FREQUENCY AND PROGNOSTIC SIGNIFICANCE OF ABNORMAL ELECTROENCEPHALOGRAPHIC FINDINGS IN ACUTE STROKE PATIENTS

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ABSTRACT

Electroencephalography (EEG)are useful in detecting changes in neuronal integrity and predicting outcome in acute stroke. Thus, the study hope to determine the frequency and prognostic importance of abnormal EEG wave changes in acute stroke. Adult patients with acute stroke who met the inclusion criteria were studied. Stroke severity, functional outcome was determined using the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin scale (MRS) respectively which were assessed on admission, 72hours, 7days, 14days and 30days after stroke. The proportion of stroke patients with slow frequencies on EEG was 63.3% compared to 16.2% in controls (p0.008). The percentage of Alpha wave, Beta wave, Delta wave, Theta wave, and Intermixed wave respectively among cases were 24.1%, 12.7%, 22.8%, 21.52%, and 18.9% respectively compared to 66.3%, 17.5%, 5.0%, 3.8%, and 7.5% respectively among the controls (p0.008). The percentage of epileptiform discharges seen among stroke patients was 31.6% compared to 11.2% in controls. Epileptiform discharge was seen 31.6%, 62.7%, 57.9%, and 44.4% respectively at presentation, day 3, day 7, day 14, and day 30 respectively in stroke patients. Presence of sharps, RAWOD, asymmetry and slowing respectively at day 14 (p0.014, 0.03, 0.02, 0.014) and at day 30 (p0.049, 0.03, 0.07, 0.034) were associated with poor outcome among those with NIHSS >20. Among stroke patients with NIHSS >20, there was association between good outcome and occurrence of Alpha rhythm within two weeks of acute stroke. EEGwaves changes are useful in predicting functional outcome in acute stroke.

Keywords: prognostic, significance, abnormal electroencephalographic, acute stroke, patients.

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Introduction

Stroke is one of the leading causes of death and disability in the adults. (Connor *et al.,* 2007; Owolabi *et al.,* 2015) Early detection, continuous monitoring of neurophysiological activities by electroencephalography (EEG), appropriate and aggressive intervention are essential in reducing the unacceptably increasing mortality rate among acute stroke patient in our environment. (Bermeo-Ovalle, 2019; Fung *et al.,* 2019; Poothrikovil *et al.,* 2015) The current incidence of stroke is 24.3 (95% CI: 11.9 - 36.0) per 1000 person year and current mortality rate is between 35-40% among stroke patients in Nigeria. (Owolabi *et al.,* 2018). The use of EEG can revealed important patterns and wave changes that are valuable in predicting functional outcome due to its ability to detect alteration and changes in cerebral metabolism and blood flow within few seconds to minutes of stroke onset. (Yang *et al.,* 2018)There are specific patterns on EEG such as absence of delta, occurrence of fast frequencies, intermittent slow delta and theta rhythm are correlates of good outcome in acute stroke.(Foreman & Claassen, 2012; Schneider & Jordan, 2005) However, Periodic Lateralized Epileptiform Discharge (PLEDs), absence of alpha rhythm, prominent polymorphic delta slowing, Regional Attenuation Without Delta (RAWOD) are abnormalities on EEG in acute stroke that are correlates of poor outcome.(Schneider & Jordan, 2005) Furthermore, Epileptiform activity and other abnormalities demonstrable on EEG can predicts Post Stroke Seizures (PSS) and Post Stoke Epilepsy (PSE). (Bentes *et al.,* 2018; Tanaka *et al.,* 2015)

In a study by Bentes and colleagues, among anterior circulation stroke patient which is aimed at identifying the predictors of post stroke epilepsy, it was revealed that an early post stroke EEG asymmetry and interictal epileptiform activity predicts epilepsy in the first year of stroke, independent of clinical and imaging findings. (Bentes *et al.,* 2018)

Generally, the risk of seizures is common after haemorrhagic stroke compared to ischaemic stroke. (Galovic *et al.,* 2018; Sarfo *et al.,* 2021) However among ischaemic stroke cohorts, those with severe disability and cortical infarct are more likely to have seizures after stroke.(Jungehulsing *et al.,* 2013; Lossius *et al.,* 2005) Despite growing evidences supporting EEG as a reliable marker of decline in neuronal integrity in acute stroke and its role in predicting functional outcome, there are little or no data on role of EEG in acute stroke in Nigeria. We therefore set out to identify and determine the frequency and prognostic value of EEG changes in acute stroke.

