Status Epilepticus After Stroke

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Background and Purpose—The main objective of our study was to determine the risk and predictive factors of status epilepticus (SE) after stroke.

Methods—From 1988 to 2000, 1174 patients were admitted to the Department of Neurology at the Karadeniz Technical University Farabi Hospital with first-time strokes. Of these, 180 patients had poststroke first-time seizures (PFSs). We followed these 180 PFS patients for an average of 3.7 years or until death to determine the occurrence rate of SE. By comparing these data with those of PFS patients without SE, we investigated whether there were significant differences.

Results—A total of 17 of the 180 PFS patients (9%) had SE. There was no relationship between the occurrence of SE and stroke risk factors, stroke type (ischemic or hemorrhagic stroke), stroke topography and cause, cortical involvement, size of lesion, seizure type, or electroencephalographic findings. SE occurred more frequently among patients with a higher disability rating (Rankin scale >3; odds ratio, 4.36). Recurrent SE was identified in 5 of 17 patients with SE. In all 5 of these patients, the first episode of SE occurred within the first 7 days after stroke (early-onset SE). Statistical analysis demonstrated that early-onset SE was associated with a higher risk for SE recurrence ($P=0.003$) and a higher mortality rate ($P=0.04$).

Conclusions—SE was not associated with a higher mortality rate but with higher functional disability. We also found that early-onset SE (within the first 7 days after stroke) was associated with a higher risk for SE recurrence and a higher mortality rate than late-onset SE (after 7 days after stroke). **(*Stroke*. 2001;32:1169-1172.)**

Key Words: epilepsy ■ seizures ■ stroke outcome ■ stroke, acute

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Status epilepticus (SE) is defined as a seizure or a series of repetitive seizures without recovery between episodes that lasts >30 minutes. The role of stroke as an etiologic factor for SE is accepted.[1,2] Although the occurrence of epileptic seizures complicating acute stroke is well recognized, SE has received little attention.[3–6] Few studies on clinic data or prognosis are available.[2,7,8]

Using a hospital-based stroke cohort, we studied a series of patients with poststroke first-time seizure (PFS) to find out which factors may be associated with SE.

Subjects and Methods

Included in this study were 1676 stroke patients without an accompanying diagnosis of brain tumor or arteriovenous malformation who were admitted consecutively to the Department of Neurology of Karadeniz Technical University Farabi Hospital (an acute-care, 492-bed hospital in Trabzon, Turkey) between February 1988 and January 2000. A retrospective chart review was performed. We excluded patients with a history of seizure, subarachnoid hemorrhage, head injury, hypertensive encephalopathy, and cerebrovenous thrombosis. We included only patients with first-time ischemic strokes and primary intracerebral hemorrhages. After these restrictions, a study population of 1174 patients with first-time stroke was defined. All patients were admitted to the hospital within the first 3 days of onset of symptoms. There were 161 patients with transient ischemic attack who had no seizures. One hundred eighty patients had a PFS; 17 of these patients had SE.

All patients with PFS had a cerebral computed tomography (CT) scan and electroencephalography (EEG). The patients with lesions that could not be identified from CT as cortical or subcortical also had magnetic resonance imaging (MRI). In all patients, plasma urea, creatinine, electrolyte, and plasma glucose levels were measured on admission. Overall, 72% of patients were studied by MRI. Other investigations included arterial digital subtraction angiography in 24%, duplex ultrasound of the carotid arteries in 42%, and echocardiography in 82%. The degree of functional disability at the end of the acute phase was graded by a modified Rankin scale.[9] Seizures were diagnosed and classified according to the definitions of the International League Against Epilepsy.[10,11] SE was defined as a seizure or a series of continuing seizures lasting >30 minutes without full recovery between seizures.[12] Unprovoked seizures refer to seizures that occurred without identifiable acute precipitants. "Early" referred to seizures and SE occurring within 1 week after stroke that were considered to be provoked by the stroke. Unprovoked seizures and SE developing beyond 1 week after stroke were called "late." The diagnosis was based on direct observation of seizures by the medical staff at the time of hospitalization or on the history of the neurologist in charge of the patient or was determined according to reliable descriptions obtained from ambulance personnel when seizures occurred during transportation or from the patients or close family members when seizures occurred at home. EEG was performed 24 to 48 hours after the seizures in all PFS patients. EEGs were considered abnormal when focal, lateralized, or generalized slowing or epileptiform discharges were present. All hospital and outpatient records since the stroke were reviewed. Survivors were contacted by telephone or in person in 1998 and again in 2000. Follow-up data were evaluated for a mean of 3.7 years.

