

# Risk Factors for Seizures after First-Time Ischemic Stroke by Magnetic Resonance Imaging

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## Abstract-

**Background:** Seizures are important neurological complications of ischemic stroke. There is a need to further clarify the risk factors of seizures following ischemic stroke and predict those who will require treatment.

**Methods:** One hundred and forty-three (143) first-time ischemic stroke patients were enrolled in this one-year (2002) retrospective study. Prognostic variables were analyzed based on the Cox's proportional hazards model after a minimum follow-up period of six years.

**Results:** Seizures occurred in 13 first-time ischemic stroke patients, including acute symptomatic seizures in two (1.4%) and unprovoked seizures in 11 (7.7%). Only one progressed to status epilepticus during hospitalization. After six years of follow-up, the median (inter-quartile range) Glasgow Outcome Scale (GOS) was 3 (3,4) for patients with seizures and 4 (3,4) for those without seizures. Regarding seizure control after discharge in the 13 cases, 12 were seizure-free with or without anti-epileptic drugs and one had 1-3 seizures per year. Only the presence of cortical distribution of ischemic infarction ( $p=0.009$ , OR=5.549, 95% CI=1.53-20.19) was independently associated with seizures by the Cox's proportional hazards model.

**Discussion:** The incidence of seizures following first-time ischemic stroke is low and may have delayed manifestation. Cortical distribution of the ischemic infarction is a risk factors for seizures.

**Key Words:** first-ever ischemic stroke; risk factors; seizure

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## INTRODUCTION

Cerebrovascular complications have long been recognized as a risk factor in the development of seizures

and epilepsy<sup>(1-4)</sup>. In terms of seizures after stroke, most large studies have focused on both ischemic and hemorrhagic stroke together or hemorrhagic stroke exclusively<sup>(1-4)</sup>. The majority of previous studies also have relatively

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small patient numbers<sup>(5)</sup>, inclusion of seizures that occur only in the acute phase of ischemic stroke<sup>(4)</sup>, mixed tomographic (CT) scan and/or magnetic resonance imaging (MRI) findings<sup>(6)</sup>, less strict patient selection (including less clearcut differentiation between first and recurrent ischemic stroke)<sup>(6,7)</sup>, or shorter follow-up period<sup>(4,8-10)</sup>. Few researches have examined the clinical features of seizure following MRI-based first-time ischemic stroke<sup>(5)</sup>.

Epilepsy may be an early or late complication of ischemic stroke, and may have delayed manifestations. Most seizures occur between 6 months and 2 years after stroke, and are associated with a high recurrence rate<sup>(11)</sup>. The occurrence of epileptic seizures following cerebral infarctions have reported frequencies of 4-10% in different series<sup>(1-4,8)</sup>, and are only limited to stroke patients with cerebral hemispheric lesions<sup>(2)</sup>.

A hospital-based study may provide a more accurate information about the relative frequency of seizure subtypes, the effect of seizure on stroke mortality and neurologic and functional outcome, and the relationship between seizure and underlying cerebral pathologic lesions. There is no currently available information on seizure outcome in these specific groups of patients with a longer follow-up period. Because of the possible beneficial effects of anti-epileptic drugs (AEDs) in reducing the degree of functional morbidity after seizures following ischemic stroke, there is a need to delineate potential prognostic factors and outcomes in more detail, so that one may more reasonably determine who should receive treatment primarily.

This study attempted to analyze clinical features, neuro-imaging findings, scientific clinical scores and measurements to determine potential risk factors that are predictive of seizures after spontaneous supratentorial ischemic stroke. It also aimed to explore the outcome after a minimum six-year follow-up.

## MATERIALS AND METHODS

Within one year (2002), 222 patients who suffered from first-time cerebral infarction were admitted to the Department of Neurology at Chang Gung Memorial

Hospital in Kaohsiung. Chang Gung Memorial Hospital-Kaohsiung was a 2482-bed acute-care teaching hospital and the largest medical center in southern Taiwan that provides both primary and tertiary referral care.

