Prevalence and factors associated with depression in women living with epilepsy

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ABSTRACT

Background: Female gender has been described as a major risk factor for depression, thus, a double problem for women with epilepsy (WWE) because the higher likelihood of developing depression.

Objective: The purpose of this study was to determine the prevalence of depression and the factors that contribute to it, as well as to compare clinical characteristics between depressed and non-depressed WWE.

Methods: This study was designed as a case control study involving one hundred (100) WWE and fifty (50) healthy controls aged 16 years and above. Zung Self-Reported Depressive Scale (ZSRDS) was used to assess the mood, while cognitive status was assessed using the Cognitive Screening Instrument for Dementia (CSID).

Results: The mean age of patients and mean age of onset of depression were 29.07±7.55 and 20.01±11.57 respectively. There was a significant difference between the Carbamazepine (CAR) and Levetiracetam (LVC) groups with regards to the mean score of total CSID score (p0.000) and its sub domains which are Language (p0.012), Memory (p0.000), Orientation (p0.035), and Attention and Calculation (p0.000). There was a statistical significant difference between depressed and not depressed groups with regards to memory (p0.000), orientation (p0.003), attention and calculation (p0.000) and total CSID (p0.000). There was a statistically significant difference between mean ZSRDS of participant with focal, generalized and no epileptiform pattern (p0.003). However, only attention and calculation predict depression (p0.010)

Conclusion: The mean ZSDRDS score was higher among those women with epilepsy compared to controls. Furthermore, the mean ZDRDS score was higher in carbamazepine compared to levetiracetam group.

Keywords: Anti-epileptic drugs, Women with epilepsy, Depression, Cognition

Prévalence et facteurs associés à la dépression chez les femmes épileptiques.

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RÉSUMÉ

Contexte: Le sexe féminin a été décrit comme un facteur de risque majeur de dépression, ce qui constitue un double problème pour les femmes épileptiques (FE) en raison de leur probabilité plus grande de développer une dépression.

Objectif: Le but de cette étude était de déterminer la prévalence de la dépression et les facteurs qui y contribuent, ainsi que de comparer les caractéristiques cliniques entre les FE déprimées et non déprimées.

Méthodes: Cette étude a été conçue comme une étude cas-témoins impliquant cent (100) FE et cinquante (50) témoins sains âgés de 16 ans et plus. L'échelle d'auto-évaluation de la dépression de Zung a été utilisée pour évaluer l'état d'esprit, tandis que l'état cognitif a été évalué à l'aide du l'instrument de dépistage cognitif de la démence (CSID).

Résultats: L'âge moyen des patients et l'âge moyen d'apparition de la dépression étaient respectivement de 29,07±7,55 et 20,01±11,57. Il y avait une différence significative entre les groupes Carbamazépine (CAR) et Lévétiracétam (LVC) en ce qui concerne le score moyen du score CSID total (p0,000) et ses sous-domaines qui sont le langage (p0,012), la mémoire (p0,000), l'orientation (p0,035) et l'attention et le calcul (p0,000). Il existe une différence statistiquement significative entre les groupes déprimés et non déprimés en ce qui concerne la mémoire (p0,000), l'orientation (p0,003), l'attention et le calcul (p0,000) et le CSID total (p0,000). Il y avait une différence statistiquement significative entre le ZSRDS moyen des participants présentant un profil épileptiforme focal, généralisé et sans profil épileptiforme (p0,003). Cependant, seuls l'attention et le calcul permettent de prédire la dépression (p0,010)

Conclusion: Le score ZSDRDS moyen était plus élevé chez les femmes épileptiques que chez les témoins. De plus, le score ZDRDS moyen était plus élevé dans le groupe Carbamazépine que dans le groupe Lévétiracétam.

