Research Article

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Prevalence of cognitive adverse outcomes in epileptic outpatients

Abstract

Background: Epilepsy accounts for 1% of the global burden of disease and affects over 65 million people worldwide imposing a large economic burden on global health care systems and is a major public health problem in low and middle income countries.

Objective: To determine prevalence of cognitive dysfunctions among epileptic patients of different socio demographic backgrounds and associated factors.

Methodology: It was cross-sectional study, interviewing patients using Mini Mental State Examination (MMSE) as a screening tool. Information from collaborators and patients' charts were also used as needed.

Results: There were 226 epileptic patients involved in this study. 77.9% were from Addis Ababa. The lowest MMSE score was 17, whereas the mean and median were 26.92 and 28, respectively. The median MMSE for females and males were 28 and 29, respectively. Educational status was found to be the single most important determinant of mean MMSE. There was also statistically significant association between MMSE and seizure frequency, as well as type of seizure disorder. Age at seizure onset, duration of seizure disorder and antiepileptic drugs treatment didn't significantly affect the MMSE scores.

Conclusion: Although MMSE is an important screening tool in patients suspected to have cognitive impairment, it cannot be a substitute for formal neuropsychological test batteries.

Keywords: Epilepsy/epileptic patients, Cognitive adverse effects (outcomes), Mini Mental State Examination (MMSE)

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Introduction

Background

Epilepsy is one of the most common and widespread neurological disorders. Recent estimates suggest that it accounts for 1% of the global burden of disease.[1] and affects over 65 million people worldwide.[2] In addition, because the relatives and friends of people with epilepsy (PWE) also bear the burden of this condition, more than 500 million people are indirectly affected by epilepsy.[3] Thus, epilepsy imposes a large economic burden on global health care systems and is a major public health problem in low and middle-income countries (LMICs).[1]

A variety of clinical epilepsy factors contribute to cognitive adverse effects (CAE) of epilepsy, including underlying brain pathology, age at seizure onset, seizure type and severity, antiepileptic medications, and other factors.[4-7] An earlier age at onset is associated with a worse prognosis. Severity and chronicity are the major sources for cognitive problems.[8] while anatomical location explains the specificity of these symptoms.

In newly diagnosed and untreated epileptic patients, cognitive problems are already present.[9] in more than 50% of patients. Psychiatric or behavioral as well as academic problems may antedate the diagnosis of epilepsy even in adults.[10] with epilepsy. The possibility exists that factors associated with underlying epileptogenesis leading to the onset of seizures may play a role.[11]

Between 20-50% of patients with epilepsy have memory impairment.[4] Memory problems are more marked in focal epilepsies, particularly short term memory. The impairment is related to the laterality with a verbal learning deficit in the dominant hemisphere, especially with the dominant mesial temporal lobe (MTL) epilepsy. The severity of the deficit is correlated with the length of active epilepsy. However, memory deficits are also described in extra-temporal epilepsy, such as frontal lobe epilepsy.[12]

Idiopathic Epilepsy

Idiopathic epilepsy is associated with less severe cognitive impairments than other seizure types. Diffuse and generalized cognitive impairment is present; but language and verbal memory, in contrast, appear unaffected.[13] Patients with idiopathic generalized epilepsy (IGE) also have focal impairments in addition to generalized slowing.[14] Juvenile myoclonus epilepsy (JME) generally begins between 12-18 years of age, and is characterized by neuropsychological and behavioral features associated with frontal executive impairment such as reasoning difficulty, poor concept formation, and decreased mental speed and flexibility.[13]

Focal symptomatic epilepsy

The cognitive profiles of patients with symptomatic epilepsy are more strongly related to epilepsy location and etiology. Approximately 70% of chronic symptomatic epilepsy is attributed to temporal lobe epilepsy (TLE). It is characterized by impaired declarative memory.[15] The nature of the memory impairment depends on when seizures begin.

