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FULL-LENGTH ORIGINAL RESEARCH

Post-stroke seizure—Do the locations, types and managements of stroke matter?

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Summary

Objective: To determine the incidence of post-stroke seizures and the associated risk factors in a government-restructured hospital in Singapore.

Methods: This retrospective study included consecutive patients (age ≥21 years) admitted to the stroke rehabilitation facility at Changi General Hospital, Singapore, between June 2008 and May 2017, with a minimum post-discharge follow-up of 6 months. Patients with known epilepsy central nervous system infection or tumor, a history of neurosurgery and or missing data were excluded from study. To determine the incidence of seizures, the patients' hospital records, including those for all initial and subsequent admissions and outpatient follow-ups, were reviewed. All prescribed medications were checked and documented. Seizures were diagnosed on the basis of clinical examination with or without electroencephalography.

Results: In total, 722 patients (women, 38%) with a mean age of 64 years were included. Of these, 48 (6.64%) experienced post-stroke seizures during a follow-up period of 6–108 months. The incidence of seizures was significantly higher in patients with hemorrhagic stroke (42%, $p = 0.010$), those with ischemic partial anterior circulation stroke (PACS) (27%, $p = 0.025$), those who underwent a neurosurgical procedure after stroke ($p < 0.001$), those with a low activated partial thromboplastin time (APTT) at admission (mean, 25.6; $p = 0.015$), and those using levodopa (21%, $p < 0.001$). Neurosurgical intervention after stroke (odds ratio [OR] 6.2, 95% confidence interval [CI] 2.9–13.1; $p < 0.001$), APTT (per-unit increase; OR 0.86, 95% CI 0.76–0.98; $p = 0.028$), and underlying ischemic heart disease (IHD; OR 2.2, 95% CI 1.08–4.60; $p = 0.029$) were found to be independent predictors of seizure occurrence after stroke.

Significance: Post-stroke seizure incidence from our study is 6.64%, with a median follow-up of 49 months. Among patients with stroke, those with underlying IHD, those who undergo a neurosurgical procedure, and those with a low APTT at admission need careful monitoring. Levodopa should be used with caution and withdrawn as soon as possible.

KEY WORDS: Stroke, Post-stroke seizure, Ischemic stroke, Hemorrhagic stroke, Levodopa, Neurosurgery.

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Stroke remains the major reason for inpatient rehabilitation because it leads to significant disabilities and long-term complications. The majority of patients with stroke require long-term follow-up for comorbidities and complications. Although seizure is a known complication of stroke, the incidence, treatment modalities, and long-term mortality associated with seizures vary among studies.

Although the incidence of epilepsy has been evaluated in local populations in Singapore, that of post-stroke seizures

Key Points

- Underlying IHD, neurosurgical intervention after stroke, and/or a low APTT at admission are risk factors for post-stroke seizures
- Increased seizure risk in patients undergoing post-stroke neurosurgery may be due to added injury or the severity of the stroke itself
- Considering a possible increase in the seizure risk, levodopa should be used with caution and withdrawn as soon as possible

remains unclear. Moreover, patients with stroke also receive cholesterol-lowering and antispasticity medications, along with antidepressants and neuromodulating agents such as levodopa for neurologic recovery. However, the effect of these medications on the occurrence of post-stroke seizures remains unknown.

In the present study, we aimed to determine the incidence of post-stroke seizures and the associated risk factors in a government-restructured hospital in Singapore.

Methods

Patients and inclusion and exclusion criteria

SingHealth Centralized Institutional Review Board approved this study and waiver of informed consent was granted due to the retrospective nature of the study.

Changi General Hospital is a government-restructured hospital with all the modern facilities for emergency and specialist care. The acute stroke unit is equipped with facilities for diagnosis and treatment, including thrombolysis, for strokes. All patients admitted with a diagnosis of stroke undergo necessary investigations, including those required to establish the underlying causes of stroke according to standardized protocols and established guidelines. Stroke management is streamlined and involves the emergency department and acute stroke unit. On the basis of the initial and subsequent clinical conditions and scan findings, the neurosurgery team is involved for further intervention. All patients are eventually referred to the inpatient neurorehabilitation department and regularly followed up after discharge.

