

Factors Predictive of Outcome in Posttraumatic Seizures

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Background: Seizures are important neurologic complications of traumatic brain injury (TBI). There is a need for better delineation of potential prognostic factors and outcomes in patients with posttraumatic seizures (PTS) who could receive treatment when brought to the hospital.

Methods: In this 10-year retrospective study, 170 adult patients with PTS were enrolled in this study. The degree of

seizure control was analyzed using a Seizure Frequency Scoring System, which classified them into excellent and nonexcellent outcomes.

Results: There were 170 patients with acute symptomatic seizure enrolled in this study, 106 of whom had early PTS, whereas 64 had late PTS. Of the 106 early PTS, 58% (61 of 106) occurred within 24 hours of trauma. Risk factors for developing nonex-

cellent outcome included patients who undergo surgical intervention and presence of late-provoked seizures during the acute phase of TBI.

Conclusions: Seizures are an important neurologic complication of TBI. Regarding the potentially side effects of antiepileptic drugs, antiepileptic therapy should be carefully administered in those nonexcellent outcome patients.

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Traumatic brain injury (TBI) is one of the major causes of disability, morbidity, and mortality among individuals younger than 45 years and is responsible for a significant proportion of traumatic deaths in developed countries.^{1,2} The overall risk of seizures after TBI ranges from 2% to 5% in the general population^{3,4} but is from 7% to 39% in patients with cortical injury and neurologic sequelae.⁵

One population-based study demonstrates that 86% of patients with a single late posttraumatic seizure (PTS) had a second seizure within 2 years.⁶ Because of the possible benefits of antiepileptic drugs (AED) to reduce the degree of functional morbidity after TBI, there is a need for better delineation of potential prognostic factors and outcomes in nonselected patients admitted to the hospital who could receive treatment.

In this study, the role of a number of clinical observations, neuroimaging findings, and Glasgow Coma Scale (GCS) score measurements were analyzed in terms of predicting the outcome of PTS. We chose to study (1) the clinical relevance of PTS and other neurologic complications that occur after TBI; (2) the types of seizures that occur during acute phase of TBI; and (3) the potential prognostic factors during the acute illness for the long-term outcome.

PATIENTS AND METHODS

During a period of 10 years (1994–2003), 9,212 patients who suffered from first event TBI were admitted to the Department of Neurosurgery at the Chang Gung Memorial Hospital in Kaohsiung. Chang Gung Memorial Hospital-Kaohsiung is a 2,482-bed acute-care teaching hospital, which is the largest medical center in southern Taiwan that provides both primary and tertiary referral care to patients. Of the 9,212 patients, 190 suffered from acute symptomatic seizures during the acute phase of TBI.

The definition of PTS was set according to that in previous studies: seizure occurring after head trauma that is causally related to the trauma itself.^{7,8} A provoked (acute symptomatic seizure) seizure is one that occurs in close temporal relation with TBI, which is presumed to be the underlying cause. In contrast, an unprovoked seizure is a seizure occurring in the absence of one or more precipitating factors, and it includes events occurring in patients with antecedent stable (nonprogressing) CNS insults, including TBI (remote symptomatic seizures).^{7,8}

The definition of onset of acute symptomatic seizure during hospitalization was modified from those of a previous study⁹ classification into two subtypes: early-provoked seizures as seizures occurring within the first 7 days after injury, and late-provoked seizures as those occurring 7 days later but before discharge. In contrast, an unprovoked seizure is a seizure occurring in the absence of one or more precipitating factors, while epilepsy is the occurrence of repeated unprovoked seizures.¹⁰ Status epilepticus was modified from those of previous reports and defined as both of the following: (1) continuous seizures lasting at least 5 minutes; and (2) two or more discrete seizures between which there is incomplete recovery of consciousness.^{11,12}

Patients initially treated in other hospitals but subsequently transferred to our hospital for further therapy were also included in the study and their initial clinical and laboratory data at the previous hospital were used for analysis.

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Patients were excluded from the study if (1) they had a history of TBI; (2) preexisting epilepsy; (3) gunshot wounds or penetrating head injuries; (4) preexisting neurologic conditions with various neurologic deficits; and (5) death within 1 month. The study had enrolled a total of 170 patients.