Frontal lobe epilepsy is seen in 20% of patients with partial onset seizures, and is associated with a less consistent neuropsychological profile than TLE. Tests of motor coordination appear particularly sensitive to frontal lobe epilepsy. No consistent lateralized impairment has been associated with focal left vs. right frontal lobe epilepsy.[16]

Antiepileptic Drug Effects

Because AEDs decrease membrane excitability, increase postsynaptic inhibition, or alter synchronization of neural networks, they are often associated with neuropsychological side effects.[17] As a result, adverse AEDs effects are strongly associated with decreased health-related quality of life.[18,19]

The effects of chronic epileptic disorders on the cognitive organization of the brain are not totally negative. For example, as a result of cerebral plasticity, symptomatic focal epilepsies originating in or close to eloquent areas of the dominant hemisphere may enforce a positive reorganization of adjacent or even distant and contralateral cortical areas in order to maintain the essential cognitive functions in question.[20]

In general, the effects exerted by an AED could vary depending on factors linked to patient characteristics and individuaaq `l susceptibility. Certain individuals may be more vulnerable to the CAEs associated with particular AEDs. Current or previous cognitive or psychiatric problems may also be linked to the cognitive effects of an AED.

Statement of the problem

Though cognitive dysfunctions are there even before the onset of seizure, epilepsy leads to further progressive deterioration of cognitive functions. However, it was not possible to trace the findings possible to know if they have a common pathophysiology. Thus, so far it is hardly possible to attribute epilepsy as the mere cause for CAE among epileptic patients.

Different factors contribute to adverse cognitive effects in epileptic patients including anti-epileptic drugs, particularly the older generations; the underlying brain lesions; and infections (e.g. HIV encephalopathy). These all contribute to both increased prevalence of epilepsy and CAE particularly in the developing part of the world, like Ethiopia.

Brain insults during early life are the other factors that contribute to the CAE of epilepsy. This includes hypoxic/ischemic brain injuries, congenital infections and cerebral palsy. In addition, age at seizure onset; seizure type and frequency, duration of the seizure and refractoriness tend to affect the prevalence of CAE in epileptic patients.

Although the magnitude of CAE of epilepsy has been known for a long period of time, there is scarcity of data from the developing countries, particularly in Africa. In Ethiopia, there is even no single study done on the prevalence of adverse cognitive effects of epilepsy. There were few studies done in countries like Tanzania, and Nigeria.

Most of the studies were mainly focusing on either memory or language abnormalities, which often times are due to focal symptomatic seizures. Therefore, these studies were not comprehensive in that they were evaluating only part of the different cognitive domains. Additionally, different studies used different methodologies. There was only one study done in Romania, using mini-mental state examination (MMSE) and the Montreal cognitive assessment (MoCA). It was conducted to assess cognitive performances in elderly patients with epilepsy.

The objective of this study is to analyze the pattern and magnitude of cognitive adverse effects in epileptic patients, using MMSE as a screening tool.

Since MMSE has an inherent drawback of picking up mild cognitive impairments (i.e., insensitive), by no means this study will be a substitute for a formal Neuropsychological tests. Therefore, in the future one may consider using the more sensitive batteries such as the different Neuropsychological tests and MoCA.

Objective

General objective

To determine prevalence of cognitive dysfunctions among epileptic patients of different sociodemographic backgrounds and factors associated with them, in Black Lion Hospital, General Neurology Outpatient, from 01 Feb., to 30 July, 2013.

Specific objectives

To determine the sociodemographic backgrounds of epileptic patients. To determine the prevalence of cognitive adverse effects of the different epileptic seizures.

To determine factors associated with CAE in epileptic patients.

To determine the role of different AEDs in cognition among epileptic patients.

Methodology

Methods and materials

Study Area: The study was conducted at Black Lion Hospital, General Neurology Outpatient, Department of Neurology, Addis Ababa University (AAU).

Study Period: Data were collected from 01 February 2013 to 30 July 2013.

Study Design: Cross-sectional study.

Study population

Target Population: All patients diagnosed with epileptic seizures.

Source Population: All epileptic patients with follow up at General Neurology Clinic, Black Lion Hospital, Addis Ababa, Ethiopia. Study Population: All epileptic patients age ≥18 years old, and having follow up at General Neurology Clinic, Black Lion Hospital, Addis Ababa, Ethiopia.

Inclusion criteria: As described above.

Exclusion criteria: Mental retardation, Blindness.

Acutely sick or patient condition/behavior doesn't allow to obtain reliable information Inability to read.

Sample Size Determination:

a. Sample size

N = Z^2pq/D^2

N = $(1.96)^2(0.2)(0.8)/ (0.05)^2$

N = 246

The response rate was 92% (226 patients). Initially 237 patients were recruited in the study, but 8 were found to be repetitions and data from three patients were found to be incomplete.

