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Original Article

Clinical Profile and Outcomes of Early Seizures in Asian Patients With Acute Intracerebral Hemorrhage

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Background: Seizures are one of the most common complications of stroke. We aimed to establish the incidence and clinical profile of post-stroke early seizure (ES) in patients with intracerebral hemorrhage (ICH).
Methods: Patients with ICH within 10 days of onset who were admitted to Landseed International Hospital were recruited consecutively between January 1, 2006, and December 31, 2009. The National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale were used to access patients' initial stroke severity and functional outcome at discharge, respectively. The occurrence of epileptic seizures within 30 days after onset of the index ICH was recorded. Early post-ICH seizure was defined by the occurrence of clinically identified seizure episodes or non-epileptic seizure within 7 days after the stroke onset.
Results: A total of 297 ICH patients were included. The mean age of the participants was 62 ± 16 years, and 72% of them were male. A total of 9 (3%) participants had seizures during acute hospitalization. Patients with seizures had higher median NIHSS scores at baseline (34 vs. 16, $p = 0.004$). No difference was noted in the cortical involvement of ICH (22% for patients with seizures and 14% for those without, $p = 0.156$). Patients with seizures had higher in-hospital mortality (56% vs. 23%, $p = 0.024$). The multivariate Cox regression model showed the factors significantly associated with ES were higher initial NIHSS scores on admission (adjusted odds ratio [aOR] = 1.1 per 1 point increased, 95% confidence interval [CI] = 1.0–1.2) and coronary artery disease (aOR = 7.0, 95% CI = 1.3–36.4).
Conclusions: The NIHSS scores and coronary heart disease were associated with ES in ICH, whereas cortical involvement was not. These findings may reflect difference in post-stroke seizure and primary ICH between Asian and Western populations.

Key words: *seizures, intracerebral hemorrhage, stroke*

Introduction

Seizures are a common complication of acute stroke and may adversely affect neurological outcomes.[1-3] Although the definition of immediate, early and late seizure after stroke varies,[4] the patients with earlier onset of post-stroke seizure were reported to have different pathogenesis, associated factors and impact on prognosis from those with onset later on.[2,4] Early seizure (ES), defined as seizure within 7–14 days of stroke onset, has been reported in 2–6% of strokes and was reported to be a predictor of recurrent

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seizures.[5-7] The occurrence of ES was highest during the first 24 hours and decreased thereafter.[2,6,8] Post-stroke seizure is more often observed in patients with intracerebral hemorrhage (ICH) than with ischemic stroke and early post-ICH seizures were associated with greater stroke severity, larger brain lesions and more lobar hemorrhage.[2,3,9-12] Onset seizure, presenting seizure as the initial symptoms of ICH, with headache, vomiting and other focal or generalized symptoms, was around 7% of all ICH patients.[2,13] The likelihood of ES, including onset seizure, is influenced by cortical involvement of ICH, younger age, stroke severity, and previous ICH.[2] Although Asian people have higher incidences of ICH than Western populations,[14-16] studies on post-ICH seizure in Asian populations are limited.[12,17] Thus, we aimed to investigate the incidence and clinical profile of early post-ICH seizures in a Taiwanese population.

Methods

We prospectively recruited consecutive ICH patients admitted to Landseed International Hospital, a teaching hospital with a qualified stroke center in Taiwan with 650 beds. The patients were recruited from a prospectively pre-specified registry with admission within 10 days onset of stroke between January 1, 2006, and December 31, 2009. The patients with epileptic seizures within 30 days onset of the index ICH during acute hospitalization were identified. ES is defined as the occurrence of clinically identified seizure episodes or non-epileptic seizures identified by EEG recordings within 7 days onset of stroke and late seizure as those occurring beyond one week after stroke, as recommended by the definition of International League Against Epilepsy for acute symptomatic seizure.[6] Demographic and clinical characteristics were recorded at baseline, during hospitalization and at discharge. Details regarding the seizure types, onset time and dates, numbers of seizures, status epilepticus, and anti-epileptic treatments were collected by reviewing medical records.

The initial stroke severity was assessed with scores of the National Institutes of Health Stroke Scale (NIHSS) and of Glasgow Coma Scale. The functional outcome was defined as mortality or assessed using the modified Rankin Scale (mRS) at discharge. Computed tomography scans of each patient were reviewed for the location of intracranial hematoma. The study was approved by the Institutional Review Board of Landseed International Hospital.

Continuous variables were summarized as medians and interquartile ranges. The Mann-Whitney *U* test, Pearson chi-squared test, or Fisher's exact test was applied for univariate analysis as appropriate. The variables with p-value < 0.05 in the univariate analysis will be analyzed in the multivariate Cox regression model for the independent predictors for ES. The ICH to seizure onset time (days) was used as time variable. All analyses were performed using Stata 11 (StataCorp LLC., College Station, TX, USA).

