

# First Episode of Unprovoked Seizure- Clinical Profile, Etiological Evaluation and Outcome Study On Follow Up

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**Abstract- Aim and objective:** To study the clinical profile, evaluation for etiological diagnosis and outcome on follow up at 3 and 6 months among patients above 14 years of age who presented with first episode of unprovoked seizure.

**Materials and methods:** The study was an observational and prospective cohort study, conducted in Gauhati Medical College and Hospital, Guwahati. The study period was from December 2019 to November 2021. Data collection included demographics, seizure type, investigations including EEG and brain imaging. Follow up was done for 6 months. Seizure recurrence, drug compliance and outcome among patients treated with anti seizure medication and patients who were deferred for treatment was studied.

**Results:** A total of 70 patients were included in the study. 41(58.6%) were male and 29(41.4%) were female with a M:F ratio of 1.41:1. The mean age was 36.63 years (Median = 31 std±19.606). GTC seizure was the most common type of seizure, seen in 55.7%(N=39). EEG abnormality was found in 27.1% (N=19). Brain imaging abnormality was found in 50% (N=35). Anti seizure medication was started in 77% (N= 54) in the first visit whereas 23% (N=16) were followed up without medication. Seizure recurrence was seen in 28.6% (N=20) during the first three months of follow up, whereas seizure recurrence was seen in 21.4% (N=15) between 3-6 months of follow up. 24.1% (N=13) defaulted treatment during the 6 months follow up period. 47.1% (N=33) were seizure free on treatment at 3 months whereas 65.7% (N=46) were seizure free on treatment at 6 months.

**Summary and Conclusion:** Generalised tonic clonic seizure is the most common presentation of seizure in patients >14 yrs of age. Symptomatic seizure account for 50% of cases of which stroke related seizure was the most common etiology. Recurrence of seizure was seen 21.4 % - 28.6% during follow up period of 6 months. Treatment with anti seizure medication improved the short term outcome.

**Index Terms-** first episode of seizure, unprovoked seizure, recurrence of first seizure, outcome of first seizure

## I. INTRODUCTION

Seizures affect an estimated 8-10% of the population over a lifetime[1]. Seizures account for 1-2% of all emergency

department visits, and one-quarter of which constitute a first seizure [2]. The goal in evaluating a patient's first seizure is to identify a treatable cause, the nature of the underlying brain pathology and to evaluate the likelihood of recurrence of seizure in the future and to decide for appropriate anti seizure medication(ASM). The clinical factors associated with an increased risk for seizure recurrence after a first unprovoked seizure include- epileptiform discharges on EEG, remote symptomatic cause on neuro-imaging, an abnormal neurologic examination and a nocturnal seizure[3]. Each of these factors has been associated with an approximately 2- to 2.5-fold increased risk for seizure recurrence<sup>3</sup>. Other less well established risk for recurrence of an unprovoked seizure include a positive family history, multiple seizures within a day or status epilepticus at presentation and history of prior febrile seizures. Most studies have shown that approximately one third of patients with single seizure will experience a recurrence, highest risk of which is during the first 2 years.[4]. The preference to initiate an antiseizure medication differs from center to center and also depends on the choice of the patient [4].

Though there are number of studies on the incidence and prevalence of epilepsy in India, studies on first episode of seizure in adults, the recurrence and outcome of first seizure on follow up are few in India [5][6].

This study was being undertaken to evaluate the profile of the first episode of seizure, the influence of various factors on the recurrence of a first seizure and the outcome at 3 and 6 months among the population of the North East India.

## II. MATERIALS AND METHODS

The study was a hospital based prospective observational cohort study, which included a total of 70 patients who are >14yrs of age, presenting with a first episode of seizure to Gauhati Medical College and Hospital, Guwahati, Assam in the North East India.

Exclusion criteria included:

1. History of seizure in the past

2. Multiple seizures at presentation
3. Patients presenting with transient or paroxysmal neurological events like syncope, TIA, Migraine, Panic attacks, Psychogenic non-epileptic seizures, transient global amnesia and paroxysmal movement disorder
4. Any patient who presented with seizures with an obvious symptomatic cause that include- metabolic disorders, seizure associated with meningitis or encephalitis, seizures due to structural brain injury- including a previously diagnosed brain tumor, recent head injury (6 months) and a history of neuro-surgical intervention in the past.
5. First seizure during pregnancy or peripartum period
6. Age <14 yrs

### III. STATISTICAL METHOD

Chi square test or Fishers exact test is used to evaluate association between categorical variables. Data were analyzed using SPSS version 21. A p value less than 0.05 is considered as statistically significant at 5% level of significance.