Demographic data of the 170 patients, characteristics and circumstances, time interval from TBI to first seizure, the types of seizure, and several other features were documented, including length of hospital stay, the presence and duration of chronic epilepsies, neurosurgical interventions, and systemic underlying diseases associated with seizures. The GCS score was analyzed by neurosurgeons when the patient arrived in the emergency room.

TBI was defined as an alteration in brain function manifesting as confusion, altered consciousness, seizure, coma, or focal sensory or motor neurologic deficit resulting from blunt or penetrating force to the head.¹³ TBI was classified as mild (loss of consciousness or amnesia lasting less than 30 minutes), moderate (loss of consciousness for 30 minutes to 24 hours or a skull fracture), or severe (loss of consciousness or amnesia for more than 24 hours, subdural hematoma, intracerebral hematoma, or brain contusion).²

All of the patients received brain computed tomography (CT) scans soon after arrival at the emergency room. Furthermore, follow-up brain CT scans were performed if clinical deterioration was noted, including acute onset of focal neurologic deficits, seizures or status epilepticus, and a progressively disturbed conscious state. All diagnoses of intracranial contusion or hematoma were based on brain CT evidence.

Our standard protocol was to administer AEDs only to those who had acute symptomatic seizure in TBI, whereas prophylactic AED therapies were not given to those without such symptoms in the acute stage of TBI. We usually administered AEDs for less than 7 days to patients who had early-provoked seizures, while AEDs were continued for longer periods to prevent the development of unprovoked seizures in those with late-provoked seizure. The basis of discontinuing AEDs of late-provoked seizure patients after hospital discharge included all of the following: (1) serial electroencephalogram (EEG) showed no evidence of epileptiform discharge or seizure-free clinically for more than 2 years; and (2) no risk factors for seizures recurrence, which include prolonged duration before seizure was controlled; high frequency of seizures before control; focal neurologic abnormalities; poor mentation; complex partial seizures; and consistently abnormal EEGs.^{14,15}

The follow-up period was terminated by death or by the end of the study itself (December 2004). Therapeutic outcomes and the degree of seizure control after discharge were analyzed by a Seizure Frequency Scoring System, which is slightly modified from Engel et al.⁷ (Table 1). For purposes of analysis, a score of 4 or below was defined as an excellent outcome, and 5 or more as nonexcellent.⁷ The outpatient department followed up most patients after discharge, with

Table 1 Scoring System for Seizure Frequency

Seizure Frequency	Score
Excellent outcome	
Seizure free, off antiepileptic drug	0
Seizure free, need for antiepileptic drug unknown	1
Seizure free, requires antiepileptic drug to remain so	2
Nondisabling simple partial seizures	3
Nondisabling nocturnal seizures only	4
Non-excellent outcome	
One to three times per yr	5
Four to 11 times per yr	6
One to three times per mo	7
One to six times per wk	8
One to three times per d	9
Four to 10 times per d	10
More than 10 times per d but not status epilepticus	11
Presence of status epilepticus	12

Slightly modified from Engel et al.⁷

others interviewed through telephone to identify neurologic outcome.

The clinical data, including gender and clinical manifestations between the two patient groups ("excellent outcome" and "nonexcellent outcome") during the acute phase of TBI, was analyzed by means of a χ^2 test or Fisher's exact test. The mean ages between the two patient groups were analyzed by Student's *t* test. GCS score at the time of admission and duration of hospitalization between the two patient groups was analyzed by Wilcoxon rank sum test.

The association between (1) early or late PTSs and (2) presence of surgical intervention, and the survival curve between the two patient groups ("excellent outcome" and "nonexcellent outcome") were assessed with Kaplan-Meier Plots and compared by log-rank test. Stepwise logistic regression was used in evaluating the relationship between clinical factors and outcome of seizure, with adjustments made for other potential confounding factors. All statistical analysis was conducted using the SAS software package, version 9.1 (2002, SAS, Inc., Cary, NC).

