©IDOSR PUBLICATIONS
International Digital Organization for Scientific Research ISSN: 2579-0730
IDOSR JOURNAL OF BIOLOGY, CHEMISTRY AND PHARMACY 6(1)41-60, 2021.

The risk factors for the cognitive dysfunction in adult patients with epilepsy and the relative contributions of these risk factors towards cognitive dysfunction

[1]Nkeiruka Chinedu-Anunaso, [2]A. O. Ogunrin, [2]F. A. Imarhiagbe and [2]F. Odiase

[1]Consultant Physician/Neurologist Internal Medicine Department
Federal Medical Centre Owerri.
[2]Consultant Physician/Neurologist, Department of Internal Medicine, University of Benin Teaching Hospital, Benin City Edo State Nigeria.

ABSTRACT

Epilepsy is a key global public health problem. There is limited evidence regarding the risk factors for cognitive dysfunction among patients with epilepsy in Nigeria.The aim of this research was to assess the burden of cognitive dysfunction and its risk factors in adult patients with epilepsy attending UBTH and FMC Owerri. A hospital-based cross-sectional case-control study of consecutively recruited 100 adult patients with 50 controls from UBTH and 50 patients with 25 controls from FMC Owerri. The patients were clinically diagnosed with epilepsy with or without Electroencephalogram (EEG) and matched for age, sex and level of education (150 cases and 75 controls in total). A pilot study was done to adapt the original Montreal Cognitive Assessment (MOCA) to the local context and a cutoff of 22 was determined. The participants were then assessed using "The Iron Psyche" (FEPSY) and the adapted MOCA tools. Statistical analysis was done using SPSS version 25. Risk factors of cognitive dysfunction were determined using logistic regression analysis. A p-value of <0.05 and 95% confidence interval were set for level of significance. The mean age of the participants was 25 years (±SD 5.2) for cases and 26 years (±SD 6.4) for controls, with male to female ratio of 1.6:1. Among the study participants, 80% of the cases and 74.7% of the controls had secondary level of education. Logistic regression showed that the type of AED [sodium Valporate] (OR-8.920; CI-1.498-53.110; p-value =0.016) and duration of seizures both [≤ 1 year] (OR-3.500; CI-1.210-17.510; p=0.014) and [> 1 year] (OR-7.200; CI-1.420-21.830; p-value =0.026) were predictive of cognitive dysfunction. In The type of AED and duration of seizures were identified as risk factors for cognitive dysfunction among PWE. MoCA promises to be an effective tool for assessing cognitive dysfunction among PWE in our locale, therefore, further studies to strengthen this evidence is needed.
Keywords: Risk factors,cognitive dysfunction, patients and epilepsy

INTRODUCTION

Seizure is a transient occurrence of signs and or symptoms due to abnormal excessive or synchronous neuronal activity of the brain [1]. Seizures are typically paroxysmal and episodic, resulting in a suddenly occurring but transient behavioural, somatosensory, motor or visual symptoms and signs and caused by abnormally excessive cortical neuronal activity [2,3].Seizures may be provoked by certain influences like trauma, brain haemorrhage, metabolic dyscrasias or drug exposure or occur simultaneously without provocation [4,5,6]. Some people with provoked seizures may have recurrent seizures without having epilepsy. Provoked seizures do not recur when provoking factors are removed. A seizure is an event while epilepsy is the disease associated with spontaneously recurring seizures [7]. In reflex epilepsy for example photosensitive epilepsy, eating epilepsy, seizures are provoked but they are considered epilepsy because if the seizure threshold was not attained, these precipitants would typically not cause seizures. Seizures can be caused by head injuries, brain tumors, lead poisoning, mal-development of the brain, genetic and infectious illnesses as well as fevers [8]. A prevalent case of

active epilepsy is defined as a person with epilepsy who has had at least one epileptic seizure in the previous 5 years, regardless of antiepileptic drug (AED) treatment [9]. Epilepsy in remission with treatment is a prevalent case of epilepsy with no seizures for ≥ 5 years and currently receiving AED treatment [10,11,12,13,14]. Resolved epilepsy is when an age dependent syndrome is outgrown or when a person is seizure free for at least 10 years, the last 5 years off anti-seizure medications. Epilepsy is the commonest neurological disorder encountered in neurological practice [15,16,17,18]. It is estimated that it affects 50 million worldwide people, with higher incidence and prevalence figures in developing countries especially sub-Saharan Africa where the exact statistics are not available [19,20]. The prevalence and incidence figures available in the literature from sub-Saharan Africa are 'tips of iceberg [21,22,23,24]. The high treatment gap in sub-Saharan African countries implies that most patients with epilepsy (PWEs) are untreated. This calls for studies to evaluate the effect of epilepsy on the cognitive functioning or performance of affected individuals.

AIM/OBJECTIVE

The aim of this research was to identify the risk factors of cognitive dysfunction in adult patients with epilepsy using FEPSY and MOCA.

RESEARCH QUESTIONS

What are the risk factors for the cognitive dysfunction in adult patients with epilepsy and the relative contributions of these risk factors towards cognitive dysfunction?

HYPOTHESIS

Duration of epilepsy before treatment, frequency of seizures before treatment and type of AEDs contribute significantly to cognitive dysfunction in adult patients with epilepsy.

METHODOLOGY AND DATA ANALYSIS

STUDY SITES

The study was carried out in the consultants' outpatient clinics and medical wards of the department of Internal Medicine, University of Benin Teaching Hospital (UBTH) Benin and Federal Medical Centre (FMC) Owerri. The institutions are tertiary hospitals located in the Southern part of Nigeria. UBTH is a 550 bedded hospital located in Benin, the capital of Edo State with `geographic coordinates (6.3350^{0}N, 5.6037^{0}E). UBTH serves as major referral centre in Edo State with a population of about 3.2 million people mainly of Bini, Esan, Owan, Afemai and Akoko Edo who speak Edo and derivatives of Edo languages. FMC is a 430 bedded hospital located in Owerri, the capital of Imo State with geographic coordinates (5.4891^{0}N, 7.0176^{0}E). FMC serves as a major referral centre in Imo state with a population of 3.9 million mainly Igbos who speak Igbo language. Although there are other peripheral hospitals that manage epilepsy, most patients in these states are usually referred to UBTH and FMC for further care due to the available expertise. So, the neurology units in these centres could be said to serve these states.

