Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2017/225

Original Article

Recurrent Seizures in Stroke and Anatomical Correlation: A Prospective Study

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Abstract

Introduction: Stroke is one of the most common causes of seizures in the elderly and seizures are among the most common neurological sequelae of stroke. Seizures can occur at the onset or may follow strokes.

Aim: To study the recurrence of seizures following stroke and the relationship between the anatomical location of the lesion in stroke and seizure.

Methods: Patients aged above 16 years presenting with seizures associated with stroke were included in this study.

Results: The recurrence seizure following early onset seizures 22% and late-onset seizure is 72%. Hence, late onset seizures have more chances of recurrence.

Conclusion: The factors contributing to recurrence in post-stroke seizures include late onset seizures, post-ischemic seizures, the presence of periodic lateralized epileptiform discharges in electroencephalogram and poor antiepileptic drug compliance.

Key words: Recurrence, Seizure, Stroke

INTRODUCTION

The incidence of post-stroke seizure in India is 13%. There have been very few prospective studies in stroke-related seizures from the Indian subcontinent. Stroke-related seizures are a neglected topic and generally considered as a benign complication occurring in the course of a progressive and longstanding cerebrovascular disease. Patients with a lesion at the cerebral cortex have a higher incidence of seizures than those with only subcortical lesions.[1,2] Seizures may occur with subcortical involvement, a possible consequence of the release of glutamate from injured thalamocortical neurons. Lobar site is considered to be more epileptogenic in hemorrhagic stroke analogs to cortical involvement in ischemic stroke. In a study by Faught *et al.*, the incidence of seizure was highest with lobar bleeding into lobar cortical structures (54%), low with hemorrhage in the region of basal ganglia (9%) and absent with thalamic hemorrhage. Caudate involvement of basal ganglia and temporal or parietal involvement within cortex predicted seizures.[3]

From the available data from stroke register about 5-20% of all individuals who have a stroke will have subsequent seizures.[1,4] Patients with early onset seizures were nearly 8 times more likely to develop late post-ischemic seizures and 16 times more likely to develop epilepsy. A prospective study found seizure recurrence is 55% in late onset seizures similar to that observed in other studies with longer follow-up period.[5] Multi-variant analysis has also proved that late onset (more than 2 weeks) seizures are an independent risk factor for epilepsy.[1] One retrospective study showed that 80% of patients with recurrent seizures were either not taking anti-seizure medications or had subtherapeutic blood levels.[6]

Access this article online

IJSS
www.ijss-sn.com

Month of Submission : 03-2017
Month of Peer Review : 04-2017
Month of Acceptance : 05-2017
Month of Publishing : 05-2017

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An underlying permanent lesion is responsible for a higher frequency of epilepsy is patients with late onset than early onset seizures. Post-stroke epilepsy develops in 35% of patients with early onset post-stroke seizures and in 90% with late onset post-stroke seizures. In case of hemorrhagic stroke, the risk of developing epilepsy is 29% with early onset seizures and 93% with late onset seizures.[7]

Post-stroke epilepsy is defined as "recurrent seizures following stroke with confirmed diagnosis of epilepsy." Epilepsy develops in about one-third of early onset and half of late-onset seizure certain actors are associated with higher incidence of post-stroke seizures. In ischemia, the severity of the neurological deficit, severity of persistent disability after a stroke, larger the infarct size, infarct involving multiple sizes, cortical damage, and hippocampus involvement are the important factors associated with the likelihood of developing seizures after stroke. The presence of structural brain lesion, electroencephalogram (EEG) abnormalities and occurrence of partial seizures also carry a higher recurrence rate.

Aim

To study the recurrence of seizures following stroke and the relationship between the anatomical location of the lesion in stroke and seizure.

MATERIALS AND METHODS

This study was conducted at the Department of Neurology, Tirunelveli Medical College Hospital, Tirunelveli, Tamil Nadu, India. Patients aged above 16 years presenting with seizures associated with stroke were included in this study. Exclusion criteria: Children and adolescents less than 16 years of age, patients with history of seizures before the occurrence of stroke, stroke-like presentation due to neurosurgical causes such as arteriovenous malformation, tumor, trauma and brain abscess, acute and chronic central nervous system infections manifesting as arthritis, patients with cortical venous thrombosis and venous stroke, stroke due to drug addiction and substance abuse, post-cardiac arrest resuscitation state, seizures associated with stroke as a sequelae of pregnancy-related complications, unwilling and non-cooperative patients. All the patients in the study group were evaluated by complete medical history, neurological examination, and routine baseline investigations. Axial computed tomography (CT), inter-ictal EEG, and 1.5 magnetic resonance imaging (MRI) brain were done in all patients.