RESULTS

The 170 patients with acute symptomatic seizure included 126 males (age range, 2 months–87 years; mean age, 39.6 years) and 44 females (age range, 3 months–83 years; mean age, 46.5 years). Among these, 134 had excellent outcome and 36 had nonexcellent outcome (Table 2). The degree of seizure control after discharge for all 170 cases is listed in Figure 1. The mean age at onset was 40.5 years $\pm$ 24.7 years for those who had an excellent outcome and 44.6 years $\pm$ 20.9 years for those who had a nonexcellent outcome. The mean time length of hospitalization was 21.4 days $\pm$ 16.8 days and 33.3 days $\pm$ 29.7 days for those with excellent and nonexcellent outcomes, respectively ($p \leq 0.001$).

No one was excluded because of loss to follow-up. Follow-up interval in the 170 patients was 1 month to 204 months

Table 2 Prognostic Factors of Posttraumatic Seizures

	Excellent Outcome, N = 134	Nonexcellent Outcome, N = 36	p Value	Odds Ratio	95% CI
Age (yrs)	40.5 ± 24.7	44.6 ± 20.9	0.358		
Gender					
Male	96	30	0.155		0.19–1.31
Female	38	6			
Clinical features					
Posttraumatic amnesia	94	23	0.472		0.61–2.88
Brief unconsciousness	72	20	0.845		0.44–1.95
Motor deficits	53	17	0.406		0.35–1.53
Severity of brain injuries*					
Mild	19	6	0.577		0.32–2.39
Moderate	10	1			0.34–22.47
Severe	105	29			
GCS at admission	10.5 ± 3.9	10.4 ± 3.7	0.726		
Neuroimaging finding†					
Depressed skull fracture	12	4	0.749		0.24–2.60
Cortical contusion	41	9	0.513		0.57–3.06
Subdural hematoma	88	27	0.288		0.28–1.47
Epidural hematoma	9	2	1.0		0.25–5.93
Intracerebral hematoma	27	12	0.095	0.51	0.22–1.14
Acute symptomatic seizure					
Onset of seizure					
Early-provoked seizures (≤7 d)	95	11	≤0.001	5.54	2.48–12.34
Late-provoked seizures (>7 d)	39	25			
Subtype of seizure					
Generalized	63	17	0.982		0.47–2.07
Focal with or without generalization	71	19			
Status epilepticus	6	2	0.677		0.24–6.50
Surgical intervention					
Nonsurgery	63	7	0.003	3.68	1.51–8.97
Surgery	71	29			
Duration of hospitalization	21.4 ± 16.8	33.3 ± 29.7	≤0.001		

The clinical data, including gender and clinical manifestations between the two patient groups ("excellent outcome" and "non-excellent outcome") was analyzed by means of a χ^2 test or Fisher's exact test. The mean ages between the two patient groups were analyzed by Student's *t* test. GCS at the time of admission and duration of hospitalization between the two patient groups was analyzed by Wilcoxon rank sum test.

* Relative to "severe brain injury".

† Fifty-one patients had more than one abnormal neuroimaging findings.

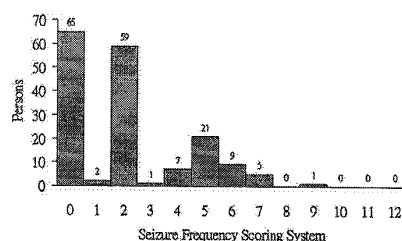


Fig. 1. Results of seizure frequency score. For the purposes of analysis, a score of four or below was defined as an excellent outcome, and five or more as nonexcellent.

(mean, 29.5 months). Aside from TBI, 42 patients had one or more other underlying conditions, which included diabetes mellitus (37), hypertension (9), iatrogenic Cushing's syndrome (6), and pneumonia (8).

During hospitalization, 106 had early PTSs, whereas 64 had late PTSs. Furthermore, 57.5% (61 of 106) oc-

curred within 24 hours of trauma. The mean time interval between the onset of TBI and early PTSs was 2.1 days ± 1.6 days, and 14.7 days ± 5.8 days for the late PTSs ($p \leq 0.001$).