SAMPLE SIZE ESTIMATION

The sample size was determined using the formula of Kish.Using Leslie Kish's formula for a single arm cross-sectional study.Where the prevalence of approximately 100/1000[5]

$N = Z^2 . P(1-P) /d^2$. Where P = prevalence Z =1.96, d = 0.05, $N = (1.96)^2$ x 0.10(1 – 0.10) / 0.05^2= 3. 8416 x 0.10 x 0.990/ 0.0025 = 0.3803184/ 0.0025= 152

Since the target population is less than 10,000, the sample size was adjusted for finite population correction using the formula, nf = n/(1 + (n-1/N). Where, nf = the desired sample size for population < 10,000, n = the earlier estimated sample size, N = the population size (1000) nf = 152 / 1 + (152-1/1000), nf = 152/1+(151/1000) = 152/1+0.151

= 152/1.151 = 132

To accommodate those patients who did not have complete data (To allow for attrition factor of 15%),Total sample was adjusted to 132 + 18,(15% of 132 = 18). Therefore, the sample size of 150.

FOR THE CONTROL

It was 2 to 1 matching, that is, for every two PWEs there was one control subject matched for age, sex and level of education. The number of controls was 75.

STUDY POPULATION

The study population consisted of cases which were patients with epilepsy attending clinics in consultants' outpatient department (COPD) and those admitted in the medical wards of the department of Internal Medicine UBTH, Benin and Federal Medical Centre Owerri while the controls consisted of mostly healthy subjects that accompanied relatives to the hospital and some hospital staff.

INCLUSION CRITERIA FOR CASES

1. Adult patients with clinically diagnosed epilepsy with or without EEG.
2. Adult patients with epilepsy who gave written informed consent.
3. Adult patients (18 years and above) with epilepsy resulting from unprovoked seizures.

EXCLUSION CRITERIA FOR CASES

1. Patients with epilepsy less than 18 years resulting from unprovoked seizures.
2. Patients with acute symptomatic seizures or from provoked seizures.
3. Patients with medical co-morbidity that will limit the assessment of cognitive dysfunction, for example, dementia.
4. Non consenting patients

INCLUSION CRITERIA FOR CONTROLS

1. Adults (18 years and above) without epilepsy or seizures who gave written informed consent.

EXCLUSION CRITERIA FOR CONTROLS

1. Adults (18 years and above) with epilepsy.
2. Adults with any form of seizures.
3. Adults with medical co-morbidity that will limit the assessment of cognitive dysfunction, for example, dementia.
4. Non consenting adults.
5. Adults with family history of epilepsy.

SAMPLING

All participants with epilepsy, who gave informed consent, and who met the inclusion with none of the exclusion criteria were enrolled consecutively into the study over a period of twelve (12) months

PILOT STUDY

A pilot study was conducted prior to the main study, to adapt the Montreal Cognitive Assessment (MOCA) tool to the local context and pretest the questionnaire. The pilot study was done to determine cutoffs that will be used for the study participants with regards to the adapted MOCA, in addition to gather feedback which were used to improve the structure and administration of the questionnaire. Thirty (30) participants were assessed using both the original Montreal cognitive assessment (MOCA) and the adapted MOCA tools and cut off score for MOCA obtained. The original MOCA was translated to vernacular (Bini) and back translated to culturally appropriate English. Each of the participants was tested with the original MOCA and then with an adapted MOCA (MoCA[1]) after 3 hours or more. Those with ≤ 12 years of education were added extra one point. The analysis was done by subtracting the 2 x standard deviation from the means (Mean - 2SD) of the original MOCA and that of the adapted version in the 3 batches; the whole group, those with ≥12 years of education and those with ≤12 years of education. The adapted MOCA was then used in the study. Feedback from the pilot study were then used for correction, modification and standardization of the questionnaire.

DATA COLLECTION

150 Patients with Epilepsy (PWE) and 75 controls who met the inclusion criteria were enrolled into the main study. Patients with epilepsy and the controls were coded and their medical case notes were used for further evaluation. Data from each participant was gotten from a standardized proforma, biodata and history of the present illness along with clinical and neurological examination. The diagnosis of Epilepsy was clinical and corroborated with Electroencephalogram (EEG) if available. Seizure frequency is basically classified into three groups namely; those that have more than 1 seizure per month (which depicts that there is more frequent seizures), those that have 1 seizure or less per month (this depicts frequent seizures) and those that have 1-2 seizures per year (this depicts less frequent seizures). Duration of seizures before treatment is divided into two groups namely; those that had seizures for a year or less and those that had seizures for more than one year. Certified and tested cognitive assessment tools; Iron Psychology (FEPSY) for windows version 2.3.3 and adapted MOCA modules were used. The Cognitive assessments were done after the participant had finished filling the questionnaire. The questionnaire for the data collection and adapted MOCA form are as shown in the appendix. Tests done using FEPSY were Auditory and Visual reactions, Binary choice tasks, Recognition simultaneously and Tapping to assess mental speed, psychomotor speed, attention, memory, constructional praxis respectively. Operationally for this study, cognitive dysfunction was defined as an adapted MOCA of ≤22. Data were dichotomized between normal and cognitive dysfunction using the cut-off of ≤22. FEPSY (scores and mean) were also compared between cases and controls.

ETHICAL CONSIDERATIONS

Ethical approval was obtained from the Ethics committee of UBTH Benin and FMC Owerri. The study was done at no cost to the participants. Informed consent was obtained from all participants in the study.

STATISTICAL ANALYSIS

The data obtained were analyzed using SPSS version 25. Results were presented in tables with data first described using frequency tables. Categorical variables between cases and Controls were compared using chi square and Fisher exact test. Continuous data were compared using ANOVA or its non-parametric equivalent where appropriate. Logistic regression was used to determine the risk factors of cognitive dysfunction in study participants. Operationally for this study, cognitive dysfunction was defined as an adapted MOCA of 22 or below. A p-value < 0.05 was considered statistically significant for all tests.

RESULTS

MOCA ADAPATION

Demographic characteristics

A total of 30 normal subjects participated in this pilot study which comprised of 16 (53.3%) males and 14 (46.7%) females. Among the participants 17 (56.7%) had tertiary level of education, secondary 8 (26.7%), primary 4 (13.3%) and none 1 (3.3%). Age range was between 18 and 40 years with a mean age of 27±SD 6.3 years.

Adaptation of MOCA assessment tool

For those with more than 12 years of education, mean values of original MOCA total and translated MOCA total were 26.06 and 27.55 respectively while their corresponding standard deviation values were 3.73 and 3.02. Using the formula (mean - 2SD), giving 18.60 approximately 19 for original MOCA and 21.53 which is approximately 22 for adapted MOCA.