Measurements:

Data collection instruments: Every eligible patient was interviewed using a structured questionnaire. Additional information was obtained from collaborator(s). Patients who had neuro-imaging and/or EEG were asked to bring the results. Mini Mental State Examination (MMSE) was used as a screening tool.

a. Study Variables:

Dependent variables

Language

Attention

Execution

Memory

Praxis

b. Indendepent variables

Seizure frequency

Seizure duration

Seizure type

Age at seizure onset

Handedness

AEDs

Brain insult

Circumstances of the study

The study was conducted at Black Lion Hospital. There were two general neurology follow up clinics. Data were collected by the principal investigator (PI).

Data quality assurance, processing and analysis

Questionnaires were checked for the completeness of information by the principal investigator (PI). Once the information was found to be complete, then it was fed into SPSS 16.0 for data analysis. P-value of less than 0.05 was considered to be significant association.

Ethical Considerations

Protocol approvals were obtained from the ethical review Committee of the Department of Neurology and the Institutional Review Board (IRB).

First, all patients were evaluated thoroughly and managed appropriately as part of the routine follow up, i.e., appropriate treatment was given (or continued if they were already on treatment) for the type of epilepsy he/she has. At the end of the routine follow up care, and before the actual data collection starts, a brief introduction of the study (the need to have this study, pros and cons, what to expect from this study, and the scope of this study) was given to each patient.

After one is sure that the patient understood all the information given above, and agreed to be involved in the study, then they were asked to sign on the consent form. It is only then after that the actual data collection started, provided that the patient agreed to participate in the study.

The subjects had full right not to participate at all as a study subject or to discontinue the study at any time during the interview, irrespective of whatever reasons he/she might have. Patient's personal information was kept confidential.

Dissemination plan

The results of this study will be submitted to the Department of Neurology, Faculty of Medicine, Addis Ababa University and will be disclosed to the respective units of the Hospital, health professionals and authorities. It will also be submitted for publication in one of the Journals.

Definition of terms:

Cognitive Adverse Effects: Include memory impairment, mental slowing, and attention deficit among others.[21]

Cognitive function: Higher brain function, that is, the capacity of the brain to programme adaptive behavior, solve problems, memorize information, focus attention, visuospatial orientation, praxis, abstract thinking, and language functions.[21]

Epilepsy: A disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition requires at least one epileptic seizure.[22]

Epileptic seizure: A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[22]

Generalized epilepsy: The source of the seizure within the brain is distributed. Seizures are divided according to the effect on the body, but all involve loss of consciousness. They include absence (petit mal), myoclonic, clonic, tonic, tonic-clonic (grand mal) and atonic seizures.[21]

Idiopathic epilepsies: Characterized by a genetic predisposition and the absence of readily identifiable brain lesions.[21]

Myoclonic seizures: Can be described as jumps. They are caused by rapid contraction and relaxation of the muscles.[21]

Partial (focal) epilepsy: The source of the seizure within the brain is localized. Partial seizures are further divided depending on the extent to which consciousness is affected. If it is unaffected, then it is a simple partial seizure; otherwise, it is a complex partial (psychomotor) seizure. A partial seizure may spread within the brain, a process known as secondary generalization.[21]

Symptomatic epilepsies: Arise from the effects of an epileptic lesion, whether that lesion is focal, such as a tumour, or a defect in metabolism causing widespread injury to the brain.[21]

Tonic–clonic seizures: A type of generalized seizure that affects the entire brain (formerly known as grand mal seizures). The seizures are divided into two phases, the tonic phase and the clonic phase, and are often preceded by anaura.[21]

Results

A total of 226 patients with seizure disorders were enrolled in this study over six months period from 01 February 2013 to 30 July 2013. Of the total study patients, 118 cases (52.21) were females. 211 patients (93.4%) were right handed, whereas one patient was ambidextrous.

More than three-fourth, i.e., 176(77.87%) patients were from Addis Ababa and 107(47.34%) were from Amhara ethnic groups. Patients in the age ranges between 20-29, and 30-39 years accounted for the majority, i.e., 79(34.95%) and 45(19.91%) of patients, respectively. The overall mean ±SD age was 33.27±13.38, whereas the means ±SD ages for females and males were 32.53±12.15 and 34.06±14.63, respectively. Females had lower mean MMSE scores than males (26.57 vs 27.31). Patients with single marital status had the highest mean MMSE scores (27.37) than the others (Table 1). None of the different sociodemographic features showed statistically significant associations with the mean MMSE.