Regarding seizure subtypes, 77 had generalized seizures and 93 had focal seizures with or without generalization. The 77 generalized seizures included generalized tonic-clonic seizures in 73 and myoclonic seizure in 4. The latter 93 focal seizures included simple focal seizures in 63 and focal seizures evolving to generalized tonic-clonic convulsions in the remaining 30 (Table 3). The frequency of seizures during the acute phase of TBI was: 95 had one episode of seizures, 67 had more than one episode, and 8 progressed to status epilepticus. Of these eight cases, two had nonexcellent outcome and six had excellent outcome (with five seizure-free after completing the treatment for TBI). The outcome of PTS was strongly associated with the development of early PTSs ($p \leq 0.001$), although no difference was noted between focal and generalized seizures ($p = 0.982$).

Table 3 Relations Between Therapeutic Outcomes, Neuroimaging Findings, and Seizure Subtypes

Seizure Subtypes	Brain CT at the Time of Admission					Outcomes		
	Depressed Skull Fracture (N = 16)	Contusion (N = 50)	EDH (N = 11)	SDH (N = 115)	ICH (N = 39)	Excellent		Nonexcellent (N = 36)
						Seizure Free (N = 126)	Score 3 & 4 (N = 8)	
Generalized seizures (N = 77)								
Tonic-clonic seizure (N = 73)	8	28 (2)*	5	42 (2)	15 (1)	54 (4)	3	16 (1)
Myoclonic seizure (N = 4)	0	0	0	3	0	4	0	0
Focal seizures with or without generalization (N = 93)								
Focal seizures (N = 63)	7	19	5	50	13	48	3	12
Focal seizures evolving to tonic-clonic convulsions (N = 30)	1	3	1	20 (1)	11 (1)	20 (1)	2 (1)	8 (1)

* Values in parentheses indicate number of cases progressed to status epilepticus during acute stage of traumatic brain injury.

Regarding the relationship of the onset of acute symptomatic seizure (early PTSs and late PTSs) to the frequency of seizures during the acute phase of TBI (one episode, more than one episode, and presence of status epilepticus), to the type of seizures (tonic-clonic seizure, focal seizures evolving to tonic-clonic convulsions, and focal seizures), to the severity of TBI (mild, moderate, and severe TBI), the statistical analysis showed the following: (1) there was no relationship between the onset of acute symptomatic seizure (early PTSs and late PTSs) and the frequency of seizures (one episode, more than one episode, and presence of status epilepticus) ($p = 0.298$); (2) there was a significant relationship between the onset of acute symptomatic seizure (early PTSs and late PTSs) and the subtypes of seizures (generalized tonic-clonic seizure, myoclonic seizure, focal seizures evolving to tonic-clonic convulsions, focal seizures, and status epilepticus) ($p \leq 0.001$); and (3) there was no relationship between the onset of acute symptomatic seizure (early PTSs and late PTSs) and the severity of TBI (mild, moderate, and severe TBI; $p = 0.425$).

The other clinical data of the 170 patients are listed in Table 2. Furthermore, the mean score of GCS score at admission between excellent and nonexcellent outcomes was 10.5 ± 3.9 and 10.4 ± 3.7 , respectively ($p = 0.726$).

Among the 170 cases, only 69 had at least one EEGs after PTE. Fifty-eight had abnormal EEG readings of which 38 had EEG readings that showed a predominantly unilateral abnormality, whereas 20 had diffuse abnormality. In the 38 cases, 10 were tonic-clonic seizures, 14 were focal seizures, 8 were focal seizures evolving into tonic-clonic convulsions, 2 were myoclonic seizures, and 4 were status epilepticus. Of the latter 20 cases, four were focal seizures, four were focal seizures evolving into tonic-clonic convulsions, one was myoclonic seizure, and two were status epilepticus. Among the 11 cases with normal EEG readings after PTS, 6 were tonic-clonic seizures, 2 were focal seizures, 2 were focal

seizures evolving into tonic-clonic convulsions, and 1 was status epilepticus.

During hospitalization, 160 had abnormal neuroimaging findings (Table 2). Of these, 128 had excellent outcome while 32 did not. In the 10 cases with normal neuroimaging findings, 6 had excellent outcome. There was no statistically significant relationship between abnormal neuroimaging findings and outcome (excellent and nonexcellent outcomes; $p = 0.222$).