For the present study, we reviewed all electronic and paper medical records (initial and subsequent admissions and follow-up visits, including all administered treatments) of consecutive patients (age ≥21 years) with stroke, including infarction and spontaneous intracerebral hemorrhage, who were admitted to the neurorehabilitation facility at Changi General Hospital, Singapore, between June 2008 and May 2017, and followed up for a minimum of 6 months after discharge. Patients with a known history of epilepsy before admission, those with a past or present history of central nervous system infection or tumor, those with a history of neurosurgical procedures, those with traumatic intracranial bleeding, those with toxic or metabolic disorders, and/or those followed up for <6 months for any reason were excluded.

Evaluation of stroke

The subtype, severity, and location of stroke were diagnosed on admission to the acute stroke unit by a stroke physician or neurosurgeon, who performed clinical examinations along with brain imaging, including computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance angiography (MRA). Patients were categorized according to the presence of ischemic stroke and hemorrhagic stroke on the basis of the imaging findings. Records of patients receiving thrombolysis treatment were maintained, along with the findings of repeat scans for suspected deterioration and hemorrhagic conversion.

Cardioembolic stroke was diagnosed using 12-lead Holter electrocardiography, carotid Doppler imaging, and echocardiography.

Other hematologic, biochemistry, and autoimmune tests were conducted to rule out secondary causes of stroke.

The location of stroke was classified using the Oxfordshire system[1]: total anterior circulation stroke (TACS), partial anterior circulation stroke (PACS), lacunar stroke (LACS), and posterior circulation stroke (POCS).

The etiology of stroke was classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) system[2]: large-artery atherosclerosis (LAA), small vessel occlusion (SVO), cardioembolism (CE), stroke of other determined etiology, and stroke of undetermined etiology. The probability of a cardioembolic (moderate or high) source was also assessed.

Evaluation of post-stroke seizures

To determine the incidence of post-stroke seizures in the study population, we reviewed all hospital records for initial and subsequent admissions and outpatient or polyclinic-based follow-up examinations by physicians, neurologists, or rehabilitation physicians. We also documented all medications prescribed during the period. Post-stroke seizures were diagnosed on the basis of clinical examinations with or without electroencephalography (EEG), after ruling out stroke mimics and secondary causes. The International League Against Epilepsy (ILAE) classification was used as a reference guide.[3] Acute symptomatic seizures were defined as seizures occurring within 1 week of stroke onset, whereas late seizures (epilepsy) were defined as seizures occurring ≥1 week after stroke onset.[4]

Evaluation of stroke treatments

Patients diagnosed with seizures were prescribed antiepileptic drugs after the first episode. Second-line agents or add-on treatments were chosen at the discretion of the neurologist.

Levodopa and fluoxetine were used for neuromodulation, neuroplasticity, and post-stroke recovery. For all patients, the use of these medications was initiated after stroke and before seizure onset. Data regarding levodopa and fluoxetine use, including the dose and duration, were recorded to determine correlations with late seizures (epilepsy). In addition, all patients with ischemic stroke and some with hemorrhagic stroke were prescribed long-term statin use after stroke; these data were recorded to determine the association with post-stroke seizure occurrence.

Neurosurgical procedures, including burr hole drainage, external ventricular drainage (EVD), intracerebral pressure (ICP) monitoring, craniotomy, and craniectomy, were performed when required.

Summary of evaluated parameters

Data collection was censored in May 2017. All collected material was stored in the hospital's medical record database and the records of the clinician at the neurorehabilitation facility.