Out of 226 subjects in this study, 17(7.52%) patients were found to have family history of epileptic seizures. The mean and median ages at seizure onset were, 19.91±13.86 and 16.5 years respectively. 134(59.29%) patients started experiencing seizures at below 20 years of age. The mean MMSE scores generally tend to decrease as the age at seizure onset increase, Individuals who started to experience seizure disorders at age between 10-19 years had the highest mean MMSE, and the lowest OR, but it was not possible to trace the findings statistically significant (Table 2).

On the other hands, the mean and median durations of the seizure disorders were 13.06±9.33 and 13 years, respectively. In 102(45.13%) subjects, the duration of the seizure disorder was less than ten years and 14(6.19%) patients lived with epilepsy for more than 30 years. Similarly, as it was true for age at seizure onset, there was no statistically significant association between mean MMSE and duration of the seizure disorders.

With regard to frequencies of seizure episodes, 106(46.90%) patients were experiencing seizure at least once in six months, and 19(8.40%) patients were having seizure almost daily or every other day. The rest, i.e., 120(53.09%) patients didn't have seizures in the past six months. 120(53.1) patients were seizures free for at least more than six months, whereas 28(12.4) patients had their seizure episode five years ago. The Odds of developing CAE was 1.61 times higher in patients with daily to every other day seizure episodes. Only patients with at least one episode of seizure in the past 1-6 months were found to have statistically significant association with mean MMSE scores (OR=2.41, P-value=0.00).

As to the seizure types, GTC seizure disorder accounted for the majority of cases, 159(57.07%). Simple focal seizure and focal seizure with secondary generalization together accounted 62(27.43%) of cases. The rests were due to atonic, myoclonic, complex partial and other uncommon seizure types. Although the Odds of developing CAE is 2.07 times higher in both simple focal and focal with secondary generalized seizure disorders, only focal with secondary generalized seizure was found to have statistically significant association with the mean MMSE (OR=2.07, P-value=0.04).

The lowest MMSE score was 17, and only 39(17.26%) patients scored less than 24 out of 30.54(23.89%) patients scored 30 out of 30. The mean MMSE score was 26.92, whereas the median was 28. The mean MMSE scores increase as the education level increases. For example, 30 out of 64 patients in the primary school scored at most 23 out of 30, whereas only nine patients out of 162 who were either in the high school or tertiary school scored 23 or less out of 30. There

was statistically significant association between MMSE scores (the traditional cutoff being 23/24) and the educational status.

Similarly, there was a statistically significant association between MMSE (the MMSE cutoff being 23/24) and age at seizure onset between 10-19 years (OR=0.16, P-value=0.00).

The mean MMSE scores and educational status was found to be statistically significant in individuals who were in the primary school; and these subjects accounted for 64(28.31%) of the whole the study subjects. The mean and median MMSE scores increase from 24.16 and 24 respectively, for individuals in the primary school, to 27.80 and 29 respectively for patients in the high school (Table 3).

Out of the 226 patients in this study, 154(68.14%) patients had at least one EEG study during their follow up. In 71(46.10%) of cases, it was not possible to trace the findings possible to trace the findings. Out of a total of 83 cases with EEG findings, 43(51.81%) were normal, and the rest were abnormal. Only in 24(28.91%) cases were found to have abnormal epileptiform discharges.

Similarly, 84(37.17%) patients had at least one brain neuroimaging, i.e., either computed tomography (CT) scan or magnetic resonance imaging (MRI). Again, as it was true in the case of EEG study, in 30(35.71%) patients, it was not possible to trace the findings possible to trace the findings. Strokes, arterio-venous malformations (AVM) and brain tumors each accounted for 7.14%; whereas brain abscess accounted for 5.95% of the findings. Neither neuro-imaging nor EEG findings showed statistically significant association (Table 4).

The mean duration of AEDs treatment was 11.89±8.99 years. 137(60.61%) patients in this study were put on one anti-epileptic drug (AEDs), i.e., monotherapy. Phenobarbitone alone was the most commonly used AED accounting for 36.28%. The most commonly used combinations were phenytoin with phenobarbitone which accounted for 15.92%. 6.19% of patients were on triple therapy. 83(36.72%) patients were on AEDs for at least 15 years, while 10.62% of patients were on AED for at least 25 years. There was no statistically significant association between mean MMSE scores and AEDs regimen and duration of treatment (Table 5).