MAIN STUDY

Demographic characteristics

The demographic characteristics of the study participants are shown in Table 1. The ages of the cases and controls were categorised into <25-, 26-34- and 35-44 years. Participants <25years had the highest proportion both in the cases and

the controls [83(55.3%) and 36(48.0%) respectively]. There was no statistically significant difference between the age distribution (p=0.244). The study participants comprised of 82 (54.7%) males and 68 (45.3%) females for the cases and 36 (48.0%) males and 39 (52.0%) females for controls. For the cases and the controls, there was no significant gender difference (p=0.345). The highest level of education of the participants was secondary for both cases and controls, and no significant difference was observed among the categories [120(80.0%) and 56 (74.7%) respectively, p=0.245]. The age distribution of the study participants, gender distribution and the level of education are represented in Figure 1, Figure 2 and Figure 3 below

Table 1: Demographic characteristics of the study participants

Variables	Cases [n(%)]	Controls [n(%)]	p-value
Age distribution <25 years 26-34 years 35-44 years	 83 (55.3) 62 (41.3) 5 (3.3)	 36 (48.0) 33 (44.0) 6 (8.0)	0.244
Gender Male Female	 82 (54.7) 68 (45.3)	 36 (48.0) 39 (52.0)	0.345
Level of Education None Primary Secondary Tertiary	 3 (2.0) 6 (4.0) 120 (80.0) 21 (14.0)	 0 2 (2.7) 56 (74.7) 17 (22.7)	0.245

Figure 1: A bar chart showing the sex distribution of the cases and controls in the study

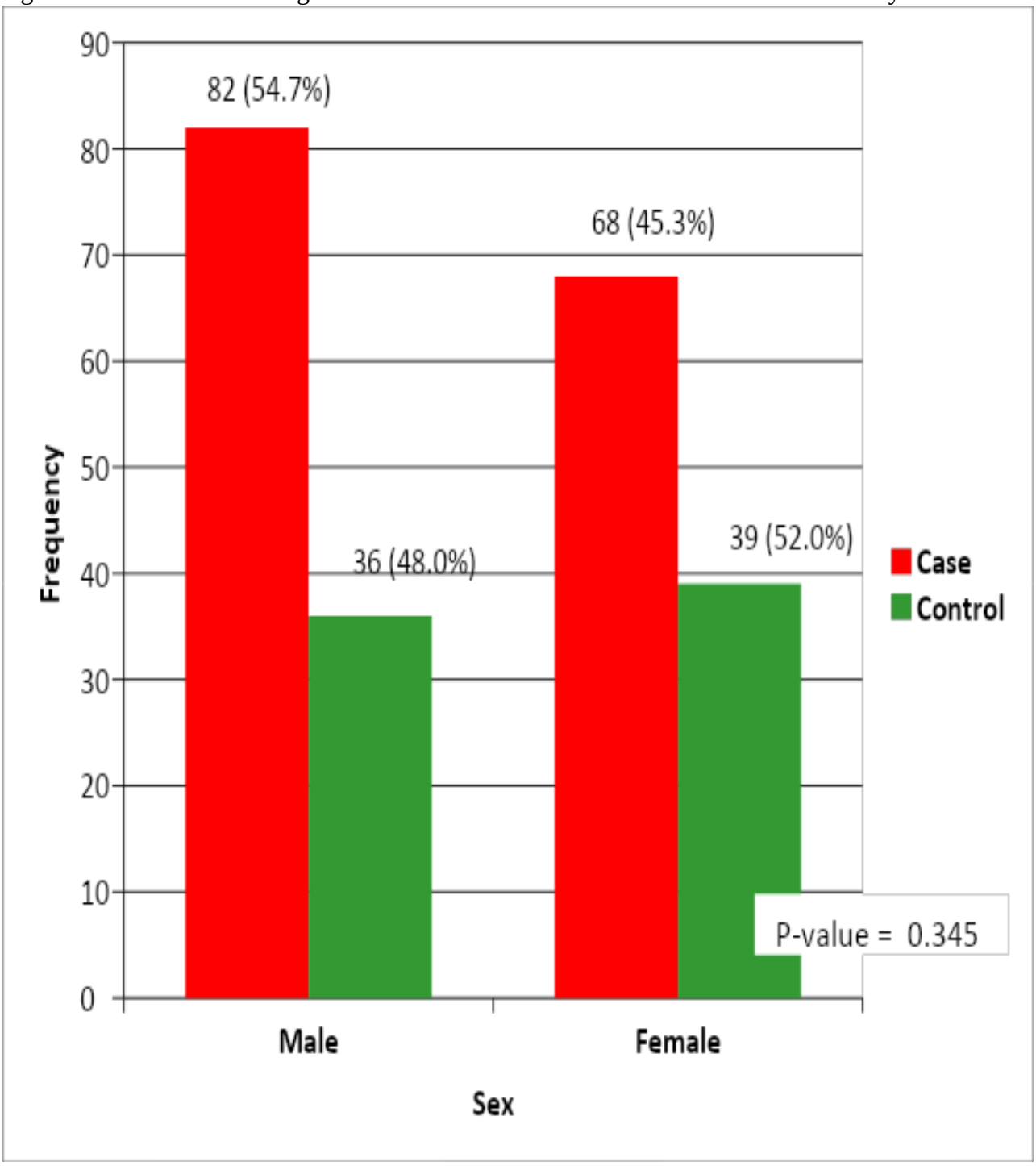


Figure 2: A bar chart showing the age distribution of the cases and controls in the study