METHODOLOGY

Assessment of Subjects

This is a case control study which took place between 24/4/2014 and 23/4/2015 with Institution Renew Board (IRB) assigned number of UI/EC/14/0008. Stroke was confirmed with cranial Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI).The study also involved age matched controls with no stroke as evidence by clinical findings on examination. Furthermore, background history of epilepsy, use of Antiepileptic Drugs(AED), documented clinical and/or radiological findings of intracranial pathology were also part of exclusion criteria for controls Consecutive and consenting stroke patients who presented to the University College Hospital(UCH), Ibadan, Oyo State, Nigeria and met the inclusion criteria were recruited. All cases had their cranial imaging done within 72 hours of stroke onset.

The phenotyping of ischaemic stroke was done using Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification. The National Institutes of Health Stroke Scale (NIHSS) was used to determine the stroke severity at day3, day7, day 14, and day30 post stroke. The NIHSS was subdivided into mild, moderate, moderate to severe, and severe stroke respectively, using the score intervals of 1-4, 5-15, 16-20, and 21-42 respectively. The Modifying Rankin Scale (MRS) was used to assess functional outcome at day 14 and day 30. Good outcome was define as MRS 1, 2, 3, while poor outcome was define as MRS 4, 5, 6.

EEG Acquisition and Interpretation

The standard international 10-20 electrodes placement method was used to acquire EEG in all cases at presentation and daily in first week, Day14, Day30 and only at presentation in controls. Avoidance of hyperventilation was ensured to prevent hypocarbia and cerebral vasoconstriction. All participants had standard sensitivity recording set at 100uv/cm which was adjusted as needed to 70uv/cm, 30uv/cm, 15uv/cm to improve on the amplitude. In other to reduce the effect of interference, the filter was set from 70uv/cm to 30uv/cm and 15uv/cm as needed for arises. The available standard international criteria were used in classifying and reporting EEG recording by two different neurologists who are blinded to the clinical parameters of the patients.

Sample Size Determination

The peacock formula was used to derive the minimum sample size of 67 each for cases and control and 80 each for cases and control after factoring 10% attrition rate.The standard normal deviate at 5% level of significance and that of corresponding to 80% was set 1.96% and 0.84% respectively. Furthermore, a value of 50% and 10% was used as prevalence of abnormal EEG in acute stroke patients and normal subjects respectively

Data Analysis

Cleaning of data was done after entering into Microsoft Excel before transferring into the Statistical Package for Social Science version 22 for analysis. Association between stroke severity, stroke type, EEG and stroke characteristic was assessed using Pearson Chi-Square Test. The difference in frequency of dyslipidaemia, diabetes, ischaemic stroke, poor and good outcome was assessed using Pearson Chi-Square Test. Furthermore, association between temperature, blood pressure, age, EEG characteristics, and size of stroke was determined by Independent Student T-test. Clinical and socio-demographic characteristics that were obtained from the participants were presented as frequencies if they are categorical variables and as mean (standard deviation) if they are quantitative variables. The level of statistical significance was set as p-value <0.05.