Out of the total of 226 patients, 106(46.90%) patients had at least one episode of seizure in the past six months. In contrast, 28(12.39%) patients didn't have any episode of seizure for the last five years, out of which four patients were on polytherapy. The Odds ratio of patients on polytherapy for at least five years despite no episode of seizure was 5.76 times higher than those who were on monotherapy. Across all the different ADEs regimen and duration of treatment, as well as the frequency of seizure disorders, there was no statistically significant association with MMSE scores (Table 6).

Table 1 Frequency distributions of sociodemographic characteristics of the study subjects, Black Lion Hospital, AAU, October 2013

Variables	Total No	Mean MMSE	Crude OR	P-value
Age in years				
18-20	35(15.48)	27.91	0.48(0.19-1.20)	0.17
20-29	**79(34.95)**	27.14	......	....
30-39	45(19.91)	26.96	0.81(0.37-1.76)	0.74
40-49	35(15.48)	26.54	1.22(0.54-2.75)	0.77
50-59	20(8.85)	26.05	1.63(0.60-4.38)	0.46
60+	12(5.31)	25.08	1.63(0.48-5.52)	0.53
Mean±SD	**33.27±13.38**			
Median	**29**			
Total	**226**			
Sex				
Female	118(52.21)	26.57	0.60(0.35-1.04)	0.09
Male	108(47.78)	27.31	......	....
Total	**226**			

Table Continued...

Variables	Total No	Mean MMSE	Crude OR	P-value
Age in years				
Marital status				
Single	130(57.52)	27.37	......	....
Married	84(37.17)	26.51	1.37(0.77-2.42)	0.33
Other	12(5.31	25	2.02(0.61-6.64)	0.34
Total	**226**			
Religion				
Orthodox	170(75.22)	27.04	....	....
Muslim	26(11.50)	26.65	1.31(0.56-3.03)	0.67
Protestant	26(11.50)	26.46	1.78(0.77-4.09)	0.24
Other	4(1.77)	26.75	1.78(0.24-13.00)	0.62
Total	**226**			
Ethnicity				
Amhara	107(47.34)	27.03	......	....
Oromo	58(25.66)	26.16	1.09(0.56-2.09)	0.92
SNNP	41(18.14)	27.34	0.80(0.37-1.70)	0.7
Others	20(8.85)	27.75	0.66(0.23-1.86)	0.59
Total	**226**			
Residency				
Addis Ababa	176(77.87)	26.94		....
Out of AA	50(22.12)	26.86	1.06(0.52-2.14)	0.99
Total	**226**			

Table 2 Characteristics of seizure disorders vs. mean MMSE scores, Black Lion Hospital, AAU, October 2013

Variables	Total No	MMSE Mean	Crude OR	P-value
Age at seizure onset				
< 10	62(27.4)	26.26	1.21(0.57-2.56)	0.71
19-Oct	72(31.9)	28.39	....	.....
20-29	41(18.1)	26.44	1.36(0.58-3.17)	0.56
30-39	25(11.1)	26.52	1.05(0.37-2.92)	0.88
40-49	17(7.5)	26.06	1.40(0.43-4.57)	0.73
50+	9(4.0)	24.78	1.26(0.25-6.06)	0.73
Mean±SD	**19.91±13.86**			
Median	**16.5**			
Total	**226**			
Family history				
Yes	17(7.5)	26.41	0.76(0.22-2.44)	0.81
No	209(92.5)	26.97	......	....
Total	**226**			
Duration of seizure disorder				
<10	102(45.1)	27.2	......	....
19-Oct	64(28.3)	26.56	1.07(0.53-2.17)	0.96
20-29	46(20.4)	26.89	1.23(0.56-2.68)	0.7
30+	14(6.2)	26.71	1.44(0.40-5.05)	0.56
Mean±SD	**13.06±9.33**			
Median	**13**			
Total	**226**			
Seizure frequency (at least)				
Daily to every other day	19(8.4)	26.11	1.61(0.55-4.72)	0.47
Weekly to every other week	8(3.5)	28	1.07(0.19-5.52)	1
Once in three to four weeks	18(8.0)	26.56	0.69(0.20-2.27)	0.68
Once in the past 1-6 months	61(27.0)	26.62	**2.41(1.23-4.76)a***	**0.00a***
6-11 months ago	29(12.8)	27.41	0.94(0.37-2.38)	0.93
1-4 years ago	63(27.9)	27.32	0.90(0.45-1.79)	0.86
>= 5 years ago	28(12.4)	26.68	0.85(0.32-2.20)	0.88
No seizure in the last 6 months	**120(53.1)**	**27.19**	......	.....
Total	**226**			
Type of epileptic seizure				
Simple focal	22(9.73)	27.18	2.07(0.83-5.16)	0.17
Focal with secondary gen.	40(17.69)	26.08	2.07(1.00-4.25) **a***	0.04
Complex partial	19(8.40)	27.84	0.95(0.33-2.69)	0.85
GTC seizure	129(57.07)	26.98	......	....

