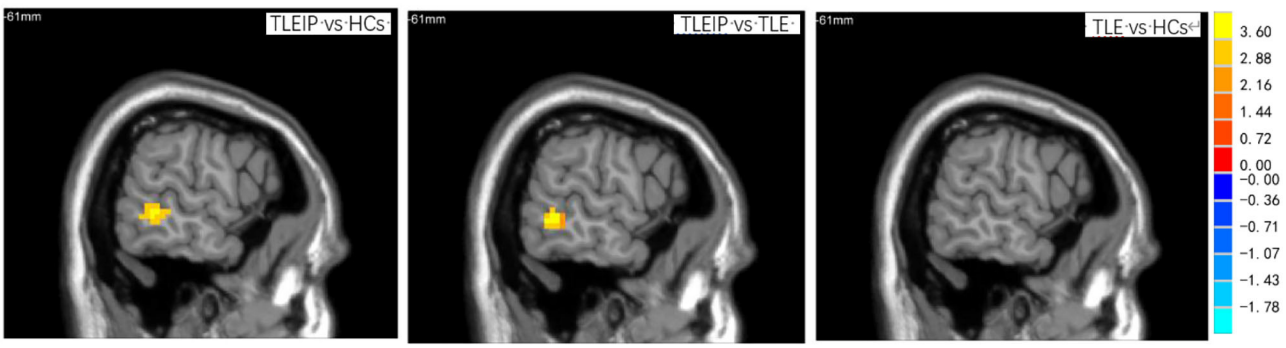

FIGURE 2 | The DC differences among TLEIP, TLE without IP, and HCs. Compared to the HCs and TLE without IP groups, the DC value of the TLEIP group in the left middle temporal gyrus (LMTG) was significantly increased (GRF correction, two-tailed, voxel level $P < 0.001$, cluster level $P < 0.05$).