Of the 170 patients enrolled in this study, 45 received more than one AEDs therapy. Of these 45 patients, 36 received 2 AEDs, 7 received 3 AEDs, and 2 received more than 3 AEDs. The other 125 patients included 103 who received phenytoin, 13 who received phenobarbital, 5 who received valproic acid, and 4 who received carbamazepine. The mean duration of AEDs use in the late-provoked seizure group was $37.1 \text{ months} \pm 36.4 \text{ months}$. The adverse effects of AEDs included the following: hematologic disorders (leukocytosis or eosinophilia) in 12, cognitive impairment in 11, abnormal liver function in 10, skin rash in 10 (with one progressing to Stevens-Johnson Syndrome), gastrointestinal symptoms in 9, lethargy or fatigue in 5, tremor in 3, phlebitis in 2, weight change in 1, and gingival hyperplasia in 1.

Comparisons of clinical features and laboratory data between excellent or nonexcellent outcome of TBI were listed in (Table 2). Statistical analysis of the clinical manifestations and laboratory data between the two patient groups revealed the following significant findings: onset of acute symptomatic seizures (early or late PTSs; $p \leq 0.001$), whether surgical intervention was necessary or not ($p = 0.003$), and duration of hospitalization ($p \leq 0.001$). Variables used in the logistic regression included onset of acute symptomatic seizures (early or late PTSs) and necessity of surgical intervention. After analysis of all the aforementioned variables, only onset of acute symptomatic seizures (early or late PTSs; $p \leq 0.001$) was independently associated with outcome of seizures.

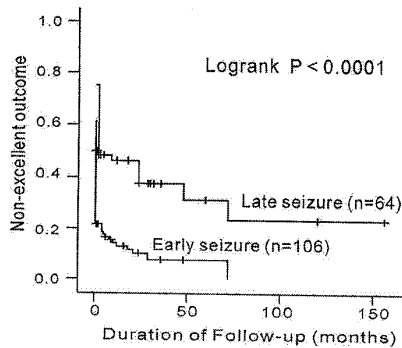


Fig. 2. Kaplan-Meier plots indicating the percentage of nonexcellent outcome in the 170 PTS patients after traumatic brain injury. The patients were divided into two groups: those with late PTSs, and those with early PTSs. The p value was obtained by log-rank comparison of data.

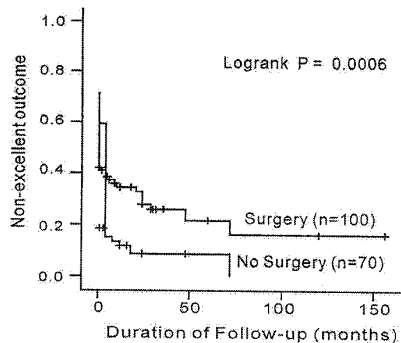


Fig. 3. Kaplan-Meier plots indicating the percentages of nonexcellent outcome in the 170 PTS patients after traumatic brain injury. The patients were divided into two groups: those with and those without surgical evacuation. The p value was obtained by log-rank comparison of data.

To look at each factor individually, we calculated Kaplan-Meier estimates of the fraction developing nonexcellent outcome by different times for each subgroup and tested for differences by using a log-rank test. Onset of acute symptomatic seizures (early or late PTSs) and necessity of surgical intervention between the two patient groups (excellent and nonexcellent outcome) showed the following: onset of acute symptomatic seizures (early or late PTSs; $p \leq 0.0001$; Fig. 2), and necessity of surgical intervention ($p = 0.0006$; Fig. 3).

DISCUSSION

The occurrence of seizures after head injury is a recognized complication of TBI and is known to worsen functional outcome significantly afterward.¹⁶ Much work has been performed in preventing the development of, or, at least, minimizing the impact of PTSs. In our study, acute symptomatic seizures accounted for 2% (190 of 9,212) of all episodes.

Among the 170 acute symptomatic seizure cases that were enrolled in this study, 44 (26%, 44 of 170) progressed to unprovoked seizures, whereas 126 (74%, 126 of 170) became seizure-free with or without AED therapy. The percent of early and late symptomatic seizures accounted for 62% (106 of 170) and 38% (64 of 170) of episodes in our study, respectively.