Mots-clés: Médicaments antiépileptiques, Femmes épileptiques, Dépression, Cognition

INTRODUCTION

Depression is highly prevalent in Patients With Epilepsy (PWE) and is the most frequent comorbid psychiatric problem among PWE.[1] Depression is both underrecognized and underrated in PWE. More recently, using the Zung Self-Reported Depressive Scale (ZSRDS), depression was found in 26.9% of epileptic patients compared with 9.7% of controls.[1] Depression is about 2-3 times more common in PWE.[2] The high magnitude of depression among PWE negatively influences their Quality of Life (QOL) and increases suicidal tendency.[3-6] The rate of suicide in PWE is approximately 25 times greater than that in the general population.[1,7] The relationship between depression and epilepsy include neurotransmitter disturbances, endocrine issues like hyperactive hypothalamic pituitary-adrenal axis, genetic, pathophysiological, environmental, and neuroinflammatory mechanisms.[5,7] Peri-ictal expression of depression or sometime atypical expression of depression is seen in epileptic patients.[1,7] Previous studies have shown that epileptiform pattern, absence of alpha or presence of theta and delta- which are the slow waves- are identified biomarkers of depression.[8,9] Treatment of depression with agents like Selective Serotonin Reuptake Inhibitors (SSRI) and Tricyclic Antidepressants in PWE is highly recommended and shown to improve QOL. Before initiating treatment for depression, several factors should be considered, such as recent discontinuation of an Anti-epileptic drugs (AED) with mood-stabilizing properties, such as Carbamazepine (CAR), Lamotrigine or Valproate, or vague nerve stimulation. Most of the recently approved anticonvulsants have positive effects on mood.[1,5,7] Female gender has been identified as a major risk factor for depression, creating a double problem for Women With epilepsy (WWE) who are more likely to develop depression. The purpose of this study was to determine the prevalence of depression and the factors that contribute to it, as well as to compare clinical characteristics between depressed and non-depressed WWE.

METHODS

Antiepileptic drugs

The choice of CAR was driven by the fact that it is the most prescribed of the first-generation AEDs but limited by significant drug interaction and induction of hepatic microsomal enzyme.[10,11] while LVC is a newer generation drug with increasing usage, lesser drug interaction and effect on hepatic microsomal enzyme.[10] The participants on CAR were on 200 mg twice daily, while those on LVC were on 250 mg twice daily. Data collection commenced after informed consents were obtained from the patients or consent from the relations of the patients.

Consent and ethical approval

This study was designed as a case-control study, carried out after due ethical clearance was obtained from the joint Institution Review Committee (IRC) of the University College Hospital (UCH) and the College of Medicine, University of Ibadan. The estimation of sample size for the groups was done using Pocock's formula to calculate the minimum sample size with mean ZUNG score in epilepsy obtained from a previous local study and the expected differences in ZUNG score of 3.0 was postulated. The study population comprised of one hundred (100) WWE and fifty (50) healthy control. Patients with no prior history of seizure was taken as control. The 2017 International League Against Epilepsy (ILAE) was used to diagnose and classify seizures. Definition of epileptiform activity and other waveforms on Electroencephalography (EEG) were in accordance with ILAE and Clinical Neurophysiology Society's Standardized Critical Care.[12-16] Information on demographics and medical history related to epilepsy was obtained from the study participants.

Assessment of depression

The Zung Self-Rating Depression Scale (ZSRDS) a previously validated 20 item with Likert type scale was used to screen for depression.[17,18] It has scores ranging from 1 to 4 with minimum possible score of 20 and score of 80 as the maximum possible score respectively. A score >50 is considered as depression among participants while <50 is non-depressed.[18,19]

Statistical Evaluation

Data obtained were entered into Microsoft Excel for cleaning and subsequent transfer to IBM Statistical Package for Social Science (SPSS) version 23. Socio-demographic and clinical characteristics of study participants were presented in tables using descriptive statistics of proportions for categorical variables. The Pearson Chi-square or Fisher's exact was used to compare categorical variable between CAR, LVC and controls while Analysis of Variance test was used to compare with age, and sub-domain of cognition. The Pearson Chi-square was also used to compare categorical variables between WWE with depression and non-depressed while independent student t-test or Wilcoxon rank-sum was used to determine difference in continuous variables. ANOVA was used to compare total ZUNG score with socio-demographic, seizure and epileptiform characteristics. Multiple logistics regression test was

used to predict depression. Statistical value was set at $p<0.05$.