The demographic details, diagnosis, type of stroke, CT/MRI findings, location of stroke, and electrolyte levels, clotting parameters, premorbid medications, and comorbidities (hypertension, diabetes, hyperlipidemia, atrial fibrillation) at the time of admission were recorded for all patients. Treatment data included data pertaining to the use of thrombolysis (with alteplase), medical treatments for increased intracranial pressure (mannitol), neurosurgical interventions, statins, antidepressants, neurostimulants/neuromodulators, and antispasticity medications. Seizure data included the time at seizure onset after stroke, start date for antiepileptic treatment, and further changes in antiepileptic treatment. All patient records were also reviewed for documentation and investigations concerning infections, falls, and head injuries; recurrence of stroke; and hemorrhagic transformation.

Statistical analysis

Categorical data are presented as frequency (percentage) and continuous data are presented as mean (±standard deviation) for parametric distributions and median (interquartile range) for nonparametric distributions. Differences between subgroups were examined using chi-square tests for categorical variables and two-sample *t*-tests or Mann-Whitney *U* tests for continuous variables. Logistic regression analysis was performed to determine the association between the incidence of post-stroke seizures and potential risk factors. Odds ratios (ORs) were presented along with 95% confidence intervals (CIs). A two-tailed *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 19.0 (IBM Corp. Armonk, New York, NY, U.S.A.).

Results

In total, 722 (women, 38%), including 531 (74%) with ischemic stroke and 191 (26%) with hemorrhagic stroke, met the selection criteria. The mean and median follow-up durations were 50.4 (±27.6) and 49 (6–180) months, respectively.

TACS, PACS, POCS, and LACS were observed in 49 (7%), 285 (40%), 152 (21%), and 45 (10%) patients, respectively. LAA was observed in 356 (67%) patients, whereas SVO was observed in 175 patients (33%). Moderate and high probabilities of a cardioembolic source were observed for 118 (20%) and 104 (18%) patients, respectively.

The average age of patients was 64 (21–97) years. In total, 48 patients (6.64%) experienced post-stroke seizures and received antiepileptic medications. From these, 12 patients (25%) experienced acute symptomatic stroke and 36 (75%) experienced late seizures (epilepsy), which occurred between 1 and 72 months after stroke (average, 15.65 months). Nine of the 36 patients with late seizures experienced recurrent seizures. The most commonly used antiepileptic drug was phenytoin, followed by levetiracetam, valproic acid, and carbamazepine.

Levodopa was initiated for 31 patients, with a starting dose of 62.5 mg twice a day. It was continued for patients who showed clinical benefits after consultation with the patient and family members, whereas it was discontinued when no benefits or low blood pressure were observed.

The incidence of post-stroke seizures was significantly higher in patients with cerebral hemorrhage ($p = 0.021$), those with ischemic PACS ($p = 0.025$), those who underwent neurosurgical procedures after stroke ($p < 0.001$), those using levodopa ($p < 0.001$), those with a low APTT at the time of admission (mean, 25.6 vs. 26.8, $p = 0.015$), and those with underlying ischemic heart disease (IHD; $p = 0.07$).

Patients with LAA were more likely to develop post-stroke seizures than were patients with SVO, with the difference showing borderline significance (14% vs. 86%, $p = 0.05$). Similarly, patients taking statins were less likely to develop seizures than were those who did not take statins, with the difference showing borderline significance ($p = 0.056$).

Antidepressant and antispasticity drug use, probability of CE, kidney function at the time of admission, and comorbidities at the time of admission did not influence the occurrence of post-stroke seizures.

In total, 100 patients (14%) displayed hemorrhagic conversion on repeat brain scans after stroke; 9% of these patients developed post-stroke seizures (Table 1).