RESULTS

A total of 100 patients were included in the study, in that 76 males, and 24 females. The sex ratio was male:female 3.2:1 (Figure 1).

The maximum number of patients ($n = 31$) were from the age group (61-70 years) showing that the elder age group prone for the development of stroke-related seizures (Table 1).

Of the 100 patients studied, the predominant left sided (dominant side) lesion was present in 53 patients and a right sided lesion in 44 patients. Three persons had bilaterally predominant lesions as demonstrated by neuroimaging (Table 2).

In the thrombotic group ($n = 56$), 38 patients had cortical lesion (68%), 11 patients (20%) had both cortical and subcortical lesion, and 7 (12%) had only subcortical lesions. Of the 32 patients with intracerebral hemorrhage (ICH), 18 (56%) had only cortical involvement, 10 (31%) had only subcortical involvement, and 4 (13%) had both cortical and subcortical bleed. In the cardioembolic subgroup, 9 (75%) had pure cortical involvement, 3 (25%) had both cortical and subcortical involvement (Table 3).

Of the patients with ischemic stroke ($n = 68$), 42 patients (62%) had large infarcts, and 26 patients (38%) had small

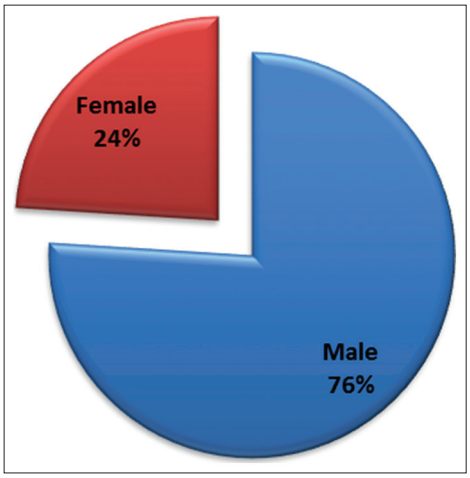

Figure 1: Distribution of gender in study patients

Table 1: Seizures in relation to age

Age group in years	Number of cases
21-30	4
31-40	13
41-50	17
51-60	26
61-70	31
Above 70	9

Table 2: Side of stroke in relation to seizure

Side of lesion	Number of patients
Left side	53
Right side	44
Bilateral	3

infarcts. The lesion size was correlated with recurrent seizures (Table 4).

Of the total 47 (38 thrombotic, 9 embolic group) patients with pure cortical infarct, 23 (49%) had parietal infarct, 16 had (34%) frontal infarct, and 8 (17%) had occipital infarcts. The post-stroke seizure was more common with the parietal group (49%) which includes parietotemporal, temporal and parietooccipital areas and least common with the occipital subgroup.

As per the methodology, the patients were studied in relation to the deep ICH, deep ICH with intraventricular extension with lobar extension, and with lobar ICH. The number of patients with the above categories of ICH is given in Table 5.

The patients with ICH were classified as two subgroups according to the volume of blood and correlated with the seizure occurrence (Table 6).

Interictal EEG was done in 75 patients only. The EEG of all the patients presenting with seizures associated with stroke was categorized into five types as given Table 7.

In this study, seizures recurred in 40. Early onset seizure was associated with seizure recurrence in 14, late-onset seizure in 26 (Table 8).

The recurrence seizure following early onset seizures 22% and late-onset seizure is 72%. Hence, late-onset seizures have more chances of recurrence (Table 9).

DISCUSSION

A total of 100 patients presenting with seizures associated with arterial stroke were included in this study. In this study maximum number of post-stroke seizures (n = 31) occurred in the age group between 61 and 70. The study by Forsgren *et al.* observed that stroke accounts for 30% of the newly diagnosed seizures in patients more than 60 years old. Hauser *et al.* in his community-based study conducted at Rochester, USA also observed a similar trend in the age-specific incidence of post-stroke seizures. Hence, it is obvious from this study and the above studies that the post-stroke seizures are more common in the elder age group.[8]

Gupta *et al.* observed that for reasons unknown, left hemispheric lesions are more prone to develop seizures after stroke than right hemispheric lesions. In this study of seizures in stroke, left sided lesions (53%) are more common than left sided lesions (44%).[6]

Table 3: Anatomical site of stroke in relation to seizure

Type of stroke (n)	Anatomical site		
	Cortical (%)	Sub cortical (%)	Cortical+Sub cortical (%)
Ischemic (56)	38 (68)	7 (12)	11 (20)
Hemorrhagic (32)	18 (56)	10 (31)	4 (13)
Embolic (12)	9 (75)	-	3 (25)