RESULTS

Clinical and sociodemographic characteristic of women with epilepsy.

Table 1 shows the socio-demographics characteristics of 100 WWE of whom 50 were on CAR and 50 were on LVC. The mean age of patients and mean age of onset were 29.07±7.55 and 20.01±11.57 respectively. As regards the level of education, 31(31%), 35(35%), 29(29%) and 5(5%) were able to obtain a primary, secondary, tertiary and postgraduate education respectively. The mean±SD Body Mass Index (BMI) among WWE was (24.05 ± 4.18). Furthermore, 67(67%), 23(23%), and 10(10%) of the patients were having a BMI <25, 25-29.9 and ≥30 respectively.

Table 1: Clinical and socio demographic characteristics of women with epilepsy (WWE).

Variable	Categorical	n(%)
Age (yrs.)	Mean±SD	(29.07±7.55)
	15-25	44(44.0)
	26-35	30(30.0)
	36-45	26(26.0)
Highest Level of Education	Primary	31(31.0)
	Secondary	35(35.0)
	Tertiary	29(29.0)
	Post -graduate	5(5.0)
Age of Onset (yrs.)	Mean±SD	(20.01±11.57)
	1-15	34(34.0)
	16-30	42(42.0)
	31-45	24(24.0)
BMI(KG/m^2)	Mean±SD	(24.05±4.18)
	<25	67(67.0)
	25-29.9	23(23.0)
	>30	10(10.0)
Type of seizures	Focal	16(16)
	Generalized	32(32)
	FTBC	40(40)
	Unclassified	12(12)
Epileptiform pattern	No	14(14)
	Focal	42(42)
	Generalized	44(44)

* Statistically significance; BMI: Body Mass Index: n: number

Socio-demographic characteristics, cognitive performance and depression in women with epilepsy and control

Table 2 shows that socio-demographic characteristics were comparable in CAR, LVC and control group except for level of education (p0.000). However, there was a significant difference between the three groups with regards to the mean score of total CSID score (p0.000) and its sub domains: Language (p0.012), Memory (p0.000), Orientation (p0.035), and Attention&Calculation (p0.000). The mean depression score was higher in WWE compared to control with (p0.000).

Table 2: Socio-demographic characteristics, cognitive performance and depression of women with epilepsy and control.

Variables	Categories	CAR N=50	LVC N=50	Controls N=50	Statistics	p-value
Age (mean±SD)		(30.04±7.99)	(28.10±7.02)	(29.50±1.74)	F=19.238	0.158
Ethnicity N (%)	Hausa	2(4.0)	3(6.0)	0(0.0)	x^2=5.191	0.268
	Igbo	2(4.0)	4(8.0)	1(2.0)		
	Yoruba	46(92.0)	43(86.0)	49(98.0)		
Handedness N(%)	Right	45(90.0)	41(82.0)	47(94.0)	x^2=3.715	0.156
	Left	5(10.0)	9(18.0)	3(6.0)		
Level of Education N(%)	Primary	18(36.0)	13(26.0)	0(0.0)	x^2=71.377	0.000*
	Secondary	17(34.0)	18(36.0)	0(0.0)		
	Tertiary	14(28.0)	15(30.0)	50(100)		
	Postgraduate	1(2.0)	4(8.0)	0(0.0)		
Language (mean±SD)		(21.62±2.55)	(22.46±1.97)	(22.70±0.46)	F=4.540	0.012*
Memory (mean±SD)		(18.04±2.89)	(19.48±2.52)	(20.82±0.39)	F=19.575	0.000*
Attention&Calculation (mean±SD)		(7.08±1.10)	(7.54±0.99)	(8.00±0.00)	F=14.387	0.000*
Orientation (mean±SD)		(9.86±0.76)	(9.96±0.28)	10.00±0.00)	F=1.197	0.035*
Total CSID (mean±SD)		(68.50±6.26)	(71.38±4.45)	(73.64±0.72)	F=16.719	0.000*
Zung Depression score (mean±SD)		(32.68±6.01)	(30.78±8.28)	(25.38±5.33)	F=16.161	0.000*