Received October 30, 2000; final revision received January 29, 2001; accepted February 2, 2001.

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TABLE 1. Comparison of Data of PFS Patients With (Group 1) and Without (Group 2) SE

	Group 1 (n=17) n (%)	Group 2 (n=163), n (%)	P
Sex, M/F	10/7	78/85	0.054
Age, (mean±SD), y	58.3±10	62.6±10	0.089
Stroke risk factors, n (%)			
Hypertension	6 (35)	73 (45)	0.62
Diabetes	4 (24)	31 (19)	0.74
Smoking	7 (41)	61 (37)	0.96
Hypercholesterolemia	2 (12)	15 (10)	0.66
Coronary heart disease	4 (24)	46 (28)	0.79
Atrial fibrillation	4 (24)	48 (29)	0.78
Seizure type, n (%)			
Generalized onset	9 (53)	91 (56)	
Partial onset	8 (47)*	67 (41)†	0.71334
Unclassifiable	0	5 (3)	
EEG findings, n (%)			
Focal or lateralized slowing	4 (24)	43 (26)	
Epileptiform discharge	3 (18)	47 (29)	0.49671
PLED	10 (58)	73 (45)	
Ischemic stroke,‡ n (%)	12 (71)	109 (67)	
Territory§			
MCA	10 (83)	101 (93)	0.2586
PCA	2 (17)	8 (7)	
Cause§			
Cardioembolism	4 (33)	35 (32)	
Large artery disease	7 (58)	64 (59)	0.9931
Other	1 (8)	7 (6)	
Undetermined	0	3 (3)	
Hematoma,‡ n (%)	5 (29)	54 (33)	
Lentricular§	2 (40)	16 (300	0.6358
Lobar§	3 (60)	38 (70)	
Size of lesion, n (%)			
≤10mm, <5 slices	6 (35)	40	0.3819
>10mm, 5 slices	11 (65)	123 (75)	
Localization of lesion, n (%)			
Cortical	13 (76)	119 (73)	1.000
Subcortical	4 (24)	44 (27)	
Functional disability (Rankin scale)			
≤3	5 (29)	114 (70)	0.00200
>3	12 (71)	49 (30)	

PLED indicates paroxysmal lateralized epileptic discharges; MCA; middle cerebral artery; and PCA; posterior cerebral artery.

*Two patients had partial seizures with secondary generalization.

†Twenty patients had partial seizures with secondary generalization.

‡P=1.00.

§Percentages with respect to the total number of different stroke subtypes.

The size of the lesion imaged on the cerebral CT scan was measured in 17 patients with SE. Lesion size was compared with a group of 163 stroke patients with cerebral infarction and intracerebral hemorrhage without SE to determine whether there was an association between SE occurrence and lesion size and between SE occurrence and cerebral cortex involvement (cortical or subcortical). Lesions were classified as ≤10 mm and <5 slices or as >10 mm and 5 slices or complete vascular territory. The term "cortical" referred to lesions that were cortical or corticosubcortical (partial or total involvement of the supratentorial arterial territories), and "subcortical" referred to lesions that were exclusively subcortical.

Univariate analysis for each variable was made with the Student t test for continuous variables and the χ^2 test (with Yates' correction when necessary) for categorical variables. Statistical significance was set at $P<0.05$. Variables were subjected to multivariate analysis with a logistic regression procedure and forward stepwise selection if $P<0.10$ after univariate testing. The level of significance to remain in the model was 0.15. The independent predictive value of each variable on SE and mortality was analyzed in 2 predictive models based on demographic (sex and age), clinical (functional disability and SE on mortality and functional disability on SE), and neuroimaging (type of stroke, size and localization of lesion) variables, with a total of 6 in the first model (on SE) and 7 in second model (on mortality). Odds ratios (ORs) and 95% confidence intervals were calculated from the β coefficients and standard errors. The hypothesis that the logistic model adequately fit the data was tested by means of the goodness-of-fit χ^2 test.[13]

We studied stroke type and cause, stroke risk factors, cerebral cortex involvement, size of lesion, and functional disability in PFS patients, and then we studied type of seizure and SE, time of onset and recurrence of SE, EEG findings, and the number of deaths in follow-up period. We also compared the characteristics of 17 patients with SE (group 1) and 163 patients with PFS without SE (group 2).