### IV. METHODOLOGY

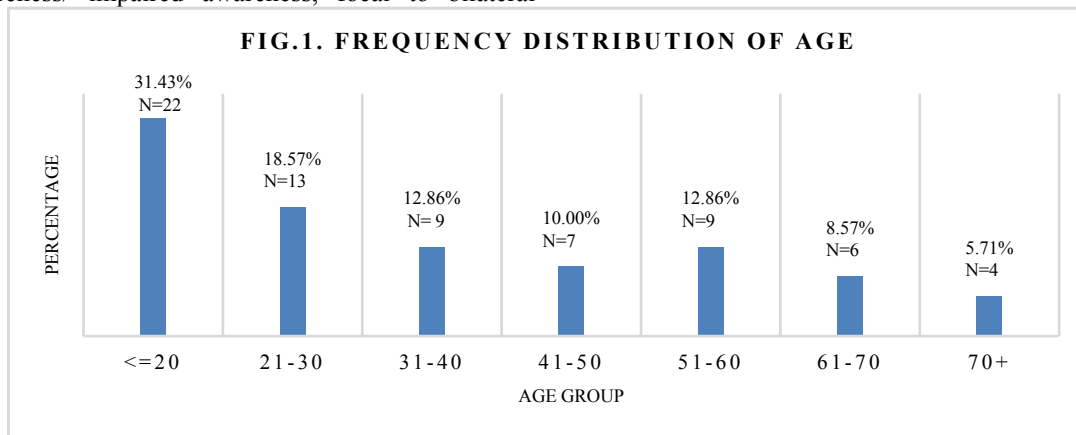
A detailed history from either the patient or the family member or a bystander was taken to diagnose a seizure and to rule out seizure mimics. Seizure classification was based on the 2017 ILAE classification of seizures as - focal onset with preserved awareness/ impaired awareness, focal to bilateral

tonic-clonic (BTC), generalized onset- generalised tonic clonic (GTC), absence or myoclonic and unknown onset seizures [7]. Evaluation of risk factors for seizure in the past was done with regard to relevant medical history, family history and previous medications. EEG and brain imaging with either CT scan or MRI was done in all patients. MRI was the preferred method but CT scan was performed for some patients due to financial constraints as imaging was not free of cost in our center.

Patients were started on ASM if the patient and their family chose/agreed to start ASM after discussing the risk and benefit of starting treatment. During follow up, medication was adjusted depending on the recurrence of seizure and the adverse effect of ASM if any. Patients who were not started on ASM in the first visit were given ASM on follow up if there was a recurrence of seizure. The outcome of seizure was evaluated at 3 months and 6 months.

### V. RESULTS AND OBSERVATIONS

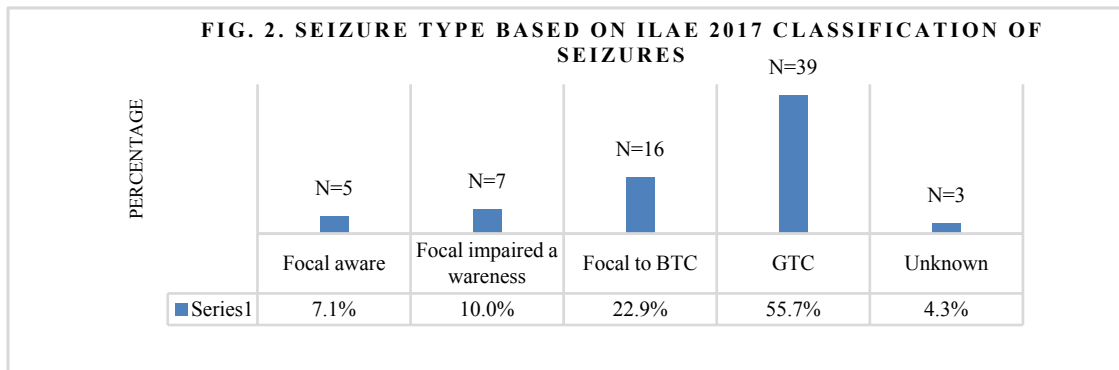
Seventy patients were included in the study, out of which 41(58.6%) were male and 29(41.4%) were female. The male to female ratio was 1.41:1. The median time to seek medical attention was  $2.0 \pm 2.17$  days. The mean age was 36.63 years, (median= $31 \pm 19.606$ ). Minimum age was 15 years and maximum age was 85 years. Patients of less than 20 yrs age group constituted 31.4% (N=22) and the study constituted a relatively younger population as only 10 patients (14.3%) were above 60 years of age. (Refer FIG 1.)