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Table Continued...

Variables	Total No	MMSE Mean	Crude OR	P-value
Age at seizure onset				
Atonic	3(1.32)	29.67	1.03(0.09-11.74)	1
Myoclonic	8(3.54)	27.25	0.69(0.13-3.56)	1
Others	5(2.21)	25.4	1.38(0.22-8.58)	0.66
Total	**226**			
Generalized (combined)	145(64.2)	27	…….	….
Focal (combined)	81(35.8)	26.79	1.61(0.89-2.91)	0.11
Total	**226**			

a*= Statistically significant

Table 3 Educational status vs. mean MMSE scores, Black Lion Hospital, AAU, October 2013

Variables	Total No	Mean MMSE	Median MMSE	Crude OR	P-value
Educational status					
Read and write only	12(5.31)	23.42	22	4.22(1.06-17.98)**a***	**0.02**
Elementary	52(23.00)	24.33	24	2.65(1.35-5.20)**a***	**0**
High school	115(50.88)	27.8	29	……	…..
Tertiary	47(20.80)	28.55	29	0.89(0.42-1.86)	0.91
Total	**226**				
Educational status					
Primary school	64(28.31)	24.16	24	3.08(1.56-6.11)**a***	**0**
High school	115(50.88)	27.8	29	…….	…..
Tertiary	47(20.80)	28.55	29	0.89(0.40-1.98)	0.91
Total	**226**				

a*= Statistically significant

Table 4 EEG and neuro-imaging findings vs. mean MMSE scores, Black Lion Hospital, AAU, October 2013

Variables	Total No	Mean MMSE	Crude OR	P-value
EEG findings				
Normal	43(51.81)	27.4	…..	….
Abnormal, nonepileptiform	16(19.27)	28.06	1.86(0.58-5.97)	0.44
Abnormal, epileptiform	24(28.91)	27.67	0.49(0.15-1.57)	0.35
Total	**83**			
Brain CT/MRI findings				
Normal	16(29.63)	26.88	0.82(0.21-3.18)	0.99
Abnormal (combined)	38(70.37)	26.5	…..	….
Total	**54**			

Table 5 Anti-epileptic medications (AEDs) vs. mean MMSE scores, Black Lion Hospital, AAU, October 2013

Variables	Total No	Mean MMSE	Crude OR	P-value
Monotherapy				
CBZ	8(4.9)	26.86	0.98(.50-1.92)	0.9
PHN	36(22.1)	26.71	0.96(0.55-1.66)	0.99
PHB	91(55.8)	26.79	……	……
VAL	25(15.3)	27.69	0.50(0.13-1.92)	0.37
CLO	3(1.8)	26.33	0.84(0.07-9.56)	1
Total	**163(72.1)**			
Polypharapy				
PHN+PHB	29(46)	26.58	……	…..
PHN+CBZ	7(11.1)	26.36	1.01(0.24-4.11)	1
PHN+VAL	3(4.8)	27.2	1.17(0.17-7.99)	1
PHB+CBZ	11(17.5)	25.44	1.99(0.61-6.41)	0.38
PHB+VAL	3(4.8)	26.67	0.88(0.07-10.72)	1
CBZ+VAL	3(4.8)	28.5	5.30(0.49-56.39)	0.28
PHN+PHB+CBZ	2(3.2)	25	0.88(0.07-10.72)	1
PHN+CBZ+VAL	5(7.9)	26.36	1.01(0.24-4.11)	1
Total	**63(27.9)**			
AEDs regimen (combined)				
Mono-therapy (combined)	**163(72.1)**	27.13	……	……
Poly-therapy (combined)	**63(27.9)**	26.38	1.09(0.58-2.05)	0.4
Total	**226**			

Table Continued...