Ethical Consideration

The Institutional Review Board of University of

Table 1: Socio-demographic characteristics of participants

	STROKE PATIENTS N= 80	CONTROLS N= 80	STATISTICS	P-VALUE
Age (Mean±SD)	57.6 ± 14.6	54.8 ± 12.4	1.29	0.198
Sex differences (N, %)				
Male	40(50.0%)	40(50.0%)	0.01	0.936
Female	40(50.0%)	40(50.0%)		
Level of Education attend (N, %)				
No formal education	18(22.5)	2(2.5)		
Primary	10(16.9)	13(16.7)	20.81	<0.001*
Secondary	32(27.1)	37(47.4)		
Tertiary	20(33.9)	28(35.9)		
Marital Status (N, %)				
Not Married	49(70.0)	58(82.9)		
Married	21(30.0)	12(17.14)		0.003*
Divorced	3(3.75)	4(5.0)		
Widows	7(8.75)	6(7.5)		

***statistically significant**

Time trend in background EEG from baseline to 30days

The proportion of stroke patients with slow frequencies on EEG was 63.3% compared to a proportion of 16.2% in controls and this was statistically significant (p0.008). The percentage of Alpha wave, Beta wave, Delta wave, Theta wave, and Intermixed wave respectively among cases group were 24.1%, 12.7%, 22.8%, 21.52%, and 18.9% respectively compared to 66.3%, 17.5%, 5.0%, 3.8%, and 7.5% respectively in the control group (p0.008) at presentation (See Table 2). In the course of 30 days monitoring of stroke cohorts recruited, while Alpha and Beta waves were on increase, Delta and Theta rhythm decreased. (See Figure 1).

TABLE 2: BASELINE BACKGROUND EEG WAVE CHANGES IN STROKE PATIENTS AND CONTROLS

EEG Background	Range	Stroke (n=80)N(%)	No stroke (n=80)N(%)	p-Value
Beta rhythm	(> 12HZ)	10(12.7)	14(17.5)	
Alpha rhythm	(8- 12HZ)	19(24.1)	53(66.3)	
Theta rhythm	(4- 7HZ)	17(21.5)	3(3.8)	
Delta rhythm	(<4HZ)	18(22.8)	4(5.0)	0.008*
INTERMIXED	-	15(18.9)	6(7.5	
Frequency	Fast frequency	51(63.3)	13(16.2)	0.001*
	Slow frequency	29(36.7)	67(83.8)	
Epileptiform pattern	Yes	25(31.6)	9(11.2)	0.041*
	No	54(68.4)	71(88.8)	

*Attain level of **statistically significant**
Intermixed (Alpha rhythm/Delta rhythm) as observed in cases 3(5.7)
Intermixed (Delta rhythm/Theta rhythm) as observed in cases 12(17.1)
Intermixed (Delta rhythm/Theta rhythm) as observed in controls 6(12.9)