One-third (30%,N=21) had history of previously diagnosed systemic illness, of which hypertension (21.4%, N=15) was the most common. Only 7.1% (N=5) had a history of epilepsy in their family. Seizure was nocturnal in 11.4% (N= 8). Aura was reported by 18.6% (N=13).

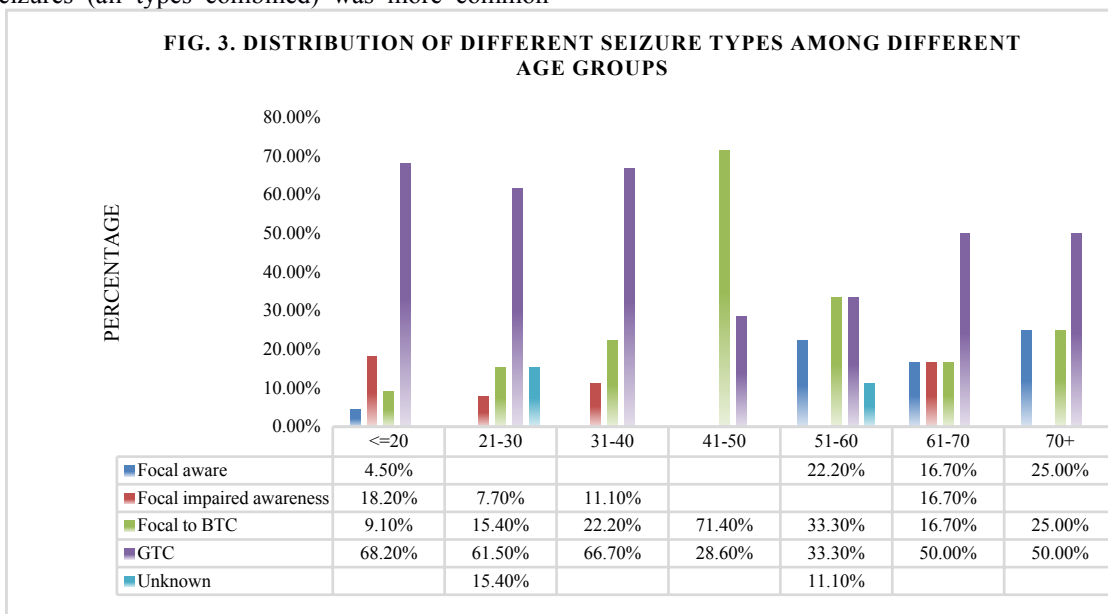
In this study, GTC seizure was the most common type of seizure, seen in 55.7%(N=39). Among the focal onset seizure,

focal to BTC was the most common type, seen in 22.9%(N=16), focal with impaired awareness and focal with preserved awareness seizure were seen in 10%(N=7) and 7%(N=5) respectively. Combining the subtypes of focal onset seizure, focal onset seizure was seen in 40% (N=28) (Refer FIG 2.). None had myoclonic or absence seizure.



GTC was the most common seizure observed in all the different age groups except for the 41-50 yrs age group where focal to BTC was more common than GTC. Above the age of 40 years, focal seizures (all types combined) was more common

than GTC seizure whereas GTC was more common than focal seizure in less than 40 years of age. (Refer FIG.3.)