Variables	Total No	Mean MMSE	Crude OR	P-value
Monotherapy				
AEDs treatment duration (yrs)				
<10	116(51.3)	26.97	…….	……
19-Oct	60(26.5)	26.68	1.06(0.52-2.15)	0.98
20-29	39(17.3)	27.15	1.23(0.54-2.79)	0.72
30+	11(4.9)	26.91	1.13(0.26-4.66)	1
Mean±SD	**11.89±8.99**			
Total	**226**			

Table 6 Seizure frequency and AEDs regimen vs mean MMSE scores, Black Lion Hospital, AAU, October 2013

Seizure frequency	AEDs regimen	Mean MMSE	Total No	Crude OR	P-value
At least once in the past six months	Monotherapy	26.89	66(29.2)	1.17(0.55-2.48)	0.78
	Polytherapy	26.18	40(17.7)	1.28(0.54-3.06)	0.66
At least one seizure episode in before 6 months to 4 years	Monotherapy	27.3	73(32.3)	…….	…..
	Polytherapy	27.53	19(8.4)	0.89(0.26-2.92)	0.95
No seizure in the past 5 years	Monotherapy	27.29	24(10.6)	1.15(0.40-3.31)	0.96
	Polytherapy	23	4(1.8)	5.76(0.49-151.78)	0.13

Discussion

The goal of this study was to determine the prevalence of CAE in epileptic patients using MMSE. The results of the previous studies regarding the effects of seizures on higher cognitive functioning have been mixed.[23-25] In the present study, it was hypothesized that different epilepsy characteristics, sociodemographic features and AEDs treatment would adversely affect higher brain functions. As such, this study is the first of its kind in Ethiopia to screen the cognitive status of patients with seizure disorders, specifically using MMSE. MMSE.[26] is one of the most widely used cognitive screening scales.[27] but populations with low schooling level present a worse performance in this test.[28]

Several strategies have been proposed in order to minimize the effects of educational level in the interpretation of MMSE results, such as:

a. Adjustment of cut-off points according to years of education.[29-32]

b. The use of cut-off points based on the distribution of MMSE scores in the study population.[33] and

c. Transcultural adaptation.[34-36]

Different countries have used different approaches, for example, in Brazil the commonest approach being use of different cut-off points according to schooling level.[29-32] In Ethiopia (Butajira), there was only one community based normative study done so far, and it used also similar approach as the Brazilian studies, i.e., the use of different cut-off points according to the years of education.[37] However, unlike the Brazilian studies, the Ethiopian study didn't include individuals with educational level of less than five years.[37]

Accordingly, different authors have recommended different cutoff points.[29-32] Crum et al.[38] recommended a cutoff score: 23 for those with 5-8 years of education, 27 for those with 9-12 years of education, and 29 for college education. Based on the study done in Ethiopia, the MMSE findings according to the years of education were: 22 for those with 5-8 years of education, 24 for those with 9-12 years of education, and 26 for college education.[37] In the current study, the median MMSE scores were: 24 for those with primary education, 29 for those with 9-12 years of education, 29 for those with college education. These findings are closely comparable with the cut-off points suggested by Crum et al.[38] but different from the study done in Butajira.[37] One possible reason could be that more than two-fifth of individuals in the

study done in Butajira were non proficient in the test language, which doesn't seem to be the case in the current study.

Education seems the single most important determinant of MMSE scores.[37,39] According to a study done in Ethiopia, the median MMSE scores with respect to years of education were: 24 for 5-8 years of education; 27 for 9-12 years of education; and 28 for college education.[37] In consistent with the prior studies, in the current study too, it has been shown that the mean MMSE score increases as the schooling level increases. On the other hands, the Odds of having cognitive adverse effects tend to be higher in individuals with lower educational levels, and it is found to be statistically significant.

Not only educational level, but also gender, marital status, and age are also among the most important determinants of MMSE scores.[37,38] In this study, females had lower MMSE scores than males, and single marital status had higher mean MMSE scores, similar to the previous study done in Ethiopia.[37] The mean MMSE scores constantly decrease as an individual age increases, although it was not possible to trace the findings found to be statistically significant. In contrast to the current study as well as other prior studies, a normative community based study done in Butajira didn't found age as an important determinant of MMSE score.[37]

According to a study done in Butajira, the overall mean and median MMSE scores were, 24.93/25.82 and 25/26, respectively (using word reversal and serial seven, respectively). In the current study, the overall mean and median MMSE scores were 26.92 and 28, respectively (using either word reversal or serial seven, whichever they scored better). Both the mean and median were of higher values than the previous studies, which could possibly be due to the difference in the sociodemographic background between the two studies, the previous study being community based normative study.[37]

A younger age at seizure onset and longer disease duration correlate with reduced memory capacity.[40-43] Unlike the previous studies, early age at seizure onset didn't show significant difference from the other age ranges at which seizure started. Rather, patients with seizure onset at age between 10-19 years had lower Odds of having CAE (OR=0.16, P-value=0.00).