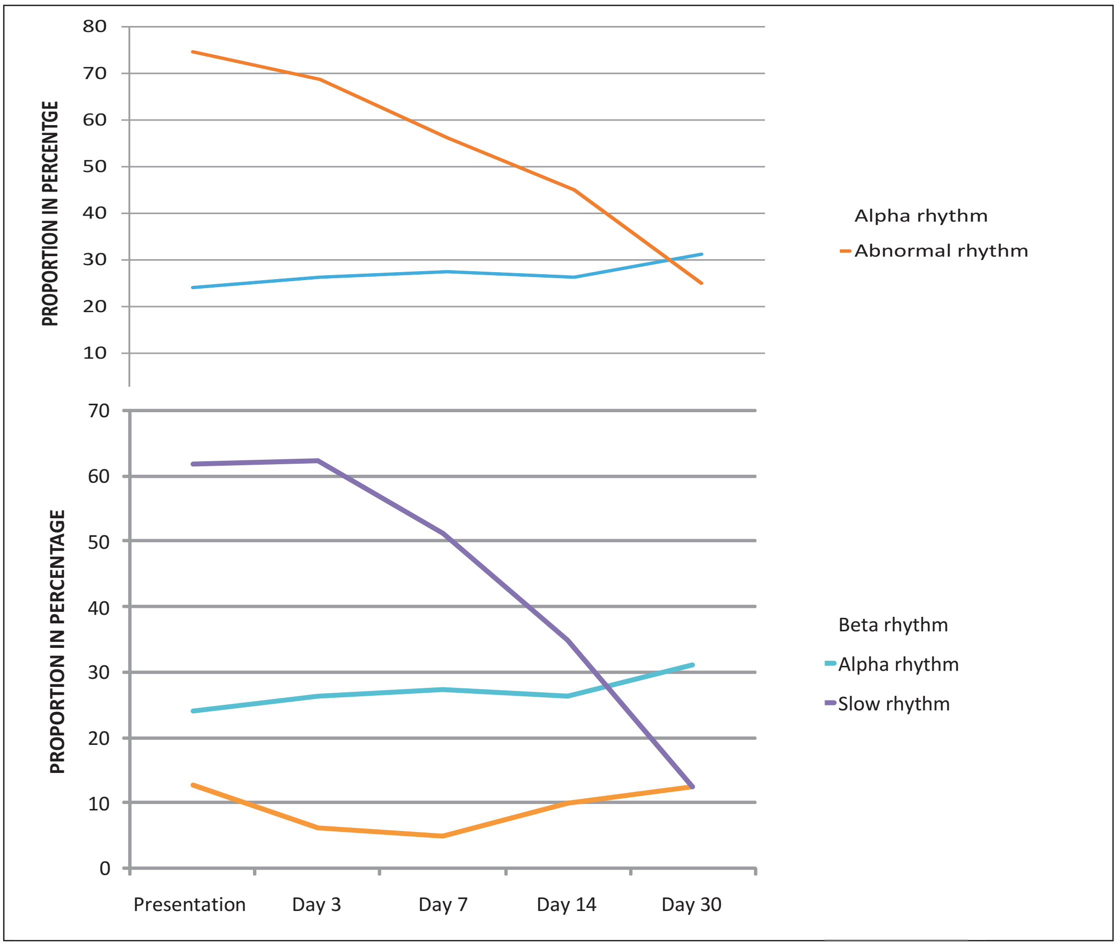
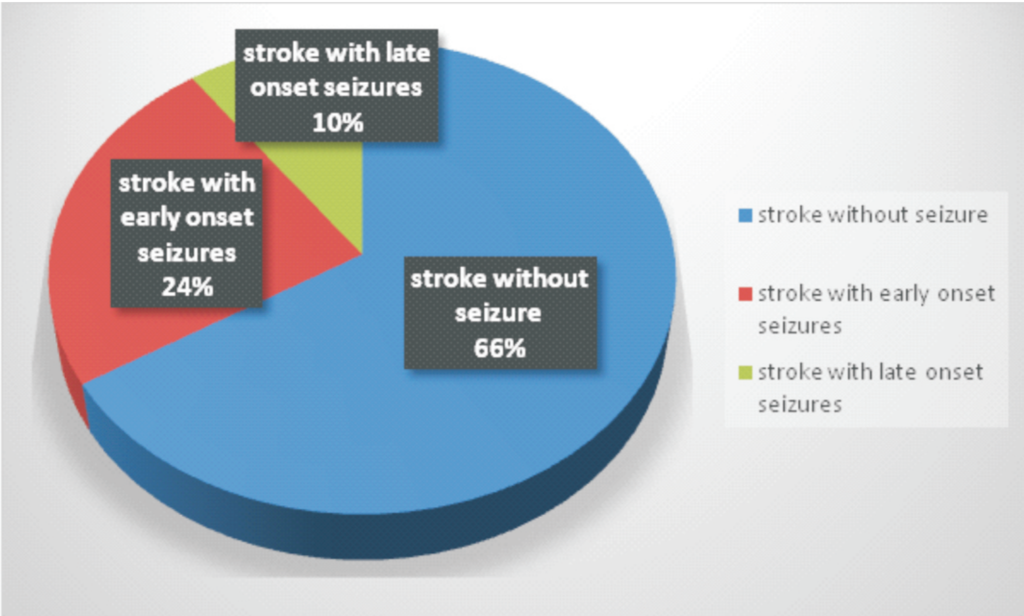


Figure 1: showing background EEG wave changes in acute stroke

Time trend in seizures and epileptiform pattern from baseline to 30 days

The percentage of epileptiform discharges seen among stroke patients was 31.6% compared to 11.2% in controls. Epileptiform discharge was seen 31.6%, 62.7%, 57.9%, and 44.4% respectively at presentation, day 3, day 7, day 14, and day 30 respectively in stroke patients. Among stroke patients that were recruited, 66%, 24%, and 10% respectively are without seizures, early onset seizures, and late onset seizures respectively. (See Figure 2). There were more epileptiform pattern on EEG compared to number of seizures detected among cases. (See Figure 3).