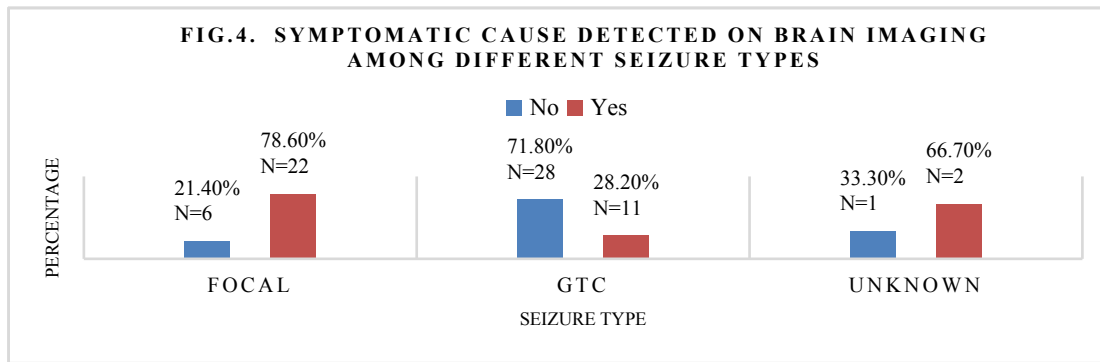


Of the 70 patients, 54.3% (N=38) had tongue bite, 14.3% (N=10) had urine incontinence, post ictal state was seen in 75.7% (N=53), and 20% (N=14) had a neurological deficit at presentation.

All patients underwent EEG test on their first visit/admission. EEG abnormality was seen in 27.1% (N=19). The abnormal EEG detected were focal epileptiform discharges in eight patients, generalized discharges in three patients, focal slowing in five patients and generalized slowing in three patients.

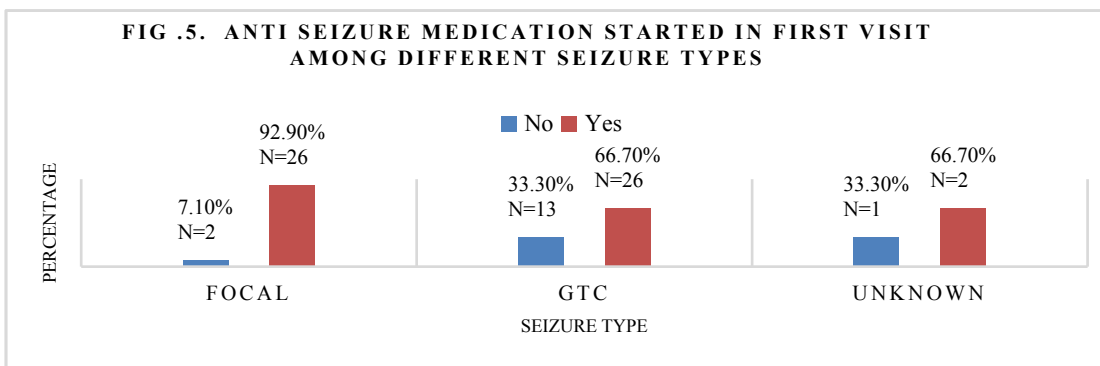
All patients included in the study underwent brain imaging by either MRI or CT scan. 75.7% (N=53) underwent MRI study and 24.3% (N=17) underwent CT brain imaging. 50% (N=35) had symptomatic cause detected with either of the imaging method

used. The most common symptomatic cause detected was stroke (acute and subacute) in seen in 15.7% (N=11). Seizure was apparently unprovoked in these patients. In this subset of stroke patients, hemorrhagic stroke was seen in five patients (all lobar hemorrhages), ischemic stroke in four patients, venous thrombosis in two patients. Post stroke encephalomalacia and gliosis accounted for 12.9% (N=9), therefore stroke related seizures accounted for 28.6% (N=20). The other etiology of symptomatic seizure were granulomatous lesions in 7.1% (N=5), tumor in 8.6% (N=6), and post traumatic encephalomalacia in 4.3% (N=3) and abscess in 1.4% (N=1). The incidence of symptomatic cause detected on brain imaging was highest for focal onset (76.8%, N=22) as compared to those of unknown onset (66.7%, N=2) and GTC seizure (28.2%, N=11). (Refer FIG. 4.)