Results

Among 1174 hospitalized first-time stroke patients (mean age, 59.7 years; range, 17 to 103 years; 681 men, 493 women), 180 (15%) experienced a PFS. Of the 180 PFS patients (mean age, 62.2 years; range, 41 to 85 years; 88 men, 92 women), 17 (%9) developed SE. Of the 180 PFS patients, 121 (67%) had ischemic stroke and 59 (33%) had an intracranial hemorrhage. Approximately one half of the patients with SE (53%; 9 of 17) had SE manifested by seizures classified as generalized in onset, and the remainder (47%; 8 of 17) had seizures that were partial in onset.

No difference was noted between PFS patients with (group 1, n=17) and without (group 2, n=163) SE for sex, age, stroke risk factors, seizure types, and EEG findings (Table 1). The presence of SE was not associated with stroke type, cause, topography, cortical involvement, or size of lesion (Table 1). However, SE occurred more frequently among the most disabled patients (Rankin scale >3, P=0.002; Table 1).

In 7 of 17 patients with SE, SE occurred within the first 7 days after stroke (early onset; Table 2). Of these 7 patients, SE occurred as the first epileptic symptom in 6 patients (In 2 of these 6 patients, stroke began with SE); in 1 patient, ≥1 seizure occurred before SE. In 10 patients, SE occurred >7 days after stroke (late onset). In 3 of these 10 patients, SE occurred as the first epileptic symptom. Stroke risk factors, stroke type, and functional disability of SE patients were not significantly different in patients with early- or late-onset SE (Table 2) .

Recurrent SE occurred in 5 of 17 patients with SE (Table 3). In 5 of 7 patients with early-onset SE, recurrent SE occurred. However, none of the 10 patients with late-onset SE experienced recurrent SE. Stroke type and functional disability did not have a significant role in the recurrence of SE. Statistical analyses demonstrated that early-onset SE was

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TABLE 2. Risk Factors, Stroke Type, and Functional Disability in SE Patients With Early- and Late-Onset SE

	Early-Onset SE (n=7)	Late-Onset SE (n=10)	P
Risk factors			
Age (mean), y	62.6±12	55.3±8.1	0.1427
Sex, M/F	3/4	7/3	0.3499
Hypertension, n	3	3	0.6436
Diabetes, n	1	3	0.6029
Smoking, n	4	3	0.3499
Hypercholesterolemia, n	...	2	0.4852
Coronary heart disease, n	2	2	1.000
Atrial fibrillation, n	3	1	0.250
Stroke type, n			
Ischemic stroke (n=12)	5	7	1.000
Hematoma (n=5)	2	3	
Functional disability (Rankin scale)			
≤3 (n=5)	2	3	0.34
>3 (n=12)	5	7	

associated with a higher risk for additional SE occurrence (P=0.003; Table 3).

Nine of the 17 patients with SE and 81 of the 163 patients without SE died, with an overall 50% mortality in patients with PFS (Table 4). Two patients in group 1 and 24 in group 2 died within the first month after the stroke (Table 4). In group 1, death was a direct consequence of SE in 2 patients (who died during the first month after stroke), was attributed to cardiovascular disease in 5 patients, and was due to unrelated causes in 2 patients. In group 2, death was related to seizures in 10 patients, 38 deaths were caused by cardiovascular disease, and 33 deaths were from unrelated causes. There was no significant difference in mortality rate between those patients with and those without SE (Table 4). However, the mortality rate of patients with early-onset SE was higher than in patients with late-onset SE (Table 4).

After multivariate analysis (Table 5), only poor functional disability (OR=4.36) appeared to be an independent clinical factor for developing SE (goodness-of-fit χ^2=11.502; df=6; P=0.0741), and only age (OR=1.06) appeared to be an independent factor for mortality (goodness-of-fit χ^2=20.419; df=6; P=0.0047).

TABLE 3. Stroke Type, Functional Disability, and Time of Onset of SE With Regard to SE Recurrence

	Nonrecurrent (n=12)	Recurrent SE (n=50	P
Stroke type			
Ischemic stroke (n=12)	7	5	0.2445
Hematoma (n=5)	5	0	
Functional disability (Rankin scale)			
≤3 (n=5)	5	0	0.2445
>3 (n=12)	7	5	
Time of onset of SE			
Early (n=7)	2	5	0.00339
Late (n=10)	10	0	

TABLE 4. Mortality in PSF Patients With (Group 1) and Without (Group 2) SE and Mortality According to the Time of Onset of SE

	Deaths, n (%)			
	During the First Month*	After the First Month*	Total	P
Group 1 (n=17)	2 (12)	7 (41)	9 (53)	
Group 2 (n=163)	24 (15)	57 (34)	81 (50)	1.0000
Time of onset of SE				
Early (n=7)	2 (29)	4 (57)	6 (86)	0.04977
Late (n=10)	0	3 (30)	3 (30)	

*Deaths occurring during and after the first month after stroke.