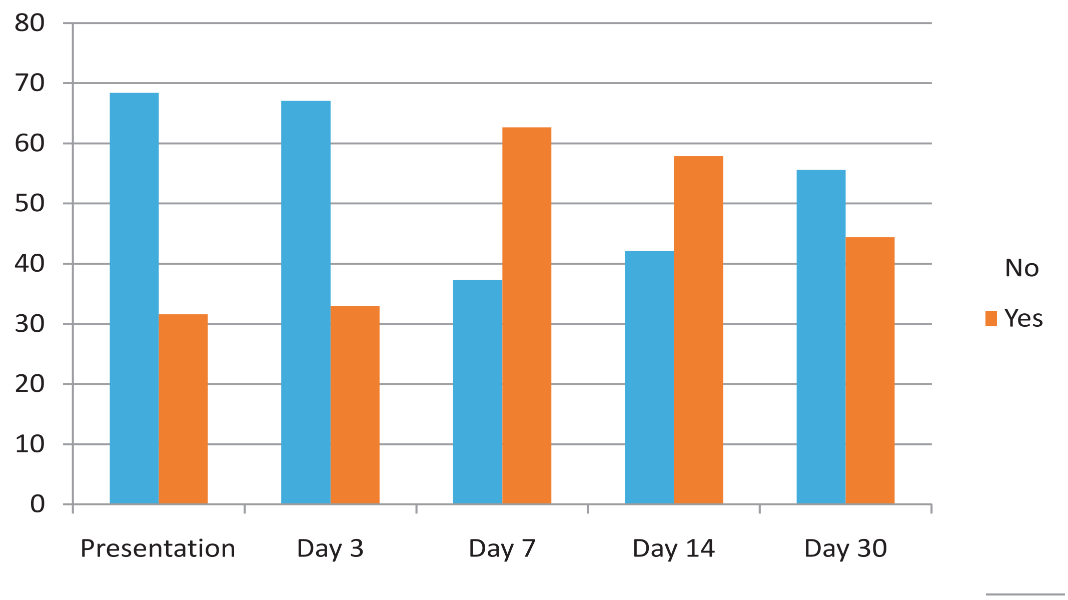


Figure 2: Time trend of epileptiform pattern and seizures

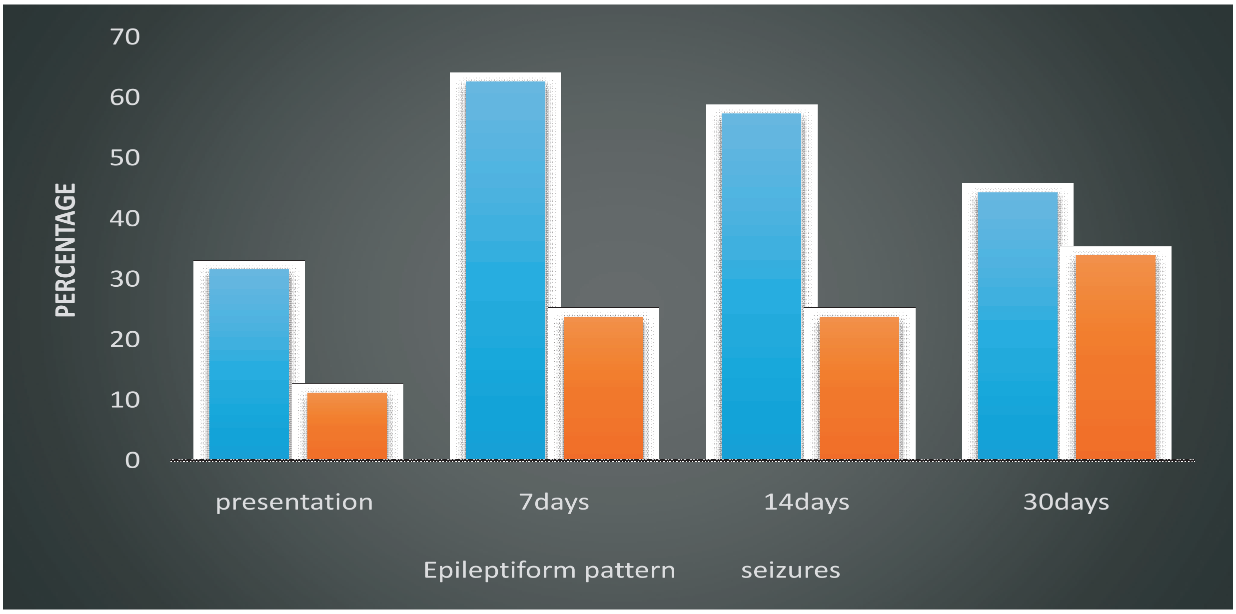


Figure3: Comparison of seizures and epileptiform pattern in acute stroke

3.4 Association between EEG waves changes and outcome among cases with NIHSS score ≤20 in acute stroke

Presence of PLED, Sharps, RAWOD and asymmetry (p0.025, 0.01, 0.01,0.07) at day 14 and (p 0.003, 0.001, 0.005, 0.010) at day 30 respectively were associated with poor outcome among participant NIHSS ≤ 20 during acute stroke. While Alpha was associated good outcome among cases with NIHSS ≤ 20 (0.010) within two weeks of acute stroke . (See Table 3)

Association between EEG wave changes and outcome among cases with NIHSS score >20 in acute stroke

Presence of sharps, RAWOD, asymmetry and slowing respectively at day 14 (p0.014, 0.03, 0.02, 0.014) and at day 30 (p0.049, 0.03, 0.07, 0.034) were associated with poor outcome among those with NIHSS >20. There was no association between the occurrence of PLED and poor outcome in stroke patients with NIHSS >20. Among stroke patients with NIHSS >20, there was association between good outcome and occurrence of Alpha rhythm within two weeks of acute stroke. (See Table3)