As the duration of uncontrolled seizures increase, the impact on CAE also increases.[42,44] In this study, the Odds ratio showed an increasing trend as the duration of seizure disorders increase. For example, those with duration of seizure disorder between 10-19

years were 1.07 times more likely to develop overt cognitive adverse outcomes, whereas those with duration of seizure disorder between 20-29 and 30+ are 1.23 times and 1.44 times more likely to develop overt cognitive adverse outcomes, respectively as compared with duration of seizure disorder less than ten years.

Similarly, increased seizure frequency is associated with significant cognitive impairments than individuals with fewerm seizure episodes.[23,45-48] In contrast with the previous studies, a frequent seizure episode was not associated with adverse cognitive outcomes. Rather, individuals with relatively good seizure control (seizure episode in the past 1-6 months) were found to have statistically significant association (OR=2.41; P-value=0.00).

The severity and patterns of CAE in epileptic patients is also dependant on the types of seizure disorder the patient has. GTC seizures (even more so if status epileptici also occur) are more likely to impair cognitive function than the other seizure types.[49,50] Herman et al.[15] suggested that individuals with MTL epilepsy display more severe cognitive deficits than patients diagnosed with epilepsy of the non-MTL type regardless of seizure laterality. This is partly due to an earlier age of onset in MTL epilepsy than the non-MTL epilepsy in addition to the hippocampal sclerosis. In our study, in contrast to the other studies, neither GTC seizures nor complex partial seizures were found to affect MMSE. Rather, focal with secondary generalized seizures showed statistically significant association with mean MMSE. This could be due to the underlying structural brain lesions, as focal seizures are usually symptomatic.

Patients with abnormal, but non-epileptiform EEG findings were close to two times as more likely to have adverse cognitive outcomes as those with normal EEG findings (OR=1.86). On the contrary to what was expected, those patients with epileptiform EEG findings had OR=0.49. This could be due to the small patients with epileptiform discharges (24 cases only) or over-interpretations of benign (or normal) EEG findings. In general, there was no significant difference between the different EEG findings and mean MMSE. Similarly, there was also no significant difference between the different brain neuroimaging findings in terms of the mean MMSE scores.

There were several studies which suggested that elderly patients with epilepsy and antiepileptic polytherapy showed greater cognitive impairment than those on monotherapy. And the initial drug section is usually based on factors other than risk of cognitive adverse outcomes. The CAE of AED monotherapy are generally not pronounced provided that anticonvulsant blood levels are within the standard therapeutic range. The risk of significant CAE increases with higher drug dosages and with polypharmacy. In our study, there was no statistically significant difference between the different monotherapies including phenobarbitone. The Odd's ratio of patients on the different mono-therapies was less than one compared to those on phenobarbitone monotherapy, and it was lowest for those on valproate monotherapy (OR=0.5). Also, the mean MMSE of patients on monotherapy (27.13) was better than that of those on polytherapy (26.38), but there was no statistically significant difference between the means in monotherapy and polytherapy was seen. Similarly, although the Odd's ratio increases as the duration of AEDs treatment increases, there was no significant association seen.

In general, MMSE remains the most commonly used clinical tool to screen the cognitive status of patients. But it also has a drawback of low sensitivity in detecting covert cognitive impairment. The other important point is different authors used different cutoff points. Therefore, it is important to do a detail neuropsychological test in patients with abnormal MMSE.

Conclusion

Limitations

Low sensitivity of the MMSE

Absence of standardized MMSE for individuals with less than five years of education.

Conclusion and recommendation

MMSE remains the most commonly used screening tool in the clinical settings for patients with suspected cognitive impairment. MMSE by no means can substitute formal neuropsychological test batteries. Despite all its limitations and drawbacks, this study has shown that educational status is the single most important determinant of mean MMSE scores, although we need to have standardized MMSE for individuals with less than five years of education. Therefore, a detailed and formal neuropsychological test is needed for highly educated individuals with mild cognitive impairments as well as in patients with abnormal MMSE findings.

Source of budget disclosure

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Conflicts of interst

None.

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