Discussion

Changes in cerebral blood flow, hypoxia, involvement of the cerebral cortex by hemorrhage or infarct, and development of epileptogenic changes in cortical neurons, their connections, or their environment have been proposed as potential mechanisms underlying seizures in patients with stroke.[14–16] In this retrospective series of 1174 patients with stroke, PFS occurred in 15%. Of the patients with PFS, 9% had SE. Many authors have examined seizure disorders after stroke, but few have noted the interaction between SE and stroke.[2,7] The incidence of SE after stroke either is low or is not cited at all in some reports.[1–5,17–20] Three studies reported the rate of SE as 19%, 17%, and 14%.[7,21,22] We found that SE occurred in 9% of all patients admitted for a PFS to our Neurology Department.

In this study, there was no relationship between the occurrence of SE and sex, age, stroke risk factors, stroke type (ischemic or hemorrhagic), stroke topography and cause, cortical involvement, or size of lesion in patients with PFS. Comparisons across studies are difficult because many authors have examined the possible etiologies of SE in large series, but only a few have noted the interaction between etiologic factors and SE in poststroke SE patients.[7] Rumbach et al,[7] in a study of 159 patients with PFS, also found no relationship between SE occurrence and risk factors and stroke type. In our series, neither seizure types, such as generalized or partial onset, nor EEG findings of SE patients were significantly different from those of patients without SE.

Consistent with a prior report, we found that SE was associated with poor functional disability score.[7] Patients with SE have poorer functional disability than those without SE.

TABLE 5. Results of Multivariate Analysis

Variable	β	SE (β)	OR (95% CI)
Functional disability*	1.4741	0.5434	4.37 (1.54–12.42)
Age†	0.0623	0.0172	1.06 (1.03–1.10)

CI indicates confidence interval.
*First model (on status epilepticus: β=−0.9927; SE (β)=1.6088.
†Second model (on mortality): β=−3.7787; SE (β)=1.1542.

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We found that in 59% of patients with SE (10 of 17), SE occurred 7 days after stroke onset; 5 of the 17 SE patients had recurrent SE. In all patients with recurrent SE, the first episode of SE occurred within the first 7 days after stroke (early-onset SE). In the univariate analysis, we showed that recurrent SE is significantly more likely in patients with early-onset SE.

Our study revealed no significant difference in mortality rate and cause of death among PFS patients with and without SE; a similar finding was reported by Rumbach et al.[7] In this study, death was directly related to SE in 2 of 17 patients with SE (12%; the remaining 7 deaths were related to other causes), which was similar to findings by Rumbach et al (16%).[7] A mortality rate of 23.3% among patients with SE secondary to all causes was reported in 1 study; this rate was even higher among patients with cerebrovascular disease.[23] Our findings also have shown that early onset of SE after stroke (within 7 days after stroke) is associated with a higher mortality rate than late-onset SE in univariate analysis. Arboix et al[24,25] showed that seizures at the onset of a first-ever stroke were an independent prognostic factor for in-hospital mortality and that cortical involvement and agitated acute confusional state at the onset of stroke were independent predictive factors of early seizures in first-ever stroke patients. This study reviews the incidence of SE in the stroke population and focuses on patients without a history of epilepsy or seizures who present with SE or seizures for the first time after an acute stroke. The retrospective design of this study is an important limitation.

Data from this group of patients permit the following statements. First, the incidence of SE in patients with PFS was 9%. Second, on the basis of results of the multivariate analysis, there was no relationship between the SE occurrence and stroke risk factors, stroke type (infarction or hemorrhage), stroke topography and cause, cortical involvement, size of lesion, seizure type, or EEG findings, and the mortality rate for PFS patients with SE was not significantly different from that of patients without SE. Third, on the basis of results of the multivariate analysis, the only identified predictor of SE was poor functional disability, and we also concluded that age at a first-ever stroke is an independent prognostic factor for mortality. Finally, early-onset SE was associated with a higher risk for SE recurrence and with a higher mortality rate than late-onset SE in the univariate analysis.