Figure 1: showing background EEG wave changes in acute stroke

Table 3: showing association between NIHSS score, EEG and outcome at day 14 and 30

Variables		NIHSS≤20 Good outcome	NIHSS≤20 Poor outcome	PVALUE	NIHSS > 20 Good outcome	NIHSS > 20 Poor outcome	P-value	Day
A.Background	Alpha	14(66.7)	2(14.29)	0.010*	1(4.8)	3(14.29)	0.049*	14
	OTHER	18(72.0)	7(28.0)		3(12.0)	22(88.0)		14
B. Special pattern	FIRDA	23 (62.16)	3(8.11)	0.230	0 (0.0)	11(29.73)	0.460	14
	PLED	2 (28.57)	3(42.86)	0.025*	0(0.0)	2(28.57)	0.090	14
	RAWOD	1 (10.0)	3 (30.0)	0.010*	0(0.0)	6(60.0)	0.030*	14
	Assymetry	4(12.9)	7(22.58)	0.007*	1(3.23)	19(61.30)	0.020*	14
	Sharps	11(13.9)	42(53.2)	0.010*	2(2.53)	24(30.38)	0.014*	14
	Slowing	32(43.84)	14(19.18)	0.001*	1 (1.37)	26(35.62)	0.014*	14
C. Background	Alpha	11(64.7)	2(11.8)	0.260	1(5.9)	3(17.7)	0.450	30
	Others	28 (75.7)	9(24.3)		3(13.0)	23(86.9)		30
	FIRDA	25(34.2)	1(2.7)	0.711	1(2.70)	10(27.02)	0.411	30
	PLED	1(16.7)	3(50.0)	0.003*	0(0.0)	2(33.3)	0.961	30
	RAWOD	1(10.0)	3(30.0)	0.010*	0(0.0)	6(60.0)	0.030*	30
	Assymetry	4(12.1)	9(27.3)	0.005*	1(3.0)	19(57.6)	0.007*	30
	Sharps	5(5.9)	38(55.9)	0.001*	3(4.4)	23(33.9)	0.049*	30
	Slowing	41(56.9)	4(5.6)	0.000*	3(4.2)	24(33.3)	0.034*	30