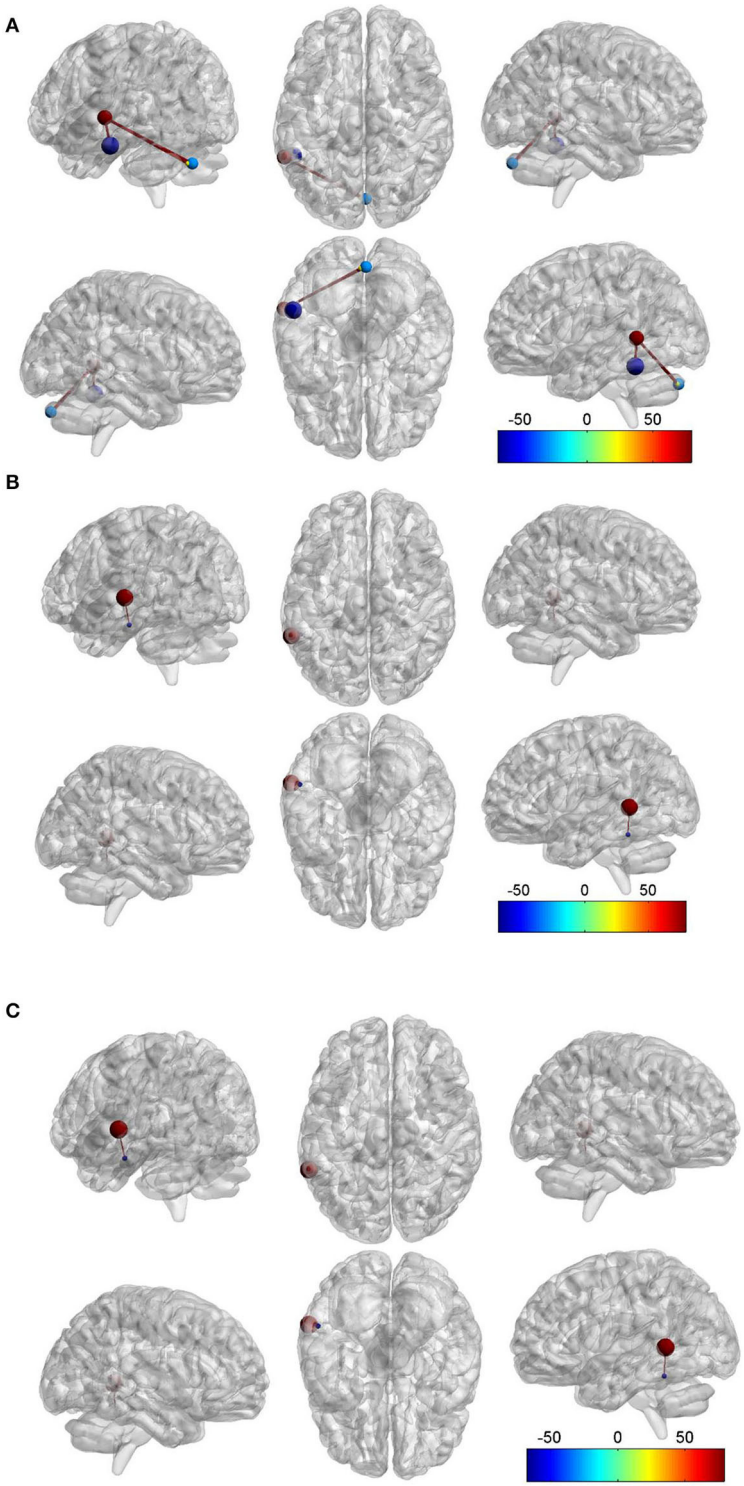

FIGURE 3 | Red ball. the left middle temporal gyrus (LMTG). Purple blue ball, the left inferior temporal gyrus (LITG). Light blue ball, the right cerebellum. Yellow ball, the left cerebellum. Red bar, functional connectivity (FC). **(A)** Compared to the HC group, we found that there was FC between the LMTG and LITG in the TLEIP group, we also found that there were FCs between the LMTG and cerebellum (both left and right) in the TLEIP group. **(B)** Compared to the TLE without IP group, we found that there was FC between the LMTG and LITG in the TLEIP group. **(C)** Compared to the HC group, we found that there was FC between the LMTG and LITG in the TLE without IP group but the area of the LITG in the TLEIP vs. HC group was larger than those in the TLE group vs. HC group. In addition, the difference in the magnitude of FC between the TLEIP vs. HC group was greater than the difference between the TLE without IP vs. HC group. (GRF correction, two-tailed, voxel level $P < 0.001$, cluster level $P < 0.05$).

Harnett et al. (58) used a temporal Pavlovian conditioning procedure to investigate brain activity that mediates the formation of temporal associations. During fixed interval trials, greater conditioned fMRI signal responses were observed within the dorsolateral prefrontal cortex, inferior parietal lobule, inferior and middle temporal cortex, hippocampus, and amygdala. They thought these brain regions constitute a neural circuit that encodes the temporal information necessary for Pavlovian fear conditioning. The result is consistent with the enhanced connection between MTG and ITG found in our study. Eser et al. (59) studied the functional correlates of cholecystokinin tetrapeptide (CCK-4)-induced experimental panic in healthy volunteers by means of fMRI and ROI analysis of the amygdala. They found CCK-4-induced experimental panic was accompanied by a robust activation (random-effects analysis, $P < 0.00001$, uncorrected for multiple testing) in the LMTG and cerebellum. In contrast, random-effects group analysis for placebo and anticipatory anxiety (AA) using the same level of significance generated no significant results. In this study, we found that the FC between the LMTG and the cerebellum was strengthened in patients with TLEIP, which also verified this result. Although no local brain and FC abnormalities were found in the amygdala, hippocampus, parahippocampal gyrus, and thalamus, we speculate that the mechanism of TLEIP may not be completely the same as the mechanism of PD. This may mainly be due to the transient and recoverable incomplete activation of the fear circuits caused by the epileptiform discharge of the local epileptogenic focus in the temporal lobe (60–62), and it may be related to some non-classical fear circuit brain regions, such as the increased connection between the LMTG and the fear circuit.

This study has some limitations that need to be recognized:

a. due to the requirements of clinical ethics, all patients had been treated with anti-epilepsy drugs (AEDs)
b. it was difficult to collect patients with TLEIP, a large number of samples were not included in this study
c. lack of horizontal comparison with patients with PD
d. participants are patients with right-onset TLE, more patients with left-onset TLE need to be collected to have a further study.

In the future, we will collect more patients with left-onset TLE and patients with PD for study to further explore the mechanism of fear in the functional brain network.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the First Affiliated Hospital's Medical Research Ethics Committee of Guangxi Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

WC is responsible for experimental design. JZ is responsible for providing overall ideas. ZL is responsible for instrument operation. XP is responsible for data analysis. JL and LN is responsible for data collection. All authors contributed to the article and approved the submitted version.

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