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Stroke and status epilepticus: stroke type, type of status epilepticus, and prognosis

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Even though stroke is known to be a common cause of status epilepticus (SE), the types of stroke or SE that may be associated are not yet clearly defined. The aims of this study were to assess the timing and type of SE in stroke patients and to observe the effects of stroke and the type of SE on the response to treatment and mortality.

From May 1998 to May 2001 a total of 121 patients were admitted with SE. Among these, 30 cases (24.8%) of poststroke SE were identified and evaluated. There were 20 early-onset, and 10 late-onset SE. All stroke types were evenly distributed within the early-onset group, whereas only ischaemic stroke was found in the late-onset group. Posterior cerebral artery (PCA) infarcts were significantly more common within the latter (*P*: 0.0017).

Nonconvulsive SE (NCS) was more frequent than convulsive SE (CS) in the early-onset group (*P*: 0.0352). There was a delay in the time-to-treatment for NCS compared to CS (*P*: 0.0007). Without, however any effect on the rate of response to first step treatment (intravenous diazepam and phenytoin; *P*: 0.6334). Thirteen patients died (43.3%) during hospitalisation. Disability was significantly associated with higher mortality in the early-onset group (*P*: 0.0201). As a conclusion, NCS seems to be an important issue in stroke, thus requiring a high degree of suspicion in an acute stroke setting to avoid further neuronal injury and morbidity.

Key words: status epilepticus; stroke; nonconvulsive status epilepticus.

INTRODUCTION

Stroke is known to be a common risk factor for status epilepticus (SE) in adults[1,2] and has been reported in 22–32% of cases in different studies[3,4]. The incidence of seizures associated with stroke varies from 4.4 to 54% due to differences in definition and study settings[5–14]. Furthermore, SE is infrequently reported in poststroke seizures series, and constitutes less than 10% of all cases[9,15]. However, recent studies have found slightly higher rates such as 14–27% in patients with cerebrovascular disease[16–18] and 17% in patients with intracerebral haemorrhage[7]. Moreover, the incidence of SE is fairly low in large stroke series, ranging from none[19], through 0.9%[7,8,17,20] to 1.4% in a recent study[21]. The aims of the present study were to investigate the timing and type of SE associated with acute or chronic stroke; and to determine the possible effects of the SE or stroke type, and lesion localisation on the response to treatment and mortality.

METHODS

The study population was derived from the Marmara University Hospital SE Data Bank which prospectively included all SE patients admitted to the hospital from May 1998 to May 2001. This hospital-based Data Bank included information on the duration and type of SE, underlying factors such as structural deficits or medical pathologies, history of epilepsy and demographic data. Thirty consecutive patients with poststroke SE were identified among a total of 121 patients. SE was defined as unremitting seizure activity or series of seizures lasting for more than 5 min[22]. Patients were evaluated by a standard protocol including EEG, neuroimaging (CT or MRI), and routine blood testing. EEG was available on a 24 h basis 7 days a week, allowing prompt assessment of all patients developing an acute confusional state. Patients were grouped as having initial (occurring at stroke onset), early-onset (occurring within 2 weeks of the

stroke), and late-onset (occurring more than 2 weeks of the stroke) SE[23]. SE was further subgrouped into convulsive or nonconvulsive according to the clinical and EEG findings. Nonconvulsive SE (NCS) was defined as an alteration of consciousness lasting at least 30 min with persistent or continuous epileptiform discharges in the EEG, with or without suppression of this activity by intravenous diazepam. NCS was further subgrouped according to a modified classification from Brodtkorb *et al.*[24] and Treiman[25] as follows: NCS following complex partial seizure NCS following simple partial seizure subdinic EEG lateralisation and undetermined NCS. Stroke was subdivided into ischaemic and haemorrhagic type. Ischaemic stroke was classified according to arterial localisation, into middle cerebral artery (MCA), posterior cerebral artery (PCA), or other (multiple or other localisation) infarcts. Similarly, haemorrhagic stroke was subdivided into lobar or deep localisation. SE treatment was performed according to a stepwise standard protocol intravenous diazepam and phenytoin as the first step, repeated intravenous phenytoin as the second step, intravenous phenobarbital (1 or 2 times) as the third step, and intravenous midazolam or propofol as the fourth step. Convulsive and NCS were analysed according to their association with different stroke types. Differences in response to treatment and mortality rates were analysed among different SE and stroke subtypes and for demographic variables. Statistical analysis was made with Student's *t*-test for normally distributed continuous random variables, and the Mann–Whitney *U*-test for nonnormally distributed continuous random variables. The Fisher's exact test was used for discrete random variables and the odds ratio was calculated.