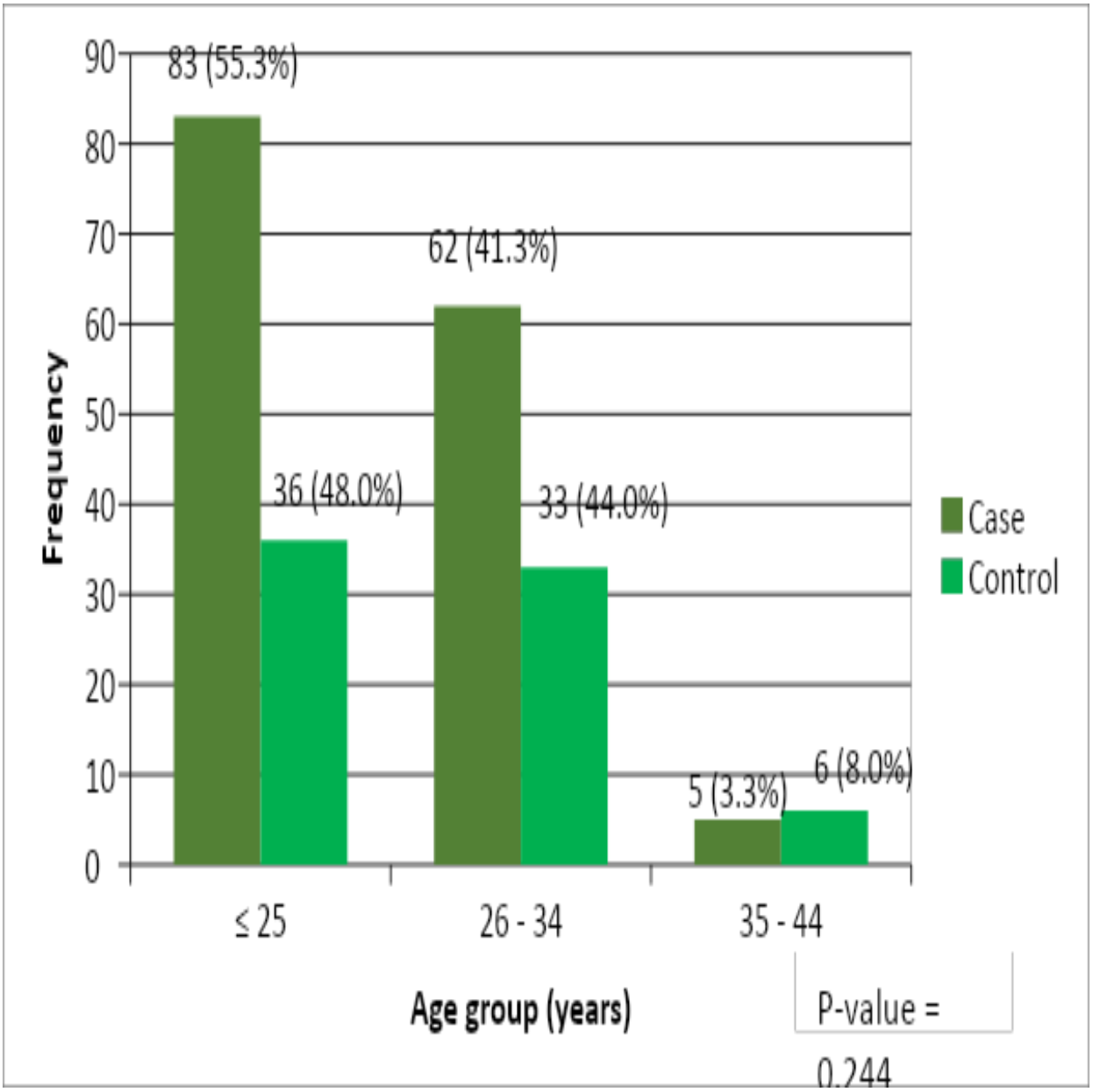
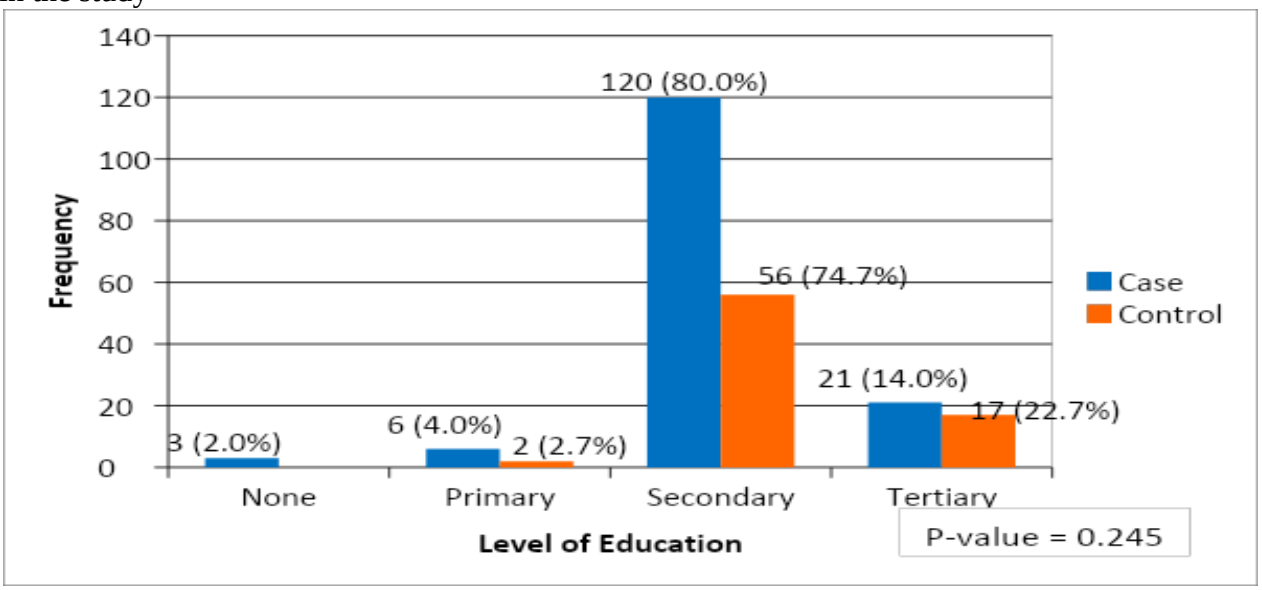


Figure 3: A bar chart showing the distribution of level of education of the cases and controls in the study



ASSOCIATION BETWEEN RISK FACTORS OF COGNITIVE DYSFUNCTION IN PWEs.

Type of AEDs

The relationship between type of AEDs and cognitive dysfunction in the study participants is illustrated in Table 2 below. There was a statistically significant relationship between type of AEDs and cognitive dysfunction (p<0.001). Among the study participants, 102 (68.0%) were on carbamazepine followed by 29 (19.33%) on Sodium Valporate then 15 (10.0%) on Levetiracetam while 2 (1.33%) were on Phenobarbitone and 2 (1.33%) were not on any AED. Cognitive dysfunction was found in 11 (10.8%) participants on Carbamazepine, 15 (51.7%) on Sodium Valporate, 3(20.0%) on Levetiracetam, 2(100%) on Phenobarbitone 2(100%) and 0 (0%) on those not on any AED.