Table 4: Size of infract in relation to seizure

Lesion size	Number of patients (%)
Large >5 cm	42 (62)
Small <5 cm	26 (38)

Table 5: Seizure in relation to ICH

Site of lesion	Number of patients n=32 (%)
Deep ICH	8 (25)
Deep ICH with IVH	2 (6)
Deep ICH with lobar extension	3 (9)
Deep ICH with lobar extension and IVH	1 (3)
Lobar ICH	18 (57)

ICH: Intracerebral hemorrhage, IVH: Intravenous hemorrhage

Table 6:Volume of ICH

Volume	Number of patients
Small (0-20 ml)	20
Large (30 ml or more)	12

ICH: Intracerebral hemorrhage

Table 7: Distribution of EEG findings

Type	Number of patients (%)
Type I – Normal	15 (20)
Type II – Diffuse slowing	7 (9)
Type III – Focal slowing with/without diffuse slowing	36 (48)
Type IV – Focal spikes, sharp waves	15 (20)
Type V – Presence of PLEDs	2 (3)

PLEDs: Periodic lateralized epileptiform discharges, EEG: Electroencephalogram

Table 8: Recurrent seizures after stroke

Type of seizures	Total	Recurrence (%)
Early onset	64	14 (28)
Late onset	36	26 (72)

Of the total 100 patients of seizures with stroke, 56 patients had ischemic stroke as evident from the CT brain (or) MRI brain. 32 patients presented with hemorrhagic stroke, 12 patients had embolic stroke mostly cardioembolic as evidenced by echocardiogram. The incidence of seizures was 10.6 in patients with hemorrhagic stroke and 8.6 with ischemic stroke as studied by Bladin *et al.*[1]

Table 9: Distribution of seizures as per the subtype of stroke

Subtype of stroke	Early onset seizure (*n*=64)		Late-onset seizure (*n*=36)	
	No recurrence	Recurrence (%)	No recurrence	Recurrence (%)
Ischemic and hemorrhagic	50	14 (22)	10	26 (72)
Ischemic	36	10 (71)	5	17 (65)
Hemorrhagic	14	4 (29)	8	6 (35)

In this study in patients with ischemic stroke, 68% had cortical infarcts, 20% had both cortical and subcortical infarcts. Only 12% had only subcortical infarcts. In patients with hemorrhagic stroke, 56% had cortical bleed, 31% had subcortical bleed with or without extension of edema into the cortical region, and 13% had both cortical and subcortical emorrhage. In patients with embolic stroke, 75% had cortical infarcts, and 25% had cortical and subcortical infarcts. Hence, it is evident from the above data that cortical site is the more common cause for seizure in stroke.

Cortical location is the best-characterized risk factor seizures after stroke and is supported by several studies. In multivariate analysis of data from the seizures after stroke study cortical location was a significant risk factor for stroke (Hazard ratio [HR] - 2.09: 95% confidence interval [CI], 1.9-3.68, $P < 0.01$). It also pointed out that the only risk factor for seizures after ICH was cortical location (HR - 12.37; 95% CI, 1.35-7.40, $P < 0.008$).

However, in a community-based prospective study by Reith *et al.*,[9] the association between cortical involvement and post-stroke seizures was not found. Lobar site is considered to be the most epileptogenic in patients with ICH. The incidence of seizures was highest with bleeding into lobar cortical structures (54%) low with basal ganglia hemorrhage (9%) as shown by the study by Faught *et al.* which included a series of 123 patients.[3] Caudate nucleus involvement and parietal or temporal lobe involvement within the cortex predicted the seizure. The study by Dhanuka *et al.*[10] observed that 85% of the post-ischemic seizures had a cortical lesion with (or) without the involvement of subcortical structures. 33% of patients with ICH had cortical hematomas while 80% of capsule ganglionic hematomas were large with the extension of edema or hematoma to the cortical area. Only 14.28% of lesions (infarcts and hematomas) were localized to subcortical regions.

In this study, 12% of patients with ischemic stroke and 13% with hemorrhagic stroke had only subcortical lesions. Since MRI studies were not conducted in all patients in the present study, the possibility of cortical involvement still cannot be ruled out in these pure subcortical cases associated with seizures.

Larger the size of the infarct, there is more risk for the development for post-stroke seizures. This is evidenced by Gupta *et al.*[6] In this study also, of the 66 patients with ischemic stroke, 42 patients (62%) had larger infarcts correlating well with the size of the infarct and occurrence of seizures.