Results

Of the 297 consecutive ICH patients (mean age 62 ± 16 years, 72% men), 9 (3%) had seizures during acute hospitalization (Table 1). All of the seizures were within 7 days of ICH onset. There was no difference in the portions of comorbidities of hypertension, diabetes mellitus, and hypertriglyceridemia between patients with ES and those without seizures. However, the percentages with hypercholesterolemia, a history of previous stroke, transient ischemic attack (TIA), and cardiac diseases and initial NIHSS scores were significantly higher in patients with ES. More cases of lobar ICH and fewer cases of deep ICH were observed in the ES group.

The ES group had longer lengths of stay (median 15 days vs. 8 days). All patients with ES had unfavorable outcomes at discharge, including 5 with in-hospital mortality and 4 with dependent states with mRS scores > 2. Patients with ES had higher in-hospital mortality (56% vs. 23%, $p = 0.024$).

The ES group had more stroke severity with higher median NIHSS scores (34 vs. 16) on admission, and 7 (78%) had severe ICH with NIHSS scores > 25. Among all ICH patients, 3 patients had surgical intervention of craniectomy. The time from ICH to seizure onset was < 24 hours for 3 patients (33.3%), and 1–7 days in other 6 patients (66.7%) (Table 2). The types of seizures of all patients were difficulty to be specified because of the lack of description of attacks in details in some records. All of them received Phenytoin as the first-line treatment.

In the multivariate Cox regression model for identifying the independent predictors for ES, including age, gender, previous stroke/TIA, hypercholesterolemia, coronary artery disease and initial NIHSS scores, we found higher NIHSS scores on admission (adjusted odds ratio [aOR] = 1.1, 95% confidence interval [CI] = 1.0–1.2, $p = 0.014$) and coronary artery disease (aOR =

7.0, 95% CI = 1.3–36.4, p = 0.022) were significantly associated with the occurrence of ES (Table 3).

Discussion

We observed a 3% incidence of ES in ICH patients during acute hospitalization. Recent studies with a follow-up of 7 days reported an incidence of post-ICH seizure ranging 3–16%.[18] The incidence was reported to be around 10 per 1,000 person-years in a nationwide retrospective matched-cohort study in Taiwan.[19] The incidence varies according to the study

Table 1. Characteristics of patients with and without early seizure (n = 297)

Variable	No seizure (n = 288)	Early seizure (n = 9)	p-value
Age, year, median (IQR)	62 (50–76)	62 (59–65)	0.732
Female	82 (28)	2 (22)	0.682
Hypertension	252 (88)	8 (89)	0.901
Diabetes mellitus	61 (21)	1 (11)	0.464
Hypercholesterolemia	66 (23)	5 (56)	0.024
Hypertriglyceridemia	49 (17)	3 (33)	0.205
Previous stroke/TIA	62 (22)	5 (56)	0.016
Atrial fibrillation	10 (3)	0 (0)	—
Heart failure	12 (4)	0 (0)	—
Coronary artery disease	16 (6)	2 (22)	0.039
ICH location			0.156
Lobar	39 (14)	2 (22)	
Deep	197 (68)	4 (44)	
Brainstem or infratentorial	41 (14)	2 (22)	
Others	11 (4)	1 (11)	
NIHSS scores on admission, median (IQR)	16 (7–31)	34 (30–35)	0.004
Length of stay, days, median (IQR)	8 (3–14)	15 (5–37)	0.155
Outcomes at discharge			
In-hospital mortality	66 (23)	5 (56)	0.024

Numbers of patients (%) are shown except otherwise indicated.
ICH: intracerebral hemorrhage; IQR: interquartile range; TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale.

Table 2. Demographics and characteristics of early post-intracerebral hemorrhage seizure

Subject No.	Age (years)	Gender	ICH location	ICH to seizure (days)	Seizure type	Seizure medication	NIHSS	GCS	Surgical intervention
1	59	Male	Putamen	< 1	Status epilepticus	Phenytoin	38	6	No
2	62	Male	Frontal	1–7	Unknown	Phenytoin	19	13	No
3	38	Male	Putamen	1–7	Focal	Phenytoin	35	5	No
4	66	Male	Putamen	< 1	Unknown	Phenytoin	20	9	Craniectomy
5	47	Male	Pons	2	Unknown	Phenytoin	35	3	No
6	74	Female	Frontal	4	Unknown	Phenytoin	30	10	No
7	61	Male	Putamen	< 1	Unknown	Phenytoin	38	3	Craniectomy
8	72	Female	Caudate	3	Unknown	Phenytoin	31	3	Craniectomy
9	63	Male	Pons	2	Unknown	Phenytoin	34	4	No

GCS: Glasgow coma scale, ICH: intracerebral hemorrhage, NIHSS: National Institutes of Health Stroke Scale.