In the first visit, 77% (N=54) were started on ASM whereas 23% (N=16) were deferred ASM. Higher number of focal onset seizure (92.9%, N=26) were started on ASM whereas only 66.7%

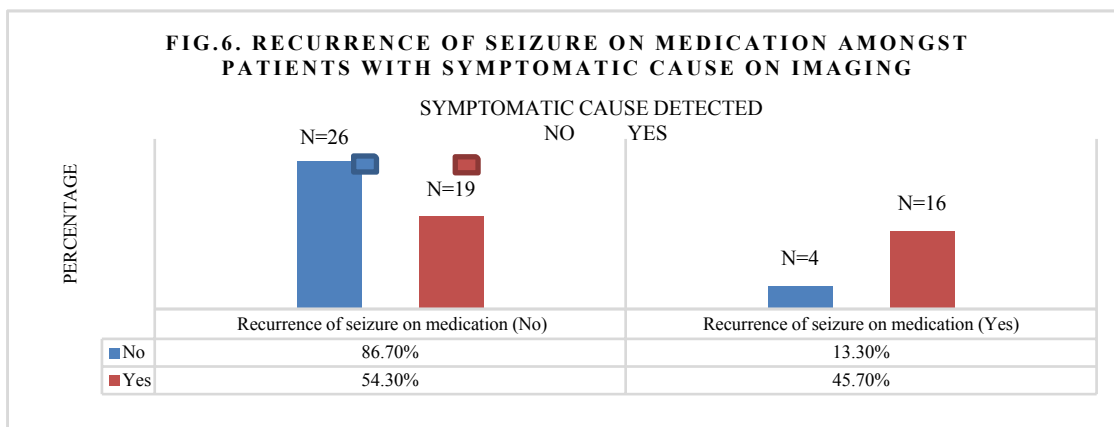
(N=26) of GTC and 66.7% (N=2) of unknown onset seizures were started on ASM in their first visit respectively.



All the patients with abnormal EEG recording except one patient who refused for ASM and all patients with abnormal brain imaging were started on ASM. Whereas 66.7% (N=36) with normal EEG and 54.2% (N=19) with normal brain imaging were started on ASM (p value <0.001). Among the 16 (23%) patients who were not started on ASM in the first visit, 15.7% (N=11) were eventually treated with ASM on follow up visits whereas 7.1% (N=5) continued to be without treatment during the 6 months follow up period. In these patients, there were no past history of systemic or neurological illnesses, no family history of seizure, no associated neurological symptoms/signs at presentation, no abnormality on brain imaging and EEG was normal in 93.8% (N=15).

During the first three months from the onset of seizure, 28.6% (N=20) had seizure recurrence regardless of their treatment status which had reduced to 21.4% (N=15) between 3-6 months from the onset of seizure.