Factors that were associated with the occurrence of post-stroke seizures at the 10% level of significance ($p < 0.10$) were entered into a logistic regression model for

Table 1. Characteristics of post-stroke patients with seizure

Patient characteristics	Percentage (number)			Comparison seizure versus no seizure (*P*- value)
	Overall (n = 722)	Seizure (n = 48)	No seizure (n = 674)	
Age (years); mean (range)	64.0 (19–97)	61.2 (35–89)	64.2 (19–97)	0.95
Male	62% (447)	60% (29)	62% (418)	0.12
Hemorrhagic stroke	26% (191)	42% (20)	25% (171)	0.021
Stroke territories				
TACS	7% (49)	12% (6)	6% (43)	0.025
PACS	40% (285)	27% (13)	40% (272)	
POCS	21% (152)	8% (4)	22% (148)	
LACS	6% (45)	10% (5)	6% (40)	
Atherosclerosis				
Small artery	33% (175)	14% (4)	34% (171)	0.05
Large artery	67% (356)	86% (24)	66% (332)	
Cardioembolic				
None	62% (358)	47% (16)	63% (342)	0.13
Moderate	20% (118)	24% (8)	20% (110)	
High	18% (104)	29% (10)	17% (94)	
APTT[a]; mean (range)	26.7 (20.2, 48.3)	25.6 (22.0, 30.7)	26.8 (20.2, 48.3)	0.015
Comorbidities				
Hypertension	81% (584)	77% (37)	81% (547)	0.62
Diabetes	44% (319)	42% (20)	44% (299)	0.82
Hyperlipidemia	62% (445)	56% (27)	62% (418)	0.52
Ischemic heart disease	22% (157)	33% (16)	21% (141)	0.07
Atrial fibrillation	16% (115)	23% (11)	16% (104)	0.25
Management				
Thrombolysis with alteplase	6% (41)	6% (3)	6% (38)	1.0
Treatment for raised ICP	26% (184)	17% (8)	26% (176)	0.20
Statin	85% (616)	75% (36)	86% (580)	0.056
Fibrate	6% (44)	8% (4)	6% (40)	0.72
Baclofen	7% (53)	12% (6)	7% (47)	0.26
SSRI	18% (131)	25% (12)	18% (119)	0.29
Levodopa	6% (44)	21% (10)	5% (34)	<0.001
Piracetam	7% (48)	10% (5)	6% (43)	0.44
Sedatives/antipsychotics	4% (28)	0% (0)	4% (28)	0.29

ICP, intracranial pressure; SSRI, selective serotonin reuptake inhibitor.
[a]Data unavailable for 104 patients.

determining the optimal subset of independent predictors. Primary analysis evaluated the predictive power of hemorrhagic stroke, neurosurgical intervention after stroke, the presence of underlying IHD, and statin and levodopa use. The results revealed that neurosurgical intervention after stroke (OR 5.0, 95% CI 2.4–10.7; $p < 0.001$), underlying IHD (OR 2.0, 95% CI, 1.03–3.80; $p = 0.039$), and levodopa use (OR 22.9, 95% CI 1.2–6.9) were found to be independent predictors of post-stroke seizures.

Secondary analysis included the 617 patients with available APTT data and evaluated the predictive power of hemorrhagic stroke, neurosurgical intervention after stroke, presence of underlying IHD, statin and levodopa use, and APTT. In this subset, neurosurgical intervention after stroke (OR 6.2, 95% CI 2.9–13.1; $p < 0.001$), underlying IHD (OR 2.2, 95% CI 1.08–4.60; $p = 0.029$), and APTT (per-unit increase; OR 0.86, 95% CI 0.76–0.98) were found to be independent predictors of post-stroke seizures.

Discussion

In the present study, the incidence of post-stroke seizures was 6.64%, with neurosurgical intervention after stroke, underlying IHD, and APTT (per-unit increase) found to be independent predictors of post-stroke seizures.

The incidence of seizures in patients with stroke was found to be approximately 11% in population studies: 11.5% at 5 years in the Oxfordshire Community Stroke Project,[1] 11% in the Rochester study conducted by Hauser et al.[5] from 1940 to 1980, and 10.5% in a study conducted in Norway by Naess et al.[6] The relatively lower incidence of post-stroke seizures in the present study may be indicative of variations among different ethnicities.