The medical records were retrospectively reviewed using pre-existing standardized evaluation forms. All of the patients underwent brain MRI examinations. Ischemic stroke was classified into different categories according to the presumed mechanism of the focal brain injury and the type as well as localization of the vascular lesion. Those initially treated in other hospitals but subsequently transferred to this hospital for further therapy were also included and their initial clinical and laboratory data done at the previous hospital were used for analysis.

Patients were excluded if they: 1) suffered from multiple infarctions or silent brain infarctions; 2) suffered from brainstem and cerebellar infarctions; 3) had pre-existing neurologic conditions various neurologic deficits (e.g. stroke, head trauma, and hypoxic encephalopathy); 4) had a history of seizure disorders or epilepsy; 5) regularly took AEDs for clinical indications other than epilepsy (e.g. trigeminal neuralgia or neuropathic pain); and 6) did not receive MRI study during hospitalization even if they had brain CT. Only 143 of the first-ever ischemic stroke patients were enrolled for analysis. The Chang Gung Memorial Hospital's Institutional Review Committee on Human Research approved the study protocol.

Seizures were classified according to the recommendations of the International League against Epilepsy<sup>(12)</sup>. Status epilepticus (SE) was defined as more or less continuous behavioral seizure activity or repetitive seizures lasting for at least 30 minutes and without full recovery of neurologic function between seizures<sup>(13)</sup>. Following the definition of seizure in the previous studies, we limited the scope of seizure to those occurring after cerebral infarctions and being causally related to the cerebral infarctions itself. A provoked (acute symptomatic seizure) seizure was one that occurred in close temporal relation with the ischemic stroke, which was thus the presumed etiology. In contrast, an unprovoked seizure was a seizure occurring in the absence of precipitating

factors, including events occurring in patients with antecedent stable (non-progressing) ischemic stroke.

Epilepsy was defined as the occurrence of repeated unprovoked seizures<sup>(2)</sup>. Based on seizure onset in relation to the clinical ictus of cerebral infarction, patients with seizures were slightly modified from those of previous studies<sup>(6)</sup> and were divided into two sub-types: early seizures (those occurring within two weeks of ischemic stroke) and late seizures (those occurring two weeks later).

The MRI examinations were performed on a 1.5T scanner (Signa; Horizon GE Medical system, Milwaukee, USA). The MRI pulse sequences included axial and sagittal T1-weighted and T2-weighted images, and gadolinium-DTPA were administered to all patients on coronal and axial T1-weighted images. Diffusion-weighted images (DWI) were also performed in all patients.

Characteristics and circumstances, time interval from cerebral infarction to the first seizure, types of seizure, and other features including length of hospital stay, presence and duration of chronic epilepsies, and systemic underlying diseases associated with seizures were documented for the 143 patients. Patients were defined as diabetic if they had a previous diagnosis of diabetes or a fasting glucose level of  $>7$  mmol/L<sup>(14)</sup>. Hypertension was defined by pre-admission history and medical records of systolic blood pressure  $>140$  mmHg or diastolic blood pressure  $>90$  mmHg<sup>(15)</sup>. Coronary artery diseases were defined by pre-admission history and medical records of myocardial infarction or angina pectoris.

The standard protocol was to administer AEDs only to those with symptomatic seizures after acute ischemic stroke. In other words, no prophylactic AED therapies were given to those without symptoms in the acute stage of ischemic stroke. AEDs were usually administered to the patients with acute symptomatic seizures during hospitalization, and were discontinued if no unprovoked seizures developed during the follow-up period.

The National Institutes of Health Stroke Scale (NIHSS) and the Glasgow Coma scale were used to assess the severity of the neurologic deficit upon admis-

sion. The follow-up period was terminated by death or by the end of the study (December 2008). The therapeutic outcome after discharge was evaluated by the Glasgow Outcome Score (GOS). Therapeutic outcome and the degree of seizure control after discharge were determined by a Seizure Frequency Scoring System, which was slightly modified from Engel et al.<sup>(16)</sup>.