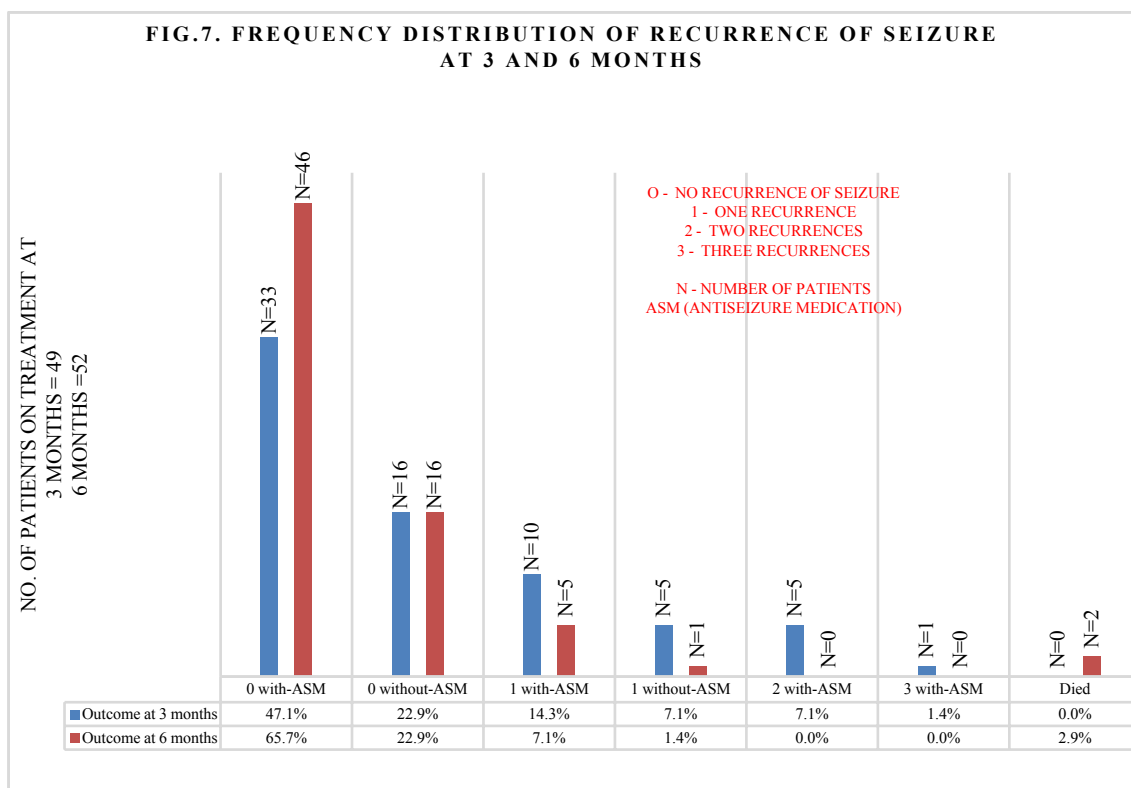
During the 6 months follow up period, 65 patients were on treatment with ASM (including all patients who defaulted treatment). Out of these, 69.2% (N=45) had no recurrence of seizure whereas 30.3% (N=20) had seizure recurrence. The recurrence of seizure in patients taking treatment with ASM who had abnormal EEG recording was higher (42.1%, N=8) than those patients taking treatment with ASM who had normal EEG recording (26.1%, N=12). But, this difference was statistically insignificant (p value 0.168). Since all patients with EEG abnormality except one were on ASM, this may have been a confounding factor. Out of the 35 patients with symptomatic cause detected on brain imaging, 45.7% (N=16) had recurrence of seizure during treatment whereas only 13.3% (N=4) of those patients with normal brain imaging had seizure recurrence during treatment, the difference was statistically significant ( p value 0.003). (Refer FIG.6.)



On follow up, 24.1% (N=13) defaulted treatment, discontinuation may have been related to no recurrence of seizure and inability to follow up on time due to logistic issues. At 6 months, among the 34 patients with symptomatic cause detected on imaging studies, 85.3% (N=29) were continuing ASM whereas 64.7% (N=22) with normal brain imaging were continuing treatment (p value <0.05). The difference was statistically significant. 83.3% (N=15) with abnormal EEG and 72% (N=36) with normal EEG were continuing ASM at 6 months follow up, and the difference was not statistically significant with

a p value of 0.341. This observation suggest that patients with symptomatic seizure with abnormal brain imaging were likely to continue ASM.

At 6 months, of the 72.8% (N=52) taking treatment with ASM, 65.7% (N=46) were seizure free whereas at 3 months, of the 70% (N=49) taking treatment with ASM only 47.1% (N=33) were seizure free. So, the frequency of seizure recurrence had reduced at 6 months as compared to 3 months among those on treatment with ASM. ( Refer FIG.7.)



**VI. DISCUSSION:**

A total of 70 patients were included in the study and all patients entered the final statistical analysis. Two patients died between 3-6 months follow up period, one due to a road traffic accident and the other due to age related illness.

Males constituted 58.6% (N=41) and females constituted 49.4% (N=29) with a male to female ratio of 1.41:1.

The male preponderance found in our study is in accordance to other epidemiological studies of seizure in India. Kaur et al. reported a male to female ratio 1.85:1 in their study of 100 patients with new onset seizure [5]. Venugopal et al. also



reported a male to female ratio 2.12:1 in their study of 50 patients of new onset seizure [8]. In our study, the highest number of patients among different age groups was seen in the age group of less than 20 years, constituting 31.4% (N=22). Also, 62.8% (N=44) were  $\leq 40$  years of age. Venugopal K et al. also had 64% of study subjects of age less than 40 years in their study [8]. Kaur et al. and Saha et al. also reported 47% and 40% of their study subjects to be less than 40 years of age respectively [5] [9].

A family history of epilepsy was observed in 7.1% (N=5) in the present study which is similar to the positive family history reported in 6% and 5% by Venugopal K et al. and Shinnar et al. respectively [8] [10].