Various studies have classified post-stroke seizures as early and late-onset seizures. The former are defined as seizures occurring between 24 hours and 2 weeks, or even 1 month in some studies, after stroke.[7–11] The latter are defined as seizures occurring ≥2 weeks after stroke.[7,9]

According to these definitions, previous studies have shown a 2–33% incidence of early post-stroke seizures, with 50–78% occurring within the first 24 hours,[1,7–10,12–15] and a 3–67% incidence of late post-stroke seizures.[1,7–10,12,14] In the present study, acute symptomatic seizures (within 1 week after stroke)[4] occurred in 12 of 48 (25%) patients with seizures, whereas late seizures (epilepsy, unprovoked seizures; ≥1 week after stroke)[4] occurred in 36 (75%) patients, 9 of whom experienced recurrent seizures.

Gliosis and meningocerebral cicatrix as sequelae of ischemic and hemorrhagic brain injuries may become epileptogenic foci and lead to late-onset seizures.[16] In addition, cortical structures, particularly the cerebral cortex, are often critically affected by ischemia and traumatic lesions, which may result in transient or permanent functional disturbances[17] that can trigger the onset of seizures or epileptiform activity. Furthermore, increased levels of glutamate, an excitatory neurotransmitter, as a result of acute ischemia may lead to secondary neuronal injury,[7,17] and the exposure of surviving neurons to glutamate may lead to recurrent epileptiform-type neuronal discharges in the neuronal network.[18]

In a study by Pohlman-Eden et al., the "preserved cortical islands" sign was particularly associated with a high risk of post-ischemic seizures. The authors also suggested that a critical mass of intact neurons within the infarcted area is necessary to generate an epileptogenic focus.[19] In the present study, ischemic PACS and, to a limited extent, LAA, were found to be associated with an increased risk of post-stroke seizures. This could be because LAA may affect a larger vascular territory and cortical area when compared with SVO.

Of interest, we observed that TACS was not significantly associated with an increased post-stroke seizure risk, probably because the area affected by stroke is too large for the surviving neurons to get excited or carry epileptiform activity from the area of gliosis. However, the incidence of seizures was higher for patients with TACS (12%) than for those with POCS (8%) and LACS (10%).

It is assumed that sudden expansion of hematoma with local ischemia and direct irritation of the cortex by the blood products may contribute to seizure activity[9,20] and subsequent gliosis.

In the present study, we found that the likelihood of spontaneous intracerebral hemorrhage (or ICH) was greater than that of other ischemic stroke types ($p = 0.010$) in patients with post-stroke seizures. We found that 10.4% of 191 patients with ICH experienced post-stroke seizures, with a statistically significant association ($p = 0.021$). The occurrence of post-stroke seizures was not associated with hemorrhagic transformation ($p = 0.43$).

Neurosurgical interventions after stroke were found to be significantly associated with the occurrence of post-stroke seizures in our study. This can be explained by the fact that neurosurgical intervention leads to additional insult to an already damaged brain. Alternatively, patients requiring neurosurgical interventions generally have massive strokes, which increases the risk of seizures.

Although prophylactic antiepileptic drugs have not shown significant benefits for seizure prevention in previous studies,[21,22] the findings of our study suggest that further research should be conducted to determine the benefits of prophylactic antiepileptic drugs for patients undergoing neurosurgical interventions after stroke, particularly hemorrhagic stroke.

Of interest, our multivariate analysis also showed that underlying IHD is an independent risk factor for post-stroke seizures. Although Gunnoo et al. reported that a third of patients with ischemic stroke demonstrated asymptomatic coronary artery diseases,[23] the relationship between IHD and post-stroke seizures remains unclear.

In the Seizure after Stroke Study (SASS), patients with a probable cardioembolic stroke were not at an increased risk of a first seizure.[24] Moreover, analysis of the National Institute of Neurological Disorders and Stroke (NINDS) Stroke Data Bank did not show an association between seizures at onset and the presence of a cardioembolic source.[25] In our study, neither a high nor a moderate probability of CE showed a significant relationship with post-stroke seizures ($p = 0.13$).