Table 2: Relationship between Type of AEDs and cognitive dysfunction in the study participants

Variables	Cognitive Dysfunction		p-value
	Yes(n=31) [n (%)]	No (n=119) [n (%)]	
Type of AEDs			
Carbamazepine	11 (10.8)	91 (89.2)	<0.001
Sodium Valporate	15(51.7)	14 (48.3)	
Levetiracetam	3 (20.0)	12 (80.8)	
Phenobarbitone	2 (100)	0	
None	0	2 (100)	

Pre-treatment Seizure frequency

The relationship between pre-treatment seizure frequency and cognitive dysfunction in the study participants is illustrated in Table 3 below. The relationship between pre-treatment seizure frequency and cognitive dysfunction was not statistically significant (p<0.245). Majority had ≤1 seizure per month. Among the participants, only 9 (6.0%) had >1 seizure per month while 139 (92.7%) had ≤1 seizure per month and 1 had ≤2 seizure per year. Also among those that had >1 seizure per month, 3 (33.3%) had cognitive dysfunction while those that had ≤1 seizure per month 28 (20.1%) had cognitive dysfunction.

Table 3: Relationship between Pre-treatment seizure frequency (PTSF) and cognitive dysfunction in the study participants

Variables	Cognitive Dysfunction		p-value
	Yes (n =31) [n(%)]	No (n = 118) [n(%)]	
PTSF			
>1 seizure/month	3 (33.3)	6 (66.7)	0.245
≤ 1 seizure/month	28 (20.1)	111 (79.9)	
1-2 seizures/year	0 (0.0)	1(100)	

Pre-treatment seizure duration

The relationship between pre-treatment seizure duration and cognitive dysfunction in the study participants is illustrated in Table 4 below. The relationship between pre-treatment seizure duration and cognitive dysfunction was statistically significant (p<0.001). 68(45.3%) of the participants have had seizures for ≤ 1 year with only 2 (2.9%) cases of cognitive dysfunction while those that had for > 1 year had 82(54.7%) with 29(35.8%) cases having cognitive dysfunction.

Table 4 Relationship between Pre-treatment seizure duration and cognitive dysfunction in the study participants

Variables	Cognitive dysfunction		p-value
	Yes (n=31) [n(%)]	No (n=119) [n(%)]	
Pre-treatment seizure duration			
≤ 1 year	2 (2.9)	66 (97.1)	<0.001
>1 year	29(35.8)	53 (64.2)	

Analysis Of Variance (Anova) Showing The Difference In Mean Between The Risk Factors For Cognitive Dysfunction Using Cognitive Assessment Tools Using MOCA

The analysis of variance showing the difference in mean between the risk factors for cognitive dysfunction using MOCA in the study participants is illustrated in Table 5 below. The risk factors type of AED (F ratio-12.586; p-value <0.001) and duration of seizures (F ratio-4.481; p-value <0.001) were statistically significant.

Table 5: Analysis of variance showing the difference in mean between the risk factors for cognitive dysfunction using MOCA in study participants

Risk Factors	Parameters	Mean ±SD	F-ratio	p-value
Type of AED	None	28.00 ± 0.000	12.586	< 0.001
	Carbamazepine	25.68 ± 4.163		
	Levetiracetam	25.73 ± 2.658		
	Na Valporate	19.69 ± 8.448		
	Phenobarbitone	9.00 ± 0.000		
Seizure frequency	>1seizure/month	26.78 ± 0.972	0.819	0.443
	≤1seizure/month	24.18 ± 6.089		
	≤1seizure/year	25.00 ± 0.000		
Duration of seizures	≤ 1 year	26.57 ± 2.809	4.481	<0.001
	≥ 1 year	22.47 ± 7.09		

Using FEPSY

Analysis of variance showing the difference in mean between the Type of AED using FEPSY

The analysis of variance showing the difference in mean between the risk factor (Type of AED) for cognitive dysfunction using FEPSY in the study participants is illustrated in Table 6 below. The domains Recognition figures simultaneously (F ratio-4.091; p-value 0.004), Recognition words simultaneously (F ratio-3.094; p-value 0.018), Tapping Left (F ratio-3.705; p-value 0.007), Tapping Right (F ratio-2.490; p-value 0.046) and Fixed binary choice (F ratio- 4.983; p-value 0.001) were statistically significant.

Table 6: Analysis of variance showing the difference in mean between the Type of AED using FEPSY in study participants

Parameters	Mean ± SD	F-Ratio	p-value
ReaudL Mean			
None	280.00 ± 0.000	0.799	0.528
CBZ	411.52 ± 109.959		
LEV	407.13 ± 147.495		
NaV	409.69 ± 103.013		
PhB	353.00 ± 0.000		

ReaudR Mean None CBZ LEV NaV PhB	 3.37 ± 0.000 446.72 ± 120.182 423.53 ± 154.71 426.24 ± 91.924 285.00 ± 0.000	1.462	0.217
RecogFsi Mean None CBZ LEV NaV PhB	 5405.00 ± 0.000 3312.402 ± 868.049 3529.00 ± 975.166 3259.10 ± 721.975 2291.00 ± 0.000	4.091	0.004
RecogWsi Mean None CBZ LEV NaV PhB	 5181.00 ± 0.000 2927.95 ± 991.82 2802.40 ± 1209.720 2875.41 ± 606.348 2361.00 ± 0.000	3.094	0.018
ReVisL Mean None CBZ LEV NaV PhB	 272.00 ± 0.000 436.539 ± 137.165 461.93 ± 177.999 393.00 ± 124.093 468.00 ± 0.000	1.463	0.217

Parameters	Mean ± SD	F-Ratio	P-value
ReVisR Mean None CBZ LEV NaV PhB	 332.00 ± 0.000 438.42 ± 132.063 437.60 ± 159.449 414.724 ± 159.212 359.00 ± 0.000	0.563	0.690
Tapping-L Mean None CBZ LEV NaV PhB	 5960.00 ± 0.000 5099.57 ± 707.555 4606.00±1067.927 5104.59 ± 712.213 6360.00 ± 0.000	3.705	0.007
Tapping-R Mean None CBZ LEV NaV PhB	 6680.00 ± 0.000 5694.47± 893.539 4992.00 ±1857.784 5768.21 ± 928.183 6460.00 ± 0.000	2.490	0.046
BCH-F Mean None CBZ LEV	 767.00 ± 0.000 448.07 ± 137.106 508.53 ± 144.913	4.983	0.001

NaV PhB	415.24 ± 91.177 60.00 ± 0.000		
BCH-R Mean None CBZ LEV NaV PhB	 616.00 ± 0.000 462.99 ± 312.987 490.47 ± 108.774 393.31 ± 94.795 343.00 ± 0.000	0.745	0.563

Analysis of variance showing the difference in mean between the pre-treatment seizure frequency using FEPSY

The analysis of variance showing the difference in mean between the risk factor (pre-treatment seizure frequency) for cognitive dysfunction using FEPSY in the study participants is illustrated in Table 7 below. In the different domains of FEPSY, none was statistically significant.