Two separate statistical analyses were performed. First, the risk factors of seizure after the six-year follow-up period were determined. The effects of individual variables on the presence of seizures, including gender, clinical manifestations, underlying diseases, stroke subtype classification, mean age, GCS and NIHSS at the time of admission, duration of hospitalization and neuroimaging findings on admission were analyzed by the univariate Cox's proportional hazards model. Second, all imbalances between the seizure and non-seizure groups in baseline prognostic variables were documented, and the analyses were repeated with adjustments based on the Cox's proportional hazards model after a minimum of six-year follow-up. All statistical analyses were conducted using the SAS software package, version 9.1 (2002, SAS Statistical Institute, Cary, North Carolina).

## RESULTS

The 143 patients with first-time ischemic stroke included 93 males (age range: 31-87 years; mean age: 66.2 years) and 50 females (age range: 47-89 years; mean age: 67.7 years). Seizures occurred in 13 of the 143 first-ever ischemic stroke patients. The mean interval from the first stroke symptom to seizure onset ranged from 2 to 2045 days (mean: 737 days) (Fig. 1). Hypertension, diabetes mellitus, atrial fibrillation, and coronary artery disease were the four most common underlying diseases.

Among the 13 cases of seizure, two had acute symptomatic seizures while the other 11 had unprovoked seizures. In terms of the relation between seizure onset and the clinical ictus, two had early seizures, and the other 11 had late seizures. Furthermore, all of the 11 patients underwent follow-up brain MRI, neurological examinations and electroencephalogram study. No evi-

dence of recurrent stroke was found.

The mean time interval from the ischemic stroke to the first seizure among the early and late seizure groups were 5.5 days and 869.9 days, respectively (Fig. 1). None died during the acute phase of the ischemic stroke during hospitalization. As for the degree of seizure control after discharge, three were seizure-free without AED therapy, 9 were seizure-free under AED therapy, and one had 1-3 seizures per year. As for seizure sub-types, 10 had focal seizure with secondary generalization while the other three had just focal seizures. One of the ten with focal seizure and secondary generalization progressed into status epilepticus during hospitalization.

The locations of the ischemic infarction of the 143 cases were listed in Table 2. The most common sites among the 13 seizure patients were the cerebral cortex (77%, 10/13), followed by the basal ganglia (15%, 2/13) and the internal capsule (8%, 1/13).

The mean follow-up interval in the 143 patients was  $62.9 \pm 11.3$  months. Of the 130 patients without seizures, 129 survived while one died during hospitalization. One of the 13 patients who had seizures received decompres-

sive hemicraniectomy during hospitalization, and none of the 13 patients died. After a minimum follow-up period for six years, the median (inter-quartile range) GOS at the end of follow-up was 3<sup>(3,4)</sup> for patients with seizures and 4<sup>(3,4)</sup> for those without seizures ( $p = 0.84$ ). Therapeutic outcomes among the 143 cases after the follow-up period as determined by GOS were as follows: seven had a normal life (4.9%, 7/143), 83 had moderate disabilities (58%, 83/143), 52 had severe disabilities (36.4%, 52/143), and one died (0.7%, 1/143). Among the 13 seizure patients, only one patient had AED therapy-related skin rash during the follow-up period.

Comparisons of clinical features and neuro-imaging findings between the patients with and without seizures following ischemic cerebral infarction were documented after the six-year follow-up period (Table 1). Statistical analysis of the baseline clinical manifestations and neuro-imaging findings between the two patient groups revealed that atrial fibrillation as the underlying diseases ( $p = 0.002$ , OR=8.24, 95% CI=2.18-31.08) and presence of cortical distribution of ischemic infarction ( $p = 0.007$ , OR=6.67, 95% CI=1.67-26.64) were significant vari-