FIRDA= Frontal Intermittent Rhythmic Discharge PLED = Periodic Lateralizing Epileptiform Discharge
RAWOOD = Regional Attenuation Without Delta *= statistically significant

Discussion

Findings from this study revealed that epileptiform discharges were 3 times commoner in stroke cohorts compared to controls and among stroke cohort there were higher epileptiform discharges on EEG compared to occurrence of clinical seizures. Furthermore, consistently, regardless of status of stroke severity, presence of sharps, RAWOOD, and asymmetry on EEG were associated with poor outcome. While slowing and PLED pattern were severity dependent in predicting poor outcome in acute stroke. These above findings are keeping with that of Bentes and colleague that reported underestimation of PSE due to inadequate neurophysiological evaluation.(Bentes *et al.,* 2017).

Emergency and routine EEG monitoring should be part of routine management of stroke patient as this can improves outcome in acute stroke.(Bermeo-Ovalle, 2019) For instance, the occurrence of Alpha rhythm on EEG has been associated with good outcome and less severity in stroke management.(Bermeo-Ovalle, 2019) Neurophysiological monitoring is underutilized but important field in our environment which can aid in diagnostic and prognostic role of EEG in acute stroke.(Foreman & Claassen, 2012; Poothrikovil *et al.,* 2015) The finding of threefold epileptiform activities in cases compared to control and finding of epileptiform pattern more than clinical seizures among cases poses question about need for prophylaxis in PSE or at best need for anti-epileptogenic drugs. Multiple insults to the brain from pathological event life, stroke syndrome, neuroplastic processes, trauma to the brain can induce epileptogenesis, after this initial insult, epileptogenesis causes. (Clossen& Reddy, 2017; Yang *et al.,* 2018) Epileptogenesis is define as a process by which brain undergoes alteration after initial insults to make it highly excitable and susceptible to recurrence seizures.(Pitkänen *et al.,* 2015; Reddy *et al.,* 2017; Yang *et al*., 2018)Neurogliosis, neuronal loss, sprouting of mossy fibre, cellular reorganization, imbalance homeostasis and cellular reorganization are some of the various alterations that occurs in converting a normal brain to an epileptogenic brain.(Di Maio, 2014; Younus & Reddy, 2017) A common feature of PSE and other epileptic disorders is a paroxysmal excitatory activity due imbalance between excitatory and inhibitory activities of neurotransmitter and ionic channels which has been central to the investigation of epileptogenic cell mechanisms and are reliable markers of epileptogenic condition.(Avanzini& Franceschetti, 2003; Clossen & Reddy, 2017; Di Maio, 2014) Predictors of PSE in the first year post stroke are asymmetry and epileptiform discharges between seizure attacks on EEG. While periodic abnormalities predict epileptiform activity during hospital stays.(Bentes *et al.,* 2018) In agreement with the findings by Bentes we demonstrated that presence of PLED, RAWOOD, slowing and asymmetry were associated with poor outcome in acute stroke. Furthermore, alpha rhythm was associated good outcome regardless of stroke severity within two weeks of acute stroke.

The good prognostic value of alpha rhythm in acute stroke can be linked to less severity and adequate intervention which is associated with return of good Cerebral Blood Flow (CBF) while slow frequencies like delta and theta rhythm are associated with decreased CBF. A 10% focal epileptiform discharge with 6% as PLED was seen in a previous study among stroke patients who had their EEG done within 24 hours of admission. The difference in this findings can be attributed to the smaller sample size in this study compare to the previous study were sample size was relatively larger.