Table 7: Analysis of variance showing the difference in mean between the pre-treatment seizure frequency using FEPSY in study participants

Parameters	Mean ± SD	F-Ratio	P-value
ReaudLMean >1seizure/month ≤1seizure/month ≤2seizures/year	 467.89 ± 169.347 405.45 ± 106.881 252.00 ± 0.000	2.350	0.101
ReaudR Mean >1seizure/month ≤1seizure/month ≤2seizures/year	 449.22 ± 171.82 436.44 ± 115.60 287.00 ± 0.000	0.835	0.436
RecogFsi Mean >1seizure/month ≤1seizure/month ≤2seizures/year	 3065.67 ± 621.060 3357.81 ± 896.427 2558.00 ± 0.000	0.851	0.429
RecogWsi Mean >1seizure/month ≤1seizure/month ≤2seizures/year	 2570.89 ±1157.933 2954.84 ± 967.155 2816.00 ± 0.000	0.658	0.520
ReVisL Mean >1seizure/month ≤1seizure/month ≤2seizures/year	 430.111 ± 202.293 429.73 ± 135.946 345.00 ± 0.000	0.181	0.835
ReVisR Mean >1seizure/month ≤1seizure/month ≤2seizures/year	 423.44 ± 162.00 431.37 ±137.888 593.00 ± 0.000	0.686	0.505
Tapping-L Mean >1seizure/month ≤1seizure/month ≤2seizures/year	 4670.00 ± 877.126 5108.41 ± 766.49 5100.00 ± 0.000	1.360	0.260

Tapping-R Mean >1seizure/month ≤1seizure/month ≤2seizures/year	 5484.44 ±1545.462 5677.08 ± 3.384 5280.00 ± 0.000	0.260	0.814
BCH-F Mean >1seizure/month ≤1seizure/month ≤2seizures/year	 417.22 ± 99.610 450.76 ±138.285 470.00 ± 0.000	0.267	0.766
BCH-R Mean >1seizure/month ≤1seizure/month ≤2seizures/year	 420.00 ± 91.955 453.73 ± 274.753 437.00 ± 0.000	0.068	0.934

Analysis of variance showing the difference in mean between the pre-treatment seizure duration using FEPSY

The analysis of variance showing the difference in mean between the risk factor (pre-treatment seizure frequency) for cognitive dysfunction using FEPSY in the study participants is illustrated in Table 8 below. In the different domains of FEPSY, none was statistically significant.

Table 8: Analysis of variance showing the difference in mean between the pre-treatment seizure duration using FEPSY in study participants

Parameters	Mean ± SD	T- test	p-value
Reaud-L Mean ≤1year >1 year	 423.38 ±118.86 395.44 ±105.36	1.52	0.13
Reaud-R Mean ≤1year >1 year	 454.82 ±124.78 420.58 ±112.78	1.76	0.08
RecogFsi Mean ≤1year >1 year	 3305.66 ± 813.98 3359.25 ± 940.81	-0.368	0.713
RecogWsi Mean ≤1year >1 year	 2935.53 ± 987.83 2926.68 ±972.68	0.055	0.956
ReVisL Mean ≤1year >1 year	 418.99 ±123.65 437.74 ± 151.97	-0.816	0.416
ReVisR Mean			

≤1year >1 year	425.00 ± 134.47 437.74 ± 143.30	-0.560	0.577
Tapping-L Mean ≤1year >1 year	 5146.99 ± 614.28 5027.21 ± 887.72	0.939	0.349
Tapping-R Mean ≤1year >1 year	 5757.47 ± 805.07 5583.28 ± 1219.78	1.007	0.315
BCH-F Mean ≤1year >1 year	 453.63 ±118.306 444.86 ± 149.49	0.392	0.696
BCH-R Mean ≤1year >1 year	 441.06 ± 114.93 460.42 ± 346.34	-0.44	0.66

LOGISTIC REGRESSION SHOWING THE RISK FACTORS OF COGNITIVE DYSFUNCTION IN STUDY POPULATION.

Logistic regression showing the risk factors of cognitive dysfunction in the study population is illustrated in Table 9. Within the variable "Type of AED", those who were on sodium valproate were nine-times more likely to have cognitive dysfunction compared to those who were not on any AED (OR-8.920; CI-1.498-53.110; p=0.016). Also, duration of seizures were statistically significant for both those that have had seizures for ≤ 1 year that had four-fold increased odds of having cognitive dysfunction (OR-3.500; CI- 1.210-17.510; p=0.014) and those who have had seizures for >1 year had six-fold increased odds of having cognitive dysfunction with respect to those who never had seizures (OR-7.200; CI-1.420-21.830;p=0.026).

Table 9: Logistic regression showing the risk factors of cognitive dysfunction in study population

Risk factors	Odd ratio	95% confidence interval	p-value
Seizure duration			
None‡	1.000		
≤ 1 year	3.500	1.210-17.510	0.014*
>1 year	7.200	1.420-21.830	0.026*
Type of AED			
None‡	1.000		
Carbamazepine	0.210	0.004-32.170	0.721
Levetiracetam	2.860	0.151-54.140	0.486
Sodium valproate	8.920	1.498-53.110	0.016*
Phenobarbitone	1.430	0.028-61.320	0.362
Seizure frequency (pre-treatment)			
>1seizure/month‡	1.000		
<1seizure/month	1.900	0.740-24.260	0.900
Up to 2seizure/year	2.970	0.220-10.450	0.414

‡ reference category, * statistically significant

DISCUSSSION

Demographics

The mean age of this study is in agreement with the study done by [21] using community screening interview for dementia (CSID). The important finding from their study was that younger adults suffer more from epilepsy in developing countries [22]. Also, other studies in developing countries, showed a general trend towards a higher prevalence of the disease during adolescence or early adulthood [23]. On the contrary, some studies in developing countries, demonstrated that the prevalence of epilepsy remained stable in the third and fourth decades and typically drops after the fifth decade of life, probably because the studies were carried out in particular age groups [24]. However in the developed countries, most studies show the prevalence of epilepsy to be stable in the adult age groups and increase with age after 50 years [25]. The variance in the age of manifestation of epilepsy between developing and developed countries could be explained by the aetiology. In developing countries, causes of epilepsy include neuro-infections, birth and head injuries and rarely brain tumours commonly found in younger age groups while in the developed countries epilepsy is usually caused by stroke and brain tumours more in adults [26]. In another study, prevalence then again increases after age 60 [27].

