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Major depressive episode, cognition, and epilepsy

Glória Maria Almeida Souza Tedrus [a], Lineu Corrêa Fonseca [a,*], Marina Nobrega Augusto [b], Fernanda Savoia Trindade [c]

[a] School of Medicine, Pontifícia Universidade Católica de Campinas (PUC-Campinas), Brazil
[b] FAPIC/Reitoria (PUC-Campinas), Pontifícia Universidade Católica de Campinas (PUC-Campinas), Brazil
[c] PIBIC/CNPq (PUC-Campinas), Pontifícia Universidade Católica de Campinas (PUC-Campinas), Brazil

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ABSTRACT

Purpose: In patients with epilepsy (PWE), relationships between depression, epilepsy characteristics, and cognitive aspects are complex. This study aimed to assess the occurrence of possible major depressive episode in PWE and to verify whether it is associated with the clinical aspects of the disease and cognition.
Methods: Two hundred consecutive PWE with a mean age and standard deviation of 47.6 (±15.1) years were included in the study. We determined whether their Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) scores were associated with their clinical, cognitive, and QOLIE-31 aspects using a significance level of 5% ($p < 0.05$).
Results: Twenty-six patients (13%) had an NDDI-E score >15, suggestive of major depressive episode. Logistic regression showed that NDDI-E >15 was associated with seizure frequency ($p = 0.022$) and worse performance in the category fluency test ($p = 0.003$). An NDDI-E >15 was also correlated with lower quality of life ($p < 0.001$).
Conclusion: The present findings suggest that possible major depressive episode is associated not only with epilepsy characteristics but also with cognitive aspects, such as category fluency, and quality of life.

1. Introduction

Mood disorders are the most common psychiatric comorbidities found in patients with epilepsy (PWE) [1], yet they are still underdiagnosed and undertreated [2,3]. The diagnostic difficulty is justified by the clinical heterogeneity of the symptoms, which frequently do not meet the international classification criteria provided by ICD-10 and DSM-IV [4,5].

Depression has a strong negative impact on the quality of life (QoL) of PWE [6,7].

Studies of associations between depression and clinical aspects of epilepsy have contradictory or inconclusive results. The pathophysiological mechanism between depression and epilepsy results from a complex interaction between neurobiological and psychosocial factors [8,9]. Relationships between depression and various clinical aspects of epilepsy, such as the chronic nature of the disease, its severity, the refractoriness of epileptic seizures (ESs), or temporal lobe involvement, have been reported [8]. Other studies have suggested that depression is more strongly associated with the difficulty of coping with the unpredictable nature of ES, social restrictions, low self-esteem, and stigma [10,11].

Cognitive impairment is a frequent clinical aspect of PWE and has most frequently been related to the underlying disease, recurrence of ES, or psychosocial aspects [12,13]. The relationship between depression and cognitive disturbance in PWE has not been well studied, and some of its aspects have not been well clarified [14]. Better knowledge of this relationship may help to improve diagnostic and intervention strategies in PWE.

The objective of this study was to assess the occurrence of depression (or depressive symptoms) in PWE using the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [15], recommended by the ILAE for the management of depressive disorders in PWE, and to investigate its relationship with sociodemographic, clinical, and cognitive aspects.

2. Methods

2.1. Patients

The study included 200 consecutive PWE (52.5% females) with a mean age of 47.6 (±15.1) years and a mean formal education level of 5.7 (±3.8) years. They were recruited at the clinical neurology outpatient clinic of the Hospital and Maternity Hospital Celso Pierro (PUC-Campinas), Campinas, Brazil. Epilepsy diagnosis was based on the International Classification of Epilepsies and Epileptic Syndromes (ILAE) criteria [16].

Age, gender, education level, age at onset, type and frequency of ES, duration of epilepsy, number of antiepileptic drugs (AEDs) currently

* Corresponding author.
E-mail address: lineu.fonseca@uol.com.br (L.C. Fonseca).

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being taken, and epileptic syndrome were noted. Patients with symptomatic focal epilepsies included a subgroup of surgery-naïve patients with temporal lobe epilepsy with hippocampal sclerosis (TLE-HS), characterized by their clinical aspects, namely the presence of hippocampal atrophy, and loss of digitations of the hippocampal head and definition of internal structure in magnetic resonance imaging. Epilepsy was considered to be under control in individuals who did not have ESs in the last twelve months.

The exclusion criteria, which had already been used in the validation of the NDDI-E Portuguese–Brazilian version [17], were the presence of neurological or severe psychiatric comorbidity (e.g., dementia, delirium, severe psychosis) that could, based on the researcher's judgment, compromise instrument understanding and replies.

The patients were invited to participate in the study, and after receiving a detailed description of the study, they signed an informed consent form. The Human Research Ethics Committee of PUC-Campinas approved the study.