## VII. TYPE OF SEIZURE

In our study, GTC seizure was the most common type of seizure (55.7%, N=39). Similar to our finding, GTC seizure was also the most common seizure type found by Kaur et al. (59%) and Narayanan and Murthy (55%) in their study of adult and elderly population respectively [5] [11].

In our study, among the older age group of 40 years and above, focal seizure was more common than other seizure types. Similarly, in a study by Kaur et al., 60% of patients more than 60 years of age had focal seizures [5]. In another study of elderly patients above 60 years, by Sinha et al., 67% of the seizure was focal onset seizures [12].

King M A et al. reported that longer duration of seizure and a more dramatic seizure are common in a first episode of seizure [13]. They also observed that focal seizure or absence or myoclonic seizures are less likely to present as a first seizure as such an isolated event may not be recognised as a seizure. In accordance to their observation, none of our patients with first seizure had a myoclonic or absence seizure.

### EEG abnormality

In our study, EEG abnormality was seen in 27.1% (N=19). Fisch L et al. in their study had opined that the timing of EEG recording after a seizure is important and an early EEG recording within 72 h after an unprovoked first seizure may improve the diagnostic yield [14]. King MA et al. reported that the yield of EEG was highest in the first 24 hours of a seizure episode and relevant abnormalities were found in 51% of patients with EEG recording done within 24 hours as compared to 34% with a later EEG recording beyond 24 hours [13]. In our study, the median time taken by the patients to seek medical attention was  $2.0 \pm 2.17$  days and this may have reduced the number of EEG abnormality. Krumholtz A et al. found epileptiform abnormalities in 29% of new onset seizures in their first electroencephalogram [15]. They have also mentioned that the yield of EEG abnormality was higher when performed within 24 to 48 hours of a new onset seizure. Llauro A et al. found EEG abnormality in 34.1% of patients with first seizure, and they opined that detection of abnormalities decreased when EEG is performed after 16 hours from seizure onset [16].

### Symptomatic cause:

MRI study is the preferred method of investigation to find out the symptomatic cause of a first seizure as compared to CT scan in a study by Krumholz A et al. [15]. In our study also, MRI was the preferred method but in some patients CT scan was done due to financial constraints as investigations were not provided free of cost in our center.

We found brain imaging abnormality in 50% (N=35). Sinha et al. had also observed MRI brain abnormality in 55.8% of elderly patients presenting with new onset seizures [12]. In another study, Hirani and Shrivastva reported symptomatic seizure in 60% of new onset seizures among Indian adult population [17]. But contrary to these studies, Murthy et al. reported CT brain lesions in 23.4% [18].

In our study, stroke related seizure (past or present) was the most common etiological diagnosis of symptomatic seizure accounting for 28.6% (N=20). Quraishi et al. and Kaur et al. also observed that stroke constituted 30% and 23% of the cause of adult onset seizure respectively [19][5]. Wadia et al. reported CT enhancing lesions in 26% of focal onset seizure [20]. Among the different seizure types in our study, 76.8% (N=22) with focal seizure, 66.7% (N=2) with unknown onset seizure and only 28.2% (N=11) with GTC seizure had an abnormal brain imaging respectively.

### Anti seizure medication (ASM):

In our study, higher number of first seizure in the adult population (77.1%) were started on ASM. This is similar to a study by Llauro A et al., who reported that 76.5% of patients with first episode of seizure were started on ASM [16].

In our study higher number of patients with focal onset seizure (92.9%, N=26) were started on ASM as compared to GTC (66.7%, N=26) and unknown onset seizures (66.7%, N=2), respectively. This may be related to the higher number of brain imaging abnormality in patients with focal onset seizures.

### Recurrence of seizure

In the present study, recurrence of seizure was higher in the first 3 months (28.6%, N=20) as compared to the recurrence of seizure between 3-6 months (21.4%, N=15). This may be due to dose adjustments or addition of another ASM. Berg A T et al. in their study also concluded that treatment can decrease the risk of a recurrence of a first seizure [21]. In the FIR.S.T. study, the risk of recurrence in the immediate treatment group of a first seizure patients was substantially lower [22]. At 3, 6, 12, and 24 months after randomization, the risk in the immediate treatment group was 7%, 8%, 17%, and 25% versus 18%, 28%, 41%, and 51% in the deferred group [22].