This study observed that more males had epilepsy compared to the females, though this was not statistically significant. This finding is consistent with previous studies done with FEPSY in the south-east and south-south of the country [27]. A study done in a developed country also showed that the prevalence is higher in males than females too. It is thought that, in most parts of Africa and Asia, males more readily go to the hospital for socioeconomic reasons and hence predominate in the hospital populations [28]. Other reasons why there are recorded lower prevalence of epilepsy in females may be explained by poor presentation of females with epilepsy to the hospital as a result of low level of education, african gender roles, fear of stigmatization or deterring marriage [29]. The male sex preponderance may also be due to occupational and social exposure to epileptogenic insults such as cranial trauma and alcohol. Another study conducted in India reported a higher prevalence of epilepsy in males and this was statistically significant. In

their population, women with epilepsy are perceived not to be marriageable and this may have led to active concealment of symptoms or diagnosis among these women [30].

The current study observed that the highest level of education among participants was secondary, however level of education was not significant. This may be due to the fact that the prevalence of epilepsy is highest in adolescence [24]. The study was in consonance with the study carried out by [23] using FEPSY but varied from the work done with CSID which may be due to varied location or the neurocognitive assessment tool used [24].

Risk factors

The current study found that type of AED was a significant risk factor for cognitive dysfunction in PWE [28]. This was in agreement with the studies carried out by [29,30]. Studies carried out by [30] noted that type of AED was not significant, this may probably due to the fact that their studies were specific to a specific domain in cognition (reaction time and attention) unlike other studies that dealt with the cognition as a whole [31]. The major cognitive effects of AEDs are impaired attention, vigilance, psychomotor speed but secondary effects on other cognitive functions are seen [32]. These cognitive effects of AEDs can be reversed in part by reduced seizures [31]. In general, the cognitive effects of AEDs are less than the sum total of other factors, but because AEDs are the major therapeutic modality for epilepsy, they are of special concern [32]. It is important to note that AED-induced cognitive side effects are increased with rapid initiation, higher doses and poly-therapy. In addition, this study also showed that those on sodium valproate were nine-times more likely to have cognitive dysfunction compared to those on other types of AED. This was in line with the studies carried out by [32,33] where old generation AEDs were noted to have marked effects on cognition than the newer generation AEDs [34,35].The reason was that the drugs that act on the GABA receptors affect cognition more than those that block the voltage gated channels [36], Sodium Valproate that acts through both mechanisms will definitely have a greater cognitive effect.

Frequency of seizures in this study was not statistically significant. This finding can be explained by the fact that the participants in this study had reduced seizure frequency. Also, the current study was cross-sectional as opposed to a longitudinal study which may have demonstrated more cognitive dysfunction in the participants if they have been followed up and reassessed for a longer period. The finding in this study agrees with works done by [36] in developed country where he assessed cognitive change in 35 patients with active focal epilepsy and 35 healthy controls at an inter-test interval of 10 years [37]. Overall, frequent seizures cause cumulative degradation in spatial performance which results in impairment of long term potentiation, precision and frequency of theta oscillation that represent the orderly communication of networks, all these factors negatively affect cognitive function [38,39].

This study observed a significant association between duration of seizures before treatment and cognitive dysfunction. This finding is similar to the study done [40] using another neurocognitive tool (CSID) and some studies done by [40]. Longer duration of epilepsy has been reported to be associated with greater cognitive dysfunction [40]. The negative impact of duration of seizures before treatment may be due to the cumulative impact of seizures, and also the pathologic interictal brain activity [32]. Two studies have reported that duration of seizures before treatment cause cognitive decline especially on the language domains [33]. Additionally, one of the studies stated that the duration of epilepsy was the best predictor of cognitive decline and other epilepsy-related variables did not make any additional contribution to the variance [34]. Late diagnosis and commencement of medications have been found to increase the risk of cognitive decline associated with duration of seizure before treatment [35]. In all, clinical studies showed that cognitive dysfunction induced by seizures are reversible for most seizure

types, when seizures are diagnosed early and controlled adequately [36].

CONCLUSION

The type of AED used in seizure treatment and duration of seizures were identified as risk factors for cognitive dysfunction among PWE using the two neurocognitive tools. Using FEPSY, the domains mostly affected in epilepsy include attention and decision making (binary choice fixed, recognition simultaneously both words and figures), perception (binary choice fixed), hemispheric language or motor dominance (finger tapping) and learning and memory (recognition simultaneously both words and figures). The adapted MOCA promises to be an effective tool for assessing cognitive dysfunction among PWE in our locale. Further studies to strengthen this evidence is needed.

RECOMMENDATIONS

Early diagnosis of epilepsy, prompt commencement of appropriate and adequate dosage of medications, effective general health promotion are necessary to reduce the prevalence and associated risk factors of cognitive dysfunction. It is also recommended that baseline cognitive function assessment should be an integral part of routine evaluation of patients with epilepsy to identify and monitor this epilepsy-related complication. This proposed protocol will be useful to develop and implement strategies aimed at prevention, control and rehabilitation of PWE. Furthermore, adapted MOCA can be used as a screening tool for cognitive dysfunction in PWE in our locale.