2.2. Procedures

The following procedures were performed:

- digital electroencephalogram (EEG) to assess the location and the side of the epileptiform activity (EA);
- investigation of psychiatric comorbidity according to the DSM-IV and ICD-10 criteria by a psychiatrist in open interviews. The patients were classified into two groups: with and without psychiatric comorbidity. Current major depression was also investigated;
- Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [15]: this questionnaire rates six items using a 4-point scale from "never" to "always or often". The NDDI-E accurately assesses the patient's affective experience for fast screening and has been validated in Brazil in 2011 [17]. Major depression was suspected when NDDI-E score >15, as proposed by the original study and by the Brazilian-validated version;
- Mini Mental State Examination (MMSE) [18]: this questionnaire performs a cognitive screening by assessing temporal and spatial orientation, registration and recall of three words, attention and calculation, language, and visual construction [19]. Its maximum score is 30 points;
- brief cognitive battery (BCB) [20]: this instrument requires the identification and naming of simple drawings of 10 common objects, followed by the incidental memory of these objects. Subsequently, the drawings are presented on two more occasions, followed each time by the recall of the objects, to obtain the scores of immediate memory and the number of learned or encoded items, called the learning scores. This is followed by an interference phase comprising a category fluency test (animals in 1 min) and the clock-drawing test. After this interference, (free) delayed recall and recognition of the 10 objects among 20 drawings (with 10 distracters) are evaluated. The brief cognitive battery is appropriate for populations with a high number of illiterate and low educated individuals and had been validated in Brazil. It was also used on different groups of neurological patients [21]; and
- Quality of Life in Epilepsy Inventory (QOLIE-31) [22]: this is an epilepsy-specific QoL inventory, which has been validated in Brazil [23]. This inventory has seven domains: seizure worry, overall quality of life, emotional wellbeing, energy-fatigue, cognitive functioning, medication effects, and social functioning. The overall score ranges from 1 to 100. Higher scores indicate higher QoL.

2.3. Data analysis

The NDDI-E screened for the presence of major depressive episode. Associations of NDDI-E scores with psychiatric diagnosis of current major depression, cognitive aspects (MMSE and BCB), clinical aspects of epilepsy, and QOLIE-31 scores were then investigated.

The continuous variables were expressed as mean and standard deviation (SD) and the categorical variables, as frequencies (%). The continuous variables of the two groups were compared by nonparametric or parametric tests, depending on data distribution.

The Pearson's chi-square test compared the categorical variables.

The NDDI-E was calculated as a binary variable, score > 15 and score ≤ 15. Logistic regression measured the relationship between predictor variables and binary or continuous outcome variables (dependent variables), using variables with $p < 0.10$ in the respective prior correlation analyses (independent variables).

The analyses were performed by the software IBM SPSS 22.0, using a significance level of 5% ($p < 0.05$).

3. Results

Generalized idiopathic epilepsy was found in 15 (7.5%) cases and symptomatic focal epilepsy and probably symptomatic focal epilepsy, in 116 (58%) and 69 (34.5%) cases, respectively. In 59 (29.5%) cases, TLE-HS was found. The mean age at ES onset was 24.1 (±18.1) years and the mean duration of epilepsy, 23.3 (±14.9) years.

The mean overall QOLIE-31 score was 65.9 (16.3).

Table 1 shows the NDDI-E (≤15 and >15) scores according to clinical and sociodemographic aspects, and Table 2 shows those scores according to cognitive aspects.

In the psychiatric assessment, 78 patients had lifetime-to-date psychiatric comorbidity, of which 52 had major depression, 27 had anxiety disorders, 6 had psychotic disorders, 6 had substance abuse disorders, and two had dissociative disorders. Some patients had more than one psychiatric diagnosis. Twenty-nine (14.5%) PWE had current major depression.

Seventy-three patients were taking two or more antiepileptic drugs. Thirty-three patients were taking antidepressants (sertraline — 15; fluoxetine — 15; venlafaxine — 3; and haloperidol — 3). Fifteen (51.7%) PWE with current major depression and 8 (30.8%) with NDDI-E >15 were taking antidepressants.

An NDDI-E score >15, suggestive of possible major depressive episode, was found in 26 (13%) cases and associated with the presence of psychiatric comorbidity and current major depression (Table 1). The NDDI-E had a sensitivity of 69.0%, specificity of 94.8%, negative predictive value of 94.8%, and positive predictive value of 76.9% for current major depression.

An NDDI-E score >15 was also associated with higher ES frequency (chi-square; $p < 0.05$ — Table 1), worse performance in the category fluency test, and worse overall QOLIE-31 score (Mann–Whitney test, $p < 0.05$ — Table 2).

The logistic regression model for determining the factors that potentially affected NDDI-E >15 included the variables age at first ES, ES frequency, epileptic syndrome, and category fluency test score (Table 3). Higher ES frequency and worse performance in the category fluency test were significantly associated with NDDI-E >15 (Homer and Leshow test = 0.553). Effect size can be considered small for this model (Nagelkerke $R^2 = 0.161$).

4. Discussion

The present study assessed the occurrence of possible major depressive episode using the Brazilian version of the NDDI-E and its possible associations with the clinical aspects of epilepsy and PWE cognition.

According to the psychiatric assessment, 52 (26%) study patients had lifetime-to-date major depression, and 29 (14.5%) had current major depression which agrees with literature reports of major depression rates of 20% to 50% in patients with refractory epilepsy and of 3% to 9% in patients with well-controlled epilepsy [2,24]. Cultural differences in the expression of depression symptoms, use of different diagnostic instruments, and sample size and characteristics are other aspects mentioned in the literature that explain data discrepancy [25].