In a previous study aimed at determining the usefulness of EEG among stroke cohorts with seizures in the acute stroke revealed that 90%, 22.5% respectively were focal slowing and inter-epileptiform discharge respectively.(Niedzielska et al., 2001) However, finding from this study reveal that EEG slowing was 61.9%, 62.4%, 51.2%, 35%, 12.5% among stroke patients respectively at presentation, day 3, day 7, day 14, and day 30 respectively. This findings is best explained by improved reperfusion of brain tissues with increased CBF following recovery from stroke. Findings from this study shows that epileptiform discharge was seen in 31.6%, 32.9%, 62.7%, 57.9%, and 44.4% among stroke patients respectively at presentation, day 3, day 7, day 14, and day 30 respectively. Furthermore, findings from this study reveals that focal abnormalities was seen in 15.2%, 17.56%, 50.75%, 47.37%, and 35.6% among stroke patients respectively at presentation, day 3, day 7, day 14, and day 30 respectively. The burden that is associated with post stroke seizure is substantial and contribute to unfavourable outcome in stroke management. (Hassani *et al.,* 2020; Jungehulsing *et al.,* 2013; Tanaka *et al.,* 2015) Furthermore, multiple and long term EEG acquisition studies improves the quality of EEG in detecting epileptiform discharges.(Bentes *et al.,* 2017; Foreman & Claassen, 2012; Poothrikovil *et al.,* 2015) In the course of 30 days monitoring of stroke cohorts recruited, while Alpha and Beta waves were on increase, Delta and Theta rhythm decreased. This finding can be explained by the plausible improved perfusion of brain tissue following intervention and subsequent recovery in acute stroke because EEG findings are highly related to changes in CBF. Ideally, CBF decreases to values like 25-35ml/100g/min when fast readings are lost. Subsequently, the proportion of slower reading increases gradually at CBF of around 17-18ml/100g/min.(Bermeo-Ovalle, 2019; Foreman & Claassen, 2012) At this crucial Ischaemic threshold, neuronal loss and said death occurs. Furthermore, at CBF of below 10-12ml/100g/min, EEG becomes flat and irreversible cell damage occurs.(Bermeo-Ovalle, 2019; Foreman & Claassen, 2012; Fung *et al.,* 2019) It is important to know that with continued perfusion and reperfusion, alpha and beta rhythm gradually resurfaces as observed in this study. The seizure occurrence of 11.25% and 23.8% respectively at presentation and 7 days suggest that early onset seizures are relatively common. Early onset seizures are seizures that occur within first week of stroke while late onset seizures occurs after first week of stroke.(Fisher *et al.,* 2014; Tanaka & Ihara, 2017)

There is a need for an increased suspicion towards identifying and treating of PSS by clinician in order to reduce its negative effect on stroke outcome and unacceptable burden. Even though international guideline from developed countries do not support use of AED in primary prevention of PSS there are increasing need to further explore the prophylactic role of AED in acute stroke management.

Generally, the incidence of epilepsy after stroke in elderly varies widely, from 3% to 45% for late seizures and 2-33% for PSE.(Camilo & Goldstein, 2004; Jungehulsing *et al.,* 2013; Tanaka *et al.,* 2015)A previous study aimed at determining incidence of epilepsy and unprovoked seizures between 1935 and 1984 showed that cerebrovascular disease (CVD) accounts for 11% of epilepsy.(Hauser *et al.,* 1993; Myint *et al.,* 2006) These findings perhaps highlight the role and need for emergency and continuous EEG monitoring in acute stroke. It further underscore the need for possible AED prophylaxis to reduce the increasing burden and unsatisfactory effect of PSS especially in management of acute stroke.

Conclusion

We demonstrated that in acute phase of stroke management, there specific EEG patterns that can predict functional outcome and severity. Furthermore, there are frequency of occurrence of epileptiform discharge on EEG were more than the rate of occurrence of clinical seizures. These findings underscore the fact that subclinical seizures are under-estimated and continuous/ emergency EEG are underutilized in management of acute stroke.

Limitations

We used only qualitative EEG techniques in this study because of non-availability of quantitative techniques, nevertheless the EEG acquisition was done multiple times during course of acute stoke. Furthermore because this study is strictly within 30days of stroke onset, we could not ascertain relationship between late onset seizures and EEG findings.

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