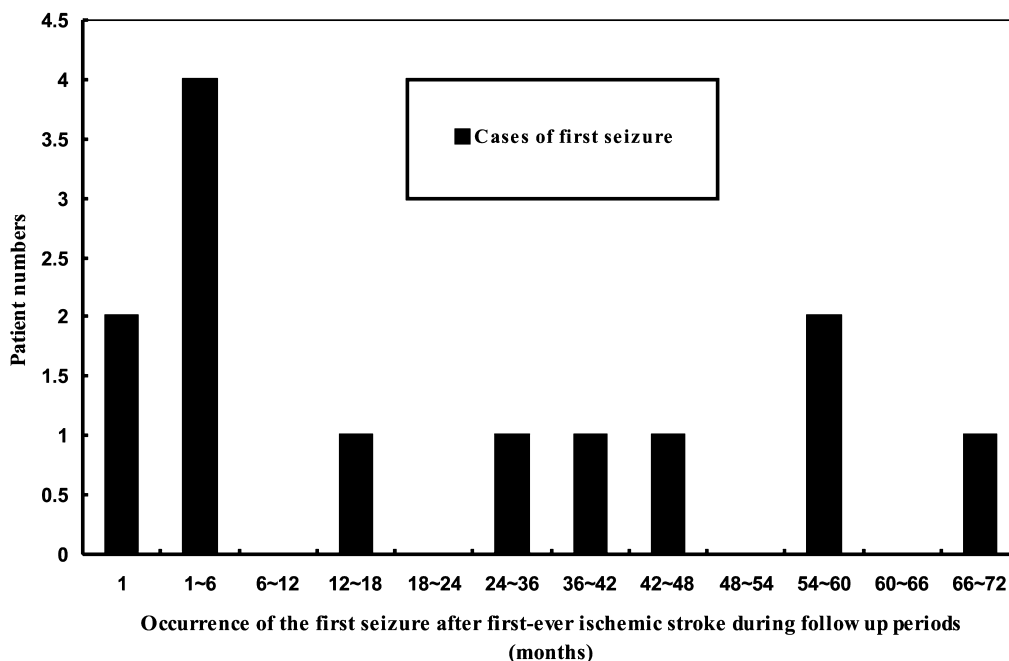


Figure 1. Numbers of patients with first seizure after cerebral infarction during the follow-up period.

**Table 1.** Comparisons of clinical features and neuro-imaging findings between patients with or without seizures following cerebral infarction after the six-year follow-up period.

	Without seizures N=130	With seizures N=13	P-value	OR	95% CI
Sex (Male/female)	81/49	12/1	0.061	7.26	0.92-57.56
Mean age at onset	66.4 ± 11.9	70.2 ± 12.8	0.28	1.03	0.98- 1.08
Mean systolic BP on admission	152 ± 25.0	141.8 ± 24.9	0.26	0.98	0.95- 1.01
Mean diastolic BP on admission	85.2 ± 15.3	81.8 ± 13.8	0.92	1.00	0.95- 1.05
Median (IQR) GCS on presentation	15 (15, 15)	15 (11.5, 15)	0.84	1.05	0.67- 1.64
Median (IQR) NIHSS on admission	4 ( 3, 9)	5 (4, 22)	0.32	1.08	0.93- 1.24
Median (IQR) Hospitalization days	9 ( 6, 16)	21 (9, 39.5)	0.19	1.01	1- 1.03
Neuroimaging findings on admission					
Mass effect	11	2	0.77	0.77	0.14- 4.20
Cortical distribution	45	10	0.007	6.67	1.67-26.64
Underlying diseases					
Hypertension	83	8	0.95	0.96	0.26- 3.55
Diabetes mellitus	47	5	0.35	1.94	0.49- 7.74
Atrial fibrillation	15	6	0.002	8.24	2.18-31.08
Coronary artery disease	14	1	0.64	0.59	0.07- 5.32
End stage renal disease	12	1	0.72	0.66	0.07- 6.63
Median (IQR) GOS at the end of follow-up	4 ( 3, 4)	3 ( 3, 4)	0.84	0.88	0.25- 3.16

Abbreviations: N, number of cases; OR, odds ratio; CI, confidence interval; ICH, Intra-cerebral hemorrhage; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; IQR, inter-quartile range

**Table 2.** Location of the ischemic stroke

	With seizures n=13	Without Seizures n=130
Location of ischemic stroke		
Cortical distribution	10	45
Basal ganglia	2	25
Corona radiata	0	24
Internal capsule	1	3
Thalamus	0	12
Others	0	21

ables. Variables used in the Cox's proportional hazards model thus included atrial fibrillation as the underlying diseases and presence of cortical distribution of ischemic infarction. After analysis of the aforementioned variables, only presence of cortical distribution of ischemic infarction ( $p=0.009$ , OR=5.549, 95% CI=1.53-20.19)

was independently associated with seizures.