Dhanuka *et al.* observed that the volume of hematoma more than 30 ml was associated with increased risk of seizures. In this study, 18 out of the 32 patients (56%) with S large volume hematoma (30 ml or more). Even in patients with small volume hematoma (44%), two third had extension of edema into the cortex.[10]

In this study, recurrent seizures were present in 40% (22% with early onset seizures and 72% with late onset post-stroke seizures). A prospective study by Bladin *et al.* reported that seizure recurrence was 55% patients with post-stroke seizures.[1] Similar findings were observed in other studies also. In another study, Kheelani *et al.* reported that the recurrent seizures were found in 21% at 1 year follow-up.[11] A study by Dhanuka *et al.*, reported recurrent seizures in all the patients who had late-onset seizures whereas none of the early onset seizures developed recurrent seizures or epilepsy.[10]

In a prospective study by Bladin *et al.*[1] recurrent seizures occurred in 55% of post ischemic stroke patients with late-onset seizure. Recurrent seizures occurred in 100% of patients with late-onset seizures after ICH. The study by De Reuck,[12] reported that late-onset seizures had a higher recurrence rate.

The most common EEG abnormality observed in this study was focal slowing (Type III) present in 48%. Similar correlation was observed in few studies (Gupta *et al.*, Dhanuka *et al.*). In this study, periodic lateralized epileptiform discharges (PLEDs) were seen only in 3%.[6,10] The study by De Reuck observed that PLEDs were present in 5.8% of the post-stroke seizures.[12]

EEG findings were correlated with recurrent seizures (discussed later). No specific EEG pattern was associated with early versus late seizures or recurrent seizures in post-stroke seizures as per the prospective study by Dhanuka *et al.* Hence, the author states that the prognostic value of EEG is of little importance.[10]

Table 10: EEG abnormalities predicting recurrence

EEG abnormality	Number of patients	Recurrence
I	15	7
II	7	5
III	36	18
IV	15	8
V	2	2

EEG: Electroencephalogram

Contrary to this, in the study by Gupta *et al.*,[6] there was no difference in the incidence of recurrence with regard to the onset of initial seizures.

In this study, the majority of the patients with recurrent stroke had Type III abnormality (i.e.) focal slowing with/without diffuse slowing. All the patients with PLEDs (2) had recurrent seizures (Table 10).

In the study by Gupta *et al.*, higher incidence of recurrent seizures was present in patients with Type II (75%) abnormality and PLEDs (100%). The higher incidence of recurrent seizures in these two abnormalities is explained by the fact that these two types (II, V) EEG abnormalities indicate a larger area of involvement of brain than the other types.

In this study, all the patients were prescribed antiepileptic drugs (AEDs) whether early or late onset. In patients presenting with recurrent seizures, 60% admit that poor compliance of the drug as the cause for recurrence. Other possible reasons for poor drug efficacy could be, drug interaction in patients taking cardiac drugs or oral anticoagulants which interfere with the metabolism of AEDs and decreasing the therapeutic levels.

However, the study by Hauser *et al.*[13] reported at least one seizure relapse in 50% of patients who received AED after the first seizure after stroke during follow-up period of 47 months. This study is limited by the shorter follow-up period, i.e., 6 months.

The first line therapy option for post-stroke seizures includes carbamazepine and phenytoin. However, the newer AEDs have been tried as first line agents for elderly patients. Gabapentin has been shown to be efficacious for partial seizures. A recent trial with lamotrigine demonstrated better tolerability and maintains longer seizure-free intervals than carbamazepine. Newer anticonvulsants topiramate, levetiracetam has been studied as monotherapy and as adjunctive agents for refractory seizures with variable results.

CONCLUSION

Seizures are common in cortical lesions than with isolated subcortical lesions, left sided lesions than with right sided lesions. In patients with ischemic stroke, seizures are more common with large infarcts (infarct size >5 cm) and in a parietal subgroup which includes a major portion of the temporal lobe. In hemorrhagic stroke, lobar ICH and large volume ICH (>30 ml) have the risk for developing post-stroke seizures. The factors contributing to recurrence in post-stroke seizures include late-onset seizures, post-ischemic seizures, the presence of PLEDs in EEG and poor AED compliance.

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How to cite this article: Packiaseeli CR, Radha M, Bobby E, Saravanan S, Murugan P, Anandan H. Recurrent Seizures in Stroke and Anatomical Correlation: A Prospective Study. Int J Sci Stud 2017;5(2):98-102.

Source of Support: Nil, **Conflict of Interest:** None declared.