*Statistically significant CSID: Congenital screening interview for depression SD: Standard Deviation
x^2: chi square value F:Analysis of variance value

Comparison of socio-demographic and clinical characteristics of Women With Epilepsy (WWE) with depression and without depression.

There was no statistically significant difference in the clinical and socio-demographic of WWE with depression and without depression.

Table 3: Comparison of socio demographic and clinical characteristics of women with epilepsy (WWE) with depression and without depression n=100

Variables	Categories	Depressed patient	Non-depressed patient	x^2	p-values
Age (yrs)	15-25 26-35 36-45	9(20.5%) 3(10.0%) 2(7.7%)	35(79.5%)	2.780	0.249
Highest Level of Education	Primary Secondary Tertiary Postgraduate	5(16.1%) 6(17.1%) 3(10.3%) -	26(83.9%) 29(82.9%) 26(89.7%) 5(100.0%)	1.540	0.673
Ethnicity	Yoruba Hausa Igbo	14(15.7%) - -	75(84.3%) 5(100.0%) 6(100.0%)	2.012	0.366
Duration of Epilepsy	<2yrs >2yrs	3(13.0%) 11(14.3%)	20(87.0%) 66(85.7%)	0.023	0.880
Age of onset (yrs.)	1-15 16-30 31-45 46 and above	7(19.4%) 4(9.5%) 3(14.3%) -	29(80.6%) 38(90.5%) 18(85.7%) 1(100.0%)	1.749	0.626
Handedness	Right Left	14(16.3%) -	72(83.7%) 14(100.0%)	2.650	0.104
Family History of Epilepsy	Yes No	1(7.1%) 13(15.1%)	13(92.9%) 73(84.9%)	0.636	0.425
Last episode of seizure	Nil <6months >6Months	- 9(15.0%) 5(13.5%)	3(100.0%) 51(85.0%) 32(86.5%)	1.855	0.603
Aetiology	Structural Metabolic Immune Unknown	7(12.7%) - - 7(17.1%)	48(87.3%) 3(100.0%) 1(100.0%) 34(82.9%)	1.047	0.709
Types of AED	Carbamazepine Levetiracetam	7(14.0%) 7(14.0%)	43(86.0%) 43(86.0%)	0.000	1.000
Seizure Type	Focal Generalized FBTC Unknown/unclassified	2(12.5%) 6(18.8%) 6((15.0%) -	14(87.5%) 26(81.3%) 34(85.0%) 12(100.0%)	2.616	0.455
Seizure Frequency	Fast Slow	5(11.9%) 9(15.5%)	37(88.1%) 49(84.5%)	0.264	0.607
Epileptiform Pattern	Nil Focal Generalized	3(21.4%) 3(7.1%) 8(18.2%)	11(78.6%) 39(92.9%) 36(81.8%)	2.921	0.232

Depressed: ZUNG score > 50 non-depressed: ZUNG score<50 **x^2:** chi square value

Comparison of socio-demographics, epileptiform and seizure characteristics with ZUNG score in women with epilepsy.

With regards to background EEG the mean±SD depression score for those with delta (32.58±8.17), theta (29.20±4.26), alpha (28.44±6.53), intermixed slow (33.93±6.30) with statistical value of 0.013 which was statistically significant.