REFERENCES

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475–82.
2. Fisher RS, Cross JH, French JA, Higurashi N, Peltola J, Roulet E, et al. Operational classification of seizure types by the International League Against Epilepsy : Position Paper of the ILAE Commission for Classification and Terminology. 2017;522–30.
3. Nazmetdinova DM, Basamygin A V, Kalinin V V. [Memory and intellectual disorders in patients with epilepsy: an analysis of the relationship between clinical characteristics and brain asymmetry]. Zhurnal Nevrol i psikhiatrii Im SS Korsakova. 2010;110:82–7.
4. Beretta S, Carone D, Zanchi C, Bianchi E, Pirovano M, Trentini C, et al. Long-term applicability of the new ILAE definition of epilepsy. Results from the PRO-LONG study. Epilepsia. 2017;58:1518–23.
5. Ogunrin O, Adamolekun B, Ogunniyi AO, Aldenkamp AP. Cognitive Function in Nigerians with Newly Diagnosed Epilepsy. Can J Neurol Sci. 2017;148–51.
6. Hermann B, Seidenberg M. Epilepsy and cognition. Epilepsy Curr. 2007;7:1–6.
7. Gulati S, Yoganathan S, Chakrabarty B. Epilepsy, cognition and behavior. Indian J Pediatr. 2014;81:1056–62.
8. Hamed SA. The aspects and mechanisms of cognitive alterations in epilepsy: the role of antiepileptic medications. CNS Neurosci Ther. 2009;15:134–56.
9. Japaridze N, Menzel E, von Ondarza G, Steinmann E, Stephani U. Risk factors of cognitive outcome in patients with atypical benign partial epilepsy/pseudo-Lennox syndrome (ABPE/PLS) and continues spike and wave during sleep (CSWS). Eur J Paediatr Neurol. 2014;18:368–75.
10. Realmuto S, Zummo L, Cerami C, Agro L, Dodich A, Canessa N, et al. Social cognition dysfunctions in patients with epilepsy: Evidence from patients with temporal lobe and idiopathic generalized epilepsies. Epilepsy Behav. 2015;47:98–103.
11. Baxendale S. Neuropsychological assessment in epilepsy. Vol. 18, Practical neurology. England; 2018. p. 43–8.
12. Witt J-A, Helmstaedter C. Cognition in epilepsy: current

clinical issues of interest. Curr Opin Neurol. 2017;30:174–9.
13. Arinzechi EO, Ogunrin OA, Nwosu CM, Nwani PO, Enwereji KO, Asumogha LA, et al. A community-based case-control study of prevalence and pattern of cognitive impairments in patients with epilepsy residing in South-Eastern Nigeria. J Neurosci Rural Pract. 2016;7:405–11.
14. Meador KJ. Cognitive outcomes and predictive factors in epilepsy. Neurology. 2002;58:S21-6.
15. Braakman HMH, Vaessen MJ, Hofman PAM, Debeij-Van Hall MHJA, Backes WH, Vles JSH, et al. Cognitive and behavioral complications of frontal lobe epilepsy in children: A review of the literature. Epilepsia. 2011;52:849–56.
16. Greener M. Beyond seizures : understanding. 2013;31–2.
17. Hirsch E, Schmitz B, Carreno M. Epilepsy, antiepileptic drugs (AEDs) and cognition. Acta Neurol Scand. 2003;108:23–32.
18. Helmstaedter C, Witt J-A. The longer-term cognitive effects of adjunctive antiepileptic treatment with lacosamide in comparison with lamotrigine and topiramate in a naturalistic outpatient setting. Epilepsy Behav. 2013;26:182–7.
19. Hallböök T, Ji S, Maudsley S, Martin B. The effects of the ketogenic diet on behavior and cognition. Epilepsy Res. 2012;100:304–9.
20. Karnam HB, Zhou J-L, Huang L-T, Zhao Q, Shatskikh T, Holmes GL. Early life seizures cause long-standing impairment of the hippocampal map. Exp Neurol. 2009;217:378–87.
21. Mula M. Emerging drugs for focal epilepsy. Expert Opin Emerg Drugs. 2018;23:243–9.
22. Kwan P, Brodie MJ. Neuropsychological effects of epilepsy and antiepileptic drugs. Lancet. 2001;357:216–22.
23. Miller LA, Galioto R, Tremont G, Davis J, Bryant K, Roth J, et al. Cognitive impairment in older adults with epilepsy: Characterization and risk factor analysis. Epilepsy Behav. 2016;56:113–7.
24. Helmstaedter C. Cognitive outcome of status epilepticus in adults. Epilepsia. 2007;48:85–90.
25. Elger CE, Helmstaedter C, Kurthen M. Chronic epilepsy and cognition. Lancet Neurol. 2004;3:663–72.
26. Dodrill CB. Progressive cognitive decline in adolescents and adults with epilepsy. Prog Brain Res. 2002;135:399–407.
27. Rodin G, Ahles TA. Accumulating evidence for the effect of chemotherapy on cognition. J Clin Oncol. 2012;10:3568–9.
28. Seidenberg M, Pulsipher DT, Hermann B. Cognitive progression in epilepsy. Neuropsychol Rev. 2007;17:445–54.
29. Loring DW, Williamson DJ, Meador KJ, Wiegand F, Hulihan J. Topiramate dose effects on cognition: a randomized double-blind study. Neurology. 2011;76:131–7.
30. Park SP, Kwon SH. Cognitive effects of antiepileptic drugs. J Clin Neurol. 2008;4:99–106.
31. Nicolai J, Kasteleijn-Nolst Trenite D. Interictal discharges and cognition. Epilepsy Behav. 2011;22:134–6.
32. Piazzini A, Turner K, Vignoli A, Canger R, Canevini MP. Frontal cognitive dysfunction in juvenile myoclonic epilepsy. Epilepsia. 2008;49:657–62.
33. Witt J-A, Werhahn KJ, Kramer G, Ruckes C, Trinka E, Helmstaedter C. Cognitive-behavioral screening in elderly patients with new-onset epilepsy before treatment. Acta Neurol Scand. 2014;130:172–7.
34. Subota A, Pham T, Jette N, Sauro K, Lorenzetti D, Holroyd-Leduc J. The association between dementia and epilepsy: A systematic review and meta-analysis. Epilepsia. 2017;58:962–72.
35. Power KN, Gramstad A, Gilhus NE, Hufthammer KO, Engelsen BA. Cognitive dysfunction after generalized tonic-clonic status epilepticus in adults. Acta Neurol Scand. 2018;137:417–24.
36. Ogunrin, Olubunmi A AB. Cognitive neuroassessment in

Nigeria Africans-Predictive validity of a computerized testing. Ann Biomed Sci. 2007;6:26–45.
37. Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ. Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults. BMC Geriatr. 2015;15:107.
38. Beath N, Asmal L, van den Heuvel L, Seedat S. Validation of the Montreal cognitive assessment against the RBANS in a healthy South African cohort. South African J Psychiatry. 2018;24:9685.
39. Phabphal K, Kanjanasatien J. Montreal Cognitive Assessment in cryptogenic epilepsy patients with normal Mini-Mental State Examination scores. Epileptic Disord. 2011;13:375–81.
40. Kish L. Survey sampling. John Wiley sons, Inc. 1965;78–94.