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Acknowledgment

We thank Gamze Çan, MD, Department of Public Health, Karadeniz Technical University, Medical Faculty, Trabzon, Turkey, for her assistance with the analysis of the data.

References

1. Lowenstein DH, Alldredge BK. Status epilepticus at an urban public hospital in the 1980s. *Neurology*. 1993;43:483–488.
2. Barry E, Hauser WA. Status epilepticus: the interaction of epilepsy and acute brain disease. *Neurology*. 1993;43:1473–1478.
3. Kilpatrick CJ, Davis SM, Tress BM, Rossiter SC, Hopper JL, Vandendriesen ML. Epileptic seizures in acute stroke. *Arch Neurol*. 1990;47:157–160.
4. Faught E, Peters D, Bartolucci A, Moore L, Miller PC. Seizures after primary intracerebral hemorrhage. *Neurology*. 1989;39:1089–1093.
5. Kilpatrick CJ, Davis SM, Hopper JL, Rossiter SC. Early seizures after acute stroke. *Arch Neurol*. 1992;49:509–511.
6. Pohlman-Eden B, Hoch DB, Cochius JI, Hennerici MG. Stroke and epilepsy: critical review of the literature, I: epidemiology and risk factors. *Cerebrovasc Dis*. 1996;6:332–338.
7. Rumbach L, Sablot D, Berger E, Tatu L, Vuillier F, Moulin T. Status epilepticus in stroke: report on a hospital-based stroke cohort. *Neurology*. 2000;54:350–354.
8. Krumholz A, Sung GY, Fisher RS Barry E, Bergey GK, Grattan LM. Complex partial status epilepticus accompanied by serious morbidity and mortality. *Neurology*. 1995;45:1499–1504.
9. Moulin T, Tatu L, Crepin-Leblond T, Chavot D, Berges S, Rumbach L. The Besancon Stroke Registry: an acute stroke registry of 2,500 consecutive patients. *Eur Neurol*. 1997;38:10–20.
10. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*. 1981;2:489–501.
11. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30:389–399.
12. Celesia GG. Modern concepts of status epilepticus. *JAMA*. 1976;235:1571–1574.
13. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley & Sons; 1989:25–37.
14. Armon C, Radtke RA, Massey EW. Therapy of seizures associated with stroke. *Clin Neuropharmacol*. 1991;14:17–27.
15. Gupta SR, Naheedy MH, Elias D, Rubino FA. Postinfarction seizures: a clinical study. *Stroke*. 1988;19:1477–1481.
16. DeCarolis P, D'Alessandro R, Ferrara R, Andreoli A, Sacquegna T, Lugaresi E. Late seizures in patients with internal carotid and middle cerebral artery occlusive disease following ischemic events. *J Neurol Neurosurg Psychiatry*. 1984;47:1345–1347.
17. Weisberg LA, Shamsnia M, Elliott D. Seizures caused by nontraumatic parenchymal brain hemorrhages. *Neurology*. 1991;41:1197–1199.
18. So EL, Annegers JF, Hauser WA, O'Brien PC, Whisnant JP. Population-based study of seizure disorders after cerebral infarction. *Neurology*. 1996;46:350–355.
19. Bogousslavsky J, Martin R, Regli F, Despland P-A, Bolyn S. Persistent worsening of stroke sequelae after delayed seizures. *Arch Neurol*. 1992;49:385–388.
20. Reith J, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Seizures in acute stroke: predictors and prognostic significance: the Copenhagen Stroke Study. *Stroke*. 1997;28:1585–1589.
21. Sung CY, Chu NS. Epileptic seizures in intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry*. 1989;52:1273–1276.
22. Milandre L, Broca P, Sambuc R, Khalil R. Les crises epileptiques au cours et au decours des accidents cerebrovasculaires: aanalyse clinique de 78 cas [in French]. *Rev Neurol*. 1992;148:767–772.
23. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. *Epilepsia*. 1994;35:27–34.
24. Arboix A, Comes E, Massons J, Garcia L, Oliveres M. Relevance of early seizures for in-hospital mortality in acute cerebrovascular disease. *Neurology*. 1996;47:1429–1435.
25. Arboix A, Garcia-Eroles L, Juan B, Massons JB, Oliveres M, Comes E. Predictive factors of early seizures after acute cerebrovascular disease. *Stroke*. 1997;28:1590–1594.