With regard to the role of levodopa in neuroplasticity, a double-blind, placebo-controlled, randomized, crossover study[26] showed that levodopa improved procedural motor learning when compared with placebo ($p < 0.05$). Scheidtmann et al. observed enhanced motor recovery and early recovery of independent walking abilities in patients receiving levodopa.[27]

Virtual-based therapy and pharmacotherapy (levodopa) may be combined for acute stroke rehabilitation.[28] Levodopa improved the walking speed and manual dexterity in a study by Acler et al.[29] Oczkowski performed a review and found that dopamine as a neurotransmitter may promote neuroplasticity and aid in improved working memory and learning.[30] In the present study, 31 patients received levodopa at a dose of 62.5 mg twice a day for post-stroke recovery, and we found that levodopa use was an independent predictor of post-stroke seizures. This suggests that patients receiving levodopa for neurostimulation should be carefully monitored. We did not find any significant association of the use of selective serotonin reuptake inhibitors (SSRIs), baclofen, piracetam, and sedatives/antipsychotics with post-stroke seizure occurrence.

In the present study, a low APTT at admission was significantly associated with post-stroke seizure occurrence ($p = 0.015$), and a per-unit increase in APTT lowered the risk of post-stroke seizures. APTT is a measure of the intrinsic pathway and common pathway of the coagulation cascade, and it is defined as the time required for the exposed fibrin to initiate the intrinsic pathway. A recent study from Taiwan showed that a decreased APTT was an indicator of

neurologic deterioration after ischemic stroke.[31] Although the mechanism remains unclear, our data suggest that patients with a low APTT at admission for stroke require careful monitoring for post-stroke seizures.

Among patients with ischemic stroke, those who received thrombolysis (with alteplase) did not show an increased risk of post-stroke seizures. Moreover, we did not find a significant relationship between post-stroke seizures and treatment for increased intracranial pressure (mannitol) in the immediate post-stroke period.

Deteriorated renal function also did not influence post-stroke seizure occurrence, similar to other underlying comorbidities such as hypertension, diabetes, hyperlipidemia, and atrial fibrillation.

Our patients were aged between 21 and 97 years (mean 64 years); however, age was not associated with seizure occurrence. In contrast, a review by Myint et al. showed that aging was a risk factor for the incidence of post-stroke seizures.[32] We also found limited evidence showing that patients with post-stroke seizures were less likely to be taking statins. Similar observations were made by Guo et al.,[33] and further investigation is needed to clarify these findings.

Strzelczyk et al. conducted a prospective study to stratify the risk factors for post-stroke seizures by using the post-stroke epilepsy risk scale (PoSERS) for 264 consecutive patients with stroke. Factors such as the stroke location, the presence of persistent neurologic deficits, the stroke subtype, an established diagnosis of vascular encephalopathy, and the timing of seizures (early or late) were collected using PoSERS, which was found to be a valuable tool for predicting the risk of post-stroke epilepsy.[34]

Strengths and Limitations

Because our hospital is a government-restructured hospital, admitted patients represent all socioeconomic levels from the local catchment area. Therefore, differences in the socioeconomic status and ethnicity were not likely to have influenced our results.

To the best of our knowledge, this is the first study of the incidence of post-stroke seizures in Singapore.

Although post-stroke seizures have been investigated in the past, the protective effect of statins has been documented in few studies.

Our study is the first one to review the role of levodopa, antidepressants, and APTT in post-stroke seizure occurrence.

However, our study also had a few limitations.

Our findings are limited by the fact that unreported focal seizure activity may not have been documented.

Some patients were prescribed gabapentin for neuropathic pain or valproic acid for mood and behavior changes. Because no seizure activity was documented for these patients, it remains unclear whether these drugs offered any prophylactic effect on seizures.

Clinical Relevance

In conclusion, the findings of our study suggest that, among patients with stroke, those with underlying IHD, those who undergo a neurosurgical procedure, and those with a low APTT at admission need careful monitoring for post-stroke seizures. Because of the possibility of an increased seizure risk, patients receiving levodopa for neuromodulation should be carefully monitored and weaned off the drug as soon as possible.

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