## DISCUSSION

The prevalence and outcome of seizures following first-time ischemic infarction may be different in differ-

ent studies because of case determination and inclusion criteria, length of the follow-up period, underlying diseases, complications, and surgery. Although the frequency of seizures after ischemic infarction is estimated to be 4-10%<sup>(2-9)</sup>, most studies are retrospective investigations with variable follow-up periods. In this study, seizures occurred in 13 out of 143 (9.1%) first-time ischemic infarction patients, including acute symptomatic seizures in 1.4% (2/143) and unprovoked seizures in 7.7% (11/143). The incidence of epileptic seizures here is lower than in the other reported series [1,6], probably because of the inclusion criteria that we had enrolled only patients with first-time ischemic stroke but excluded the high risk group of ischemic stroke patients (e.g. pre-existing neurologic deficits and multiple silent or symptomatic cerebral infarctions).

The present study examines the predictive factors and outcome of seizures after first-time ischemic infarction. There are three major findings. First, the presence of cortical distribution of ischemic infarction is predictive of seizure occurrence. This is consistent with another study<sup>(2)</sup>. Second, atrial fibrillation is the major underlying disease in this specific patient group. Most cerebral emboli arise from the heart (e.g. atrial fibrillation, myocardial infarction with mural thrombi, and endocarditis). Unlike a thrombus, which adheres to the vessel wall, embolic particles are friable and migratory. In embolic types of ischemic stroke, branches of the middle cerebral arteries are the most frequently involved, thereby causing cortical distribution of ischemic infarctions<sup>(17,18)</sup>. Third, the incidence of seizures following first-time ischemic stroke is low, and most of the patients have delayed manifestations.

However, this study has several limitations. First, this is a retrospective analysis and therefore subject to the bias of unmeasured factors. It is also not possible to assess the effect of prophylactic AEDs after the acute stage of first-time ischemic infarction in the prevention of subsequent epilepsy or in the making of final conclusions. Second, patients with infratentorial infarction (e.g. cerebellum or brain stem), pre-existing neurologic deficits, and multiple silent or symptomatic cerebral infarctions have been excluded. Thus, there is continued uncertainty in assessing the incidence of seizures after

ischemic infarction in non-selected patients. Third, decompressive hemicraniectomy for massive middle cerebral artery infarction may cause potential brain insults and may result in unprovoked seizures during the follow-up period. Fourth, most patients in this study have been treated with anti-convulsants after the first acute symptomatic seizure, in accordance with the study protocol. Thus, the findings may underestimate the "true" frequency of seizures associated with the "natural history" of untreated unprovoked seizures.

This study demonstrates that the long-term outcome of patients with seizures tends to be worse than those without seizures, although the difference is not statistically significant. There are several possible causes of this tendency, including older age, association with cortical infarction, and decrease in the performance as well as independence in daily activities.

The use of prophylactic AED therapy in the prevention of seizures in patients with ischemic infarction remains controversial. The potential benefit is the reduction in functional morbidity. However, pharmacotherapeutic uncertainty exists regarding the need, choice of drug, dosing, and duration of seizure prophylaxis following ischemic infarction. In this study, most of the cases have remained seizure-free regardless of AED therapy. Based on currently available well-designed randomized controlled trials, no formal recommendations can be made for the use of prophylactic AEDs in patients with first-time ischemic infarction<sup>(19,20)</sup>.

In conclusion, the incidence of seizures following first-time ischemic stroke is low, and may have delayed manifestations. Cortical distribution of the ischemic infarction is a risk factor for the occurrence of seizures. The patients with seizure following ischemic stroke tends to have a worse outcome, which may be attributable to underlying brain pathologies. In regard to the potential side effects of anti-epileptic drugs, anti-epileptic therapy should be carefully administered to high risk patients with seizures after ischemic stroke (e.g. atrial fibrillation with embolic stroke and cortical infarction). Therefore, more prospective, randomized, double-blind trials are warranted to evaluate the efficacy of prophylactic AEDs in first-time ischemic infarction patients and to clarify the optimal treatment.

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