The mean±SD depression score among those without epileptiform (33.64±7.56) generalized epileptiform (33.82±8.00) compared to focal epileptiform (28.90±5.30) was statistically significant (p0.003).

The remaining clinical parameters which include age range, age of onset, duration of epilepsy, medication, type of seizure in comparison to the mean depression score was not statistically significant.

Table 4: Showing comparison of socio-demographics, epileptiform and seizure characteristics with ZUNG score in women with epilepsy n=100.

Variables	Categories	N (100)	TOTAL ZUNG SCORE	F	P
Age range	15-25	44	32.25±8.51	0.426	0.655
	26-35	30	31.93±6.59		
	36 45	26	30.62±5.67		
Age of onset	1-15	34	32.59±7.27	0.252	0.860
	16 30	42	31.21±8.10		
	31-45	24	31.43±5.80		
	=46	0	30.00±0.00		
Duration of Epilepsy	<1 month	6	32.67±2.73	0.387	0.817
	1-6 months	5	32.00±5.83		
	6months - 1yr	12	33.83±10.50		
	2-5yrs	31	30.84±6.23		
	>5yrs	46	31.71±7.58		
Medication	Carbamazepine	50	32.68±6.02	1.723	0.192
	Levetiracetam	50	30.78±8.28		
EEG pattern					
Background	Delta	12	32.58±8.17	3.354	0.013*
	Theta	20	29.20±4.26		
	Alpha	18	28.44±6.53		
	Intermixed	20	31.60±9.24		
	Intermixed-slow	30	33.93±6.30		
Epileptiform	Nil	14	33.64±7.56	6.038	0.003*
	Focal	42	28.90±5.30		
	Generalized	44	33.82±8.00		
Periodicity	Absent	71	31.03±7.52	2.316	0.131
	Present	29	33.45±6.40		
Slowing	Absent	46	30.70±7.96	1.740	0.190
	Present	54	32.61±6.57		
Frequency	Fast	42	30.17±8.13	3.437	0.067
	Slow	58	32.86±6.40		
Type of seizures					
Focal	Yes	16	31.50±9.65	0.019	0.891
	No	84	31.77±6.79		
Generalized	Yes	32	32.47±8.14	0.484	0.488
	No	68	31.38±6.85		
Unknown	Yes	13	29.15±4.51	1.896	1.172
	No	87	32.11±7.53		
Focal to bilateral Tonic-clonic	Yes	40	31.68±7.77	0.006	0.938
	No	60	31.80±6.52		
Unclassified	Yes	6	30.67±7.37	0.136	0.714
	No	94	31.80±7.37		

F:Analysis of variance test value *****Statistically significant

Association between cognition and depression.

There was consistent statistical difference among various sub-domain of cognition and total CSID when compared with depressed and non-depressed except for language [21.29±3.69 vs 22.16±2.00; p0.189].

Table 5: Association between cognition and depression in women with epilepsy

Variable Mean±SD	Depressed N=14	Non depressed N=86	F	p-values
Language	21.29±3.69	22.16±2.00	1.750	0.189
Memory	15.57±3.23	19.28±2.35	26.822	0.000*
Orientation	9.50±1.40	9.98±0.22	9.105	0.003*
Attention and calculation	5.86±1.5 1	7.55±0.76	42.611	0.000*
Total CSID	63.79±8.71	70.94±4.20	24.335	0.000*

*Statistically significant SD: Standard Deviation F: Analysis of variance value

Multiple logistics regression of the determinants of depression

While memory, attention and calculation, orientation, total CSID, background, and epileptiform shows association with depression, however, only attention and calculation predict depression (p0.010).