Table 3. Possible precipitating factors of early seizure (n = 297)

Variables	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Age (year)	1.0 (0.9–1.0)	0.689	1.0 (0.9–1.0)	0.694
Gender (male)	1.6 (0.3–7.8)	0.550	1.8 (0.3–8.8)	0.497
NIHSS on admission	1.1 (1.0–1.3)	0.010	1.1 (1.0–1.2)	0.014
Hypercholesterolemia	2.6 (0.7–9.8)	0.148	2.9 (0.8–11.4)	0.120
Previous stroke/TIA	2.5 (0.7–9.2)	0.177	2.9 (0.7–12.2)	0.157
Coronary artery disease	4.0 (0.8–19.4)	0.083	7.0 (1.3–36.4)	0.022

CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; OR: odds ratio; TIA: transient ischemic attack.

design and clinical attention of the seizure and EEG study may underestimate post-stroke seizure in certain cases.[20] The presence of status epilepticus in the ES group is associated with later recurrence.[21]

Most studies define seizures occurring within 7 days of stroke onset as ES, and a review of ICH reported that about 50–70% of seizures occur within the first 24 hours after onset, with 90% occurring in the first 3 days.[2,3,22,23] In our study, over 30% of seizures occurred within 24 hours, and all cases occurred within 7 days after the onset of ICH. It could vary in different studies since some ICH patients might be too critical to have the definite diagnosis of ICH at Emergency Room, and some seizures might not be clinically overt.

Our results did not support the cortical involvement of ICH being associated with ES, although several studies reported the association.[1,3,10] For supratentorial ICH, greater initial stroke severity on admission might imply more extensive parenchyma damage to the brain and the subsequent development of cortical irritation and seizure.[24] Larger and cortical lesions of ischemic stroke were also associated with post-stroke seizure in ischemic stroke.[17,25]

ES was associated with more initial severity of ICH as higher baseline NIHSS scores in our study. Notably, an earlier hospital-based registry in Taiwan reported that among 2021 ICH patients, 518 (26%) had lobar ICH (including cortical and subcortical lesions).[15,16] However, Western studies reported 25–38% cortical involvement and more lobar lesions (39%) in patients with ICH.[10,14] In our study, the cortical involvement failed to show an association with post-ICH seizure. There could be difference in both the rates of cortical involvement in primary ICH and the characteristics of post-ICH seizure between Taiwanese and Western populations. Our study showed coronary artery disease was significantly associated with post-ICH seizure.[26] Hypercholesterolemia, no longer significant in our multivariate analysis, is strongly associated with increased risk of coronary heart events, but its relationship with ICH is complex. The recent study and meta-analysis showed the risk of ICH decreases with higher cholesterol levels, but statin treatment did not increase or might even decrease ICH risk.[27,28] Statin use was also reported to decrease the risk of hospitalization for epilepsy.[29]

The patients with post-ICH seizure had higher in-hospital mortality in our study, which is in line with higher initial severity of ICH in the group.

As higher initial NIHSS scores are correlated with the incidence of early post-ICH seizure, higher index of suspicion and attention should be kept for the patients with high NIHSS scores. ES is not associated with higher risks of mortality at 7 days, 1 month, or 1 year in previous studies.[1,3,7] The association between initial severity, early post-ICH seizure, and the prognosis varied among studies. In a large administrative dataset, patients with post-ICH seizure did not have increased in-hospital mortality.[3,10,30] In a recent review of post-stroke seizure, the initial severity and cortical involvement of patients with acute ischemic strokes were factors that predict the likelihood of developing post-stroke seizures.[9]

This study had several limitations. Our findings were based on data obtained from a single hospital-based stroke registry, and patients with severe ICH might be transferred to other medical centers and were thus not included. Due to a low incidence of seizure after ICH onset, only a limited number of cases within 3 years is available. The recruited population was too small to support a more solid conclusion. However, we do find the difference in post-stroke seizure and primary ICH between Asian and Western populations. EEG study was not regularly conducted in all ICH cases, so underestimation of the cerebral epileptic discharge

could occur.[20] Cortical involvement failed to show an association with post-ICH seizure. More studies are required to investigate whether the lower incidence of lobar ICH in Taiwanese people implies less significant contribution of cortical involvement to ESs.

Conflicts of Interest Statement

No conflict of interest.

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