In the present study, EEG abnormality was associated with a higher recurrence (42.1%, N=8) when compared to recurrence among the study subjects with normal EEG (26.1%, N=12), but the difference was statistically insignificant (p value 0.168). Das C P et al. also reported that EEG abnormality was associated with increased risk of recurrence (75%) as compared to normal EEG (16%) [6]. In our study, there was statistically significant difference on the recurrence rate with abnormal brain imaging (42.1%, N=16) when compared to those with normal brain imaging (13.3%, N= 4) (p value 0.003). Berg A T et al. had reported that higher risk of recurrence are associated with abnormal neurological examination, abnormal brain imaging, abnormal EEG, or a prior brain injury [21]. In the present study, there was no statistically significant difference between focal onset, GTC and unknown onset seizure in regard to recurrence of seizure (p value 0.984).

Outcome at 3 and 6 months

In the present study, out of 70 patients, 49 (70%) patients with first episode of seizure were on treatment with an ASM and 21(30%) patients were without ASM (either ASM were not started in the first visit or had defaulted treatment during the follow up period). Drug compliance was better in patients with abnormal brain imaging as compared to the those with normal brain imaging (p value 0.05), but there was no statistically significant difference in the drug compliance between patients with abnormal or normal EEG recordings (p value 0.341). In the present study, at 6 months from the onset of the first episode of seizure, two patients had died. Out of the 68 still alive, 72.8%(N=52) were on ASM whereas 24.3% (N=17) were without ASM. The number of patients on treatment with ASM at 6 months (72.8%, N=52) had increased from those at 3 months (70%, N=49). Study subjects with abnormalities on brain imaging were more likely to continue ASM as compared to those who have normal brain imaging (p value <0.005). At 6 months from the onset of the first seizure, there was no statistically significant (p value 0.442) difference among the different seizure types in regard to whether they are on treatment with ASM (78.6% of focal onset seizure, 70.3% of GTC seizure, 100% of unknown onset seizure were on treatment with an ASM). However, it was observed that 66.7% of GTC seizure were started on ASM in their first visit, but this has increased to 70.3% at 6 months suggesting that many patients with GTC seizure (N=14) who were not started on treatment with ASM in their first visit eventually required ASM during follow up due to seizure recurrence.

Ndeufeld M Y et al. reported that the major risk associated with not treating a first seizure is experiencing a seizure recurrence and that evidence indicates that immediate treatment reduce the risk of recurrence of seizure by 50% even though treatment itself does not affect the long term outcome of epilepsy [23].

In our study, 23%(N=16) were deferred ASM in the first visit, but 15.7% (N=11) eventually required ASM during follow up due to recurrence of seizure. In the treated group, the recurrence of seizure at 3 months (22.8%, N=16) was higher than at 6 months (7.1%, N=5). Also, seizure freedom on ASM increased at 6 months (65.7%, N=46) compared to 3 months (47.1%, N=33). The significant reduction in seizure freedom

among the treated group at 6 months as compared to 3 months may be attributed to the dose titration or addition of another ASM during the follow up period.

## VIII. SUMMARY AND CONCLUSION

In this study, generalised tonic clonic seizure is the most common presentation of first episode of seizure among the adult population of >14 years. Focal onset seizure is the predominant seizure type in the older age of >40 years due to higher incidence of symptomatic seizure in the older age group. Symptomatic cause with abnormal brain imaging was seen in 50%, the most common etiology detected is stroke related. More number of adults presenting with first episode of seizure are started on anti seizure medication, especially those above 40 years of age. Recurrence of seizure is seen 21.4 % - 28.6% during follow up period of 6 months. Recurrence of seizure is significantly higher with brain imaging abnormality even with anti seizure medications. Drug discontinuation is not uncommon during the first 6 months of follow up among patients with normal brain imaging and normal EEG. Treatment with anti seizure medication and proper follow up improved the short term outcome. Therefore, a holistic approach is required in the management of first episode of seizure. Treatment has to be individualized, patients should be properly informed about the risk of recurrence of seizure, they should be allowed to participate in the decision making process and a close follow up is advised during the first 6 months from the first episode of seizure.

## CONFLICT OF INTEREST

The authors have no conflicts of interest.

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