Table 6: Multiple logistics regression showing the determinants of depression

Variables	B	S.E	p-value	95%CI
Memory	1.454	0.780	0.062	.928 -19.718
Orientation	1.371	1.181	0.246	.389 -39.866
Attention and Calculation	2.805	1.128	0.013*	1.813 -150.658
Total CSID	-0.776	0.474	0.102	.182 -1.166
Background				
Delta	1.202	1.848	0.515	.089 -124.523
Theta	46.773	10157.72	0.996	.000
Alpha	16.428	5552.672	0.998	.000
Intermixed	-0.605	1.493	0.685	.029 -10.182
Intermixed-slow	Reference			
Epileptiform				
Nil	-1.470	1.926	0.445	.005 -10.030
Focal	-0.703	1.580	0.656	.022 -10.946
Generalized	Reference			

*Statistically significant CI-Confidence Interval S.E-Standard Error
CSID-Community Screening Instrument for Dementia B-Beta

DISCUSSION

The prevalence of depression in this population was with equal percentage in both CAR and LVC groups (CAR 7% and LVC 7%). Zung depression score was higher in the epilepsy group compared to control. In our study CAR and LVC was 14% Previous studies put the prevalence at between 23.1% to 48%.[1,5,20] Perhaps this may be due to the narrow scope of our study which involved only WWE. Across all domains of cognition, WWE had worst score compared to control. The socio-demographic characteristics were comparable in both depressed and non depressed patients. We also identified the determinant of depression as presence of epileptiform pattern specifically generalized, absence of alpha and presence of slow waves. Zung depression score correlated significantly with memory, orientation, attention and calculation and total CSID. In line with our study it has shown that depression is common in PWE than control.[1,5,7,20] Again our study was in tandem with previous reports that there is a bi-directional interplay between depression and cognition.[21-23] In previous study, academic failure and attention problem have also been reported in people with epilepsy who are experiencing depression.[3,24] Anoth study reported higher frequency of depression and poorer quality of life among WWE compared to control.[20] The bi-directional relationship between depression and cognition was further confirmed in our study in view of the finding of lower scores in the cognitive domain among depressed patients. Identified mechanism of dysfunction in depressed patient include inhibitory processes and deficits in working memory, ruminating responses to negative mood states and the inability to use positive and rewarding stimuli to regulate negative mood.[22,23] Previous study had identified epileptiform activities and alpha asymmetry, absence of alpha and slowing pattern on EEG as biomarkers of depression and cognitive impairment.[2,9,25] Depression in PWE was correlated with female gender, prior hospitalization for epilepsy, greater seizure frequency, and prolonged duration of epilepsy. Increased seizure frequency, longer seizure length, and prior hospitalization which were independent risk factors for depression[6]. In a Nigeria study among 96 participants aimed at determining the frequency and clinical correlates of depression and suicidal ideation in PWE. It was shown that PWE had a higher prevalence of depression (26.0%) compared to normal controls (9.7%). The only factor that was substantially correlated with depression was the mean duration of epilepsy in years was 12.7±8.8 in depressed PWE vs. 8.3±6.6 in non-depressed PWE (P=0.01).[1] In this study the mean duration in years of depressed PWE and non-depressed PWE were comparable. This may be due to the fact that treatment duration for this cohort was less than 2 years in contrast with other studies of longer duration Also, most patients in this study were on monotherapy (CAR and LVC) while numbers of medications used in other studies were not stated. Furthermore, this study shows a relationship between epileptiform pattern, and presence of slow wave on background EEG which were associated with depression. These findings appear to support the use of EEG as a marker of depression. The limitations of our study include the fact that it is a hospital based study and only female patients were recruited In addition, the effect of other drugs were not assessed as only two AEDs (CAR and LVC) were considered in this study.

CONCLUSION

The prevalence of depression is 14% in WWE with equal percentage in both groups. The mean Zung depression score was higher among those WWE compared to those without epilepsy. And the mean depression score was higher in CAR group than the LEV group. Zung depression score correlated significantly with memory, orientation, attention, and calculation and total CSID. There should be increased awareness about depression in WWE. Thus, evaluation of WWE should include routine screening for depression and cognitive impairment to improve overall quality of life and wellbeing of PWE. The authors declare no conflicts of interest

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