The onset of PTSs has significant implications for subsequent treatment and the quality of life of the patient. An important question, therefore, is whether there are prognostic factors that can identify the seizure frequencies of patients after the first acute symptomatic seizures. The risk of developing PTSs is primarily analyzed by the severity of the antecedent head injury, with high-risk factors that include neurologic characteristics such as acute intracranial hematoma, depressed skull fracture, dural penetration, the presence of focal neurologic deficits, a deep and lengthy coma, or prolonged impairment of consciousness.^{17,18}

In this study, we demonstrated that early acute symptomatic seizures (<7 days) during the acute phase of TBI had better outcomes than for those who did not, though there was no difference noted between focal and generalized seizures. The mean duration of hospitalization during the acute phase of TBI was shorter among those who had excellent outcomes. Our study also demonstrated that there was a significant relationship between the onset of acute symptomatic seizure (early or late PTSs) and seizure subtypes (generalized tonic-clonic seizures, myoclonic seizures, focal seizures evolving to tonic-clonic convulsions, and focal seizures). We also found that the necessity of neurosurgical interventions strongly influenced the outcome of seizure frequency.¹⁷ The nonexcellent outcome in this study may be attributed to an underlying brain pathology, surgical intervention, or a combination of complications.

Significant differences in study methods, particularly in case ascertainment and inclusion criteria, make study comparisons difficult, particularly among subgroups of TBI patients. Furthermore, clinical research for seizure prevention have several methodologic disadvantages,¹⁸⁻²² including: (1) the patients are heterogeneous and have different propensities in developing unprovoked seizures; (2) prolonged period required for the occurrence of unprovoked seizures in several individuals, which may affect patient compliance; (3) long-term treatment in patients developing seizures during the treatment; and (4) the increasingly predominant practice of starting AEDs after just one seizure, which may lessen the difference seen after the study drugs are discontinued and changing the natural history of PTS.

Based on the above studies, AED prophylaxis seems to control provoked seizures in patients with TBI, although it does not seem to prevent the subsequent development of unprovoked seizures, which are poorly tolerated and even detrimental to cognitive and behavioral function. Our standard protocol in administering AEDs is only for those who have had seizures in the acute stage of TBI, continuing this to

prevent the development of later epilepsy. We do not use prophylactic AEDs therapy for those who do not have seizures in the acute stage of TBI.

Although our study demonstrates that the time of onset of acute symptomatic seizures after TBI influences the outcome after PTSs, our study has several limitations. First, this is a retrospective analysis and is, therefore, subject to bias of unmeasured factors. It was also not possible to assess the effect of prophylactic AEDs after the acute stage of TBI to prevent later epilepsy or draw any conclusions. Second, only those who had acute symptomatic seizures during the acute phase of TBI were enrolled. Thus, continued uncertainty was present in assessing the incidence of unprovoked seizures after TBI in nonselected patients. Third, most patients in this study were treated with anticonvulsant medication after their first acute symptomatic seizure, in accordance with our study protocols. Thus, our findings may underestimate the "true" frequency of seizure associated with the "natural history" of untreated unprovoked seizures.

Several studies focused on the effects of AEDs for preventing seizure after TBI.^{8,19-26} All of their conclusions showed that the use of AEDs should be short (usually less than 7 days). The adverse effects of AEDs accounted for 0.6% to 19.4% in different series.^{25,26} Because this is a retrospective study, the start of AED therapy would differ for each patient according to the preference of his or her doctor, which may cause potential bias in statistical analysis. Furthermore, our study only focused on patients who had seizures after acute traumatic head injury. It would be difficult to evaluate both the efficacy and adverse effects of AED prophylaxis for PTS and draw a conclusion.

In conclusion, seizures are an important neurologic complication of TBI. Although antiepileptic therapy is usually short-term for patients with early-provoked seizures, 26% (44 of 170) of cases with early-provoked seizures progress to unprovoked seizures. Regarding the potentially side effects of AEDs, antiepileptic therapy should be carefully administered in those nonexcellent outcome patients including those patients who undergo surgical intervention and have late-provoked seizures during the acute phase of TBI.

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