RESULTS

There were 30 patients (25 women and 5 men) out of 121 in the SE data bank (24.8% of all SE) associated with stroke, with a mean age of 73.6 ± 8.8 (range 50–89). Five patients had initial SE, 15 had early-onset SE and 10 had late-onset SE, 22 patients had NCS, 8 had convulsive SE (CS). Two patients had NCS following a complex partial seizure one had NCS following a simple partial seizure, 13 had subclinical EEG lateralisation, and 6 had undetermined NCS.

Patients with initial and early SE constituted 2.8% of the 715 patients from the Stroke Data Bank of our Institution evaluated during the same period of time. Only two patients had a history of previous seizures and the SE episode was considered to be a first-time seizure. The detailed distribution of SE and stroke types is shown in Table 1. Ischaemic stroke type was predominant among all SE subgroups and was present in 5 out of 5 in initial, in 8 of 15 in early, and in 9 of 9 in late SE groups. The stroke severity as a whole was quite important with a median NIH stroke scale (NIHSS) of 16.7±4.5. The distribution of NCS and CS among SE groups was as follows; 3 and 2 in the initial SE, 14 and 1 in the early-onset, and 5 and 5 in the late-onset groups, respectively. NCS was significantly more frequent within the early-SE group compared to the 2 others (*P*: 0.0352; OR: 12.250).

Table 1: Distribution of nonconvulsive SE, convulsive SE, and type of stroke among initial, early- and late-onset patients.

	Initial SE, *n*: 5	Early-onset SE, *n*: 15	Late-onset SE, *n*: 10
NCS (*n*: 21)[a]			
Ischaemic	3	8	5
Haemorrhagic	–	6	–
CS (*n*: 9)			
Ischaemic	2	–	5
Haemorrhagic	–	1	–

SE: status epilepticus; NCS: nonconvulsive SE; CS: convulsive SE.
[a] NCS significantly more common in early group (*P*: 0.0352; OR: 12.250).

Lesion localisation in the early- and late-onset SE group is summarised in Table 2. For further analysis, patients with initial SE was considered together with the early-onset SE group due to the limited number of cases. All stroke subtypes were evenly distributed within the early-onset group, whereas only ischaemic stroke subtypes were found in the late-onset group. PCA infarcts were significantly more common within the late-onset group (*P*: 0.0017; OR: 21.000).

The detailed comparison between the NCS and CS groups as to disability, time-to-treatment, and response to treatment is summarised in Table 3. There was a striking delay in the time-to-treatment for the NCS group. This difference disappeared when the late group was analysed alone (12.4 ± 9.0 vs. 3.8 ± 1.6 *P*: 0.22). No significant difference was found in time-to-treatment between the early- and late-onset groups (*P*: 0.4008). It is also noteworthy that the delay in treatment seemed to be greater for MCA infarcts compared to PCA infarcts (36.0±16.9 vs. 12.7±9.6),

Table 2: Distribution of stroke subtypes among early- and late-onset SE patients.

Stroke subtype and localisation	Early-onset SE		Late-onset SE	
	NCS	CS	NCS	CS
MCA	4	2	–	3
PCA[a]	2	–	5	2
Other ischaemic	5	–	–	–
Haemorrhage: lobar	4	1	–	–
Haemorrhage: deep	2	–	–	–

SE: status epilepticus; NCS: nonconvulsive SE; CS: convulsive SE; MCA: middle cerebral artery; PCA: posterior cerebral artery.
[a] PCA infarcts significantly more frequent in late group (*P*: 0.0017; OR: 21.000).

Table 3: Detailed comparison between nonconvulsive SE and convulsive SE groups as to disability, time-to-treatment and response to treatment.

	NCS	CS	*P*
Stroke severity (NIHSS scores)	16.1 ± 4.8	18.6 ± 2.8	0.2188
Time-to-treatment (hours)	18.8 ± 14.6	4.1 ± 3.6	**0.0007**
Early SE group	20.6 ± 15.6	4.7 ± 6.3	0.4008
MCA	36.0 ± 17.8	2.6 ± 1.7	**0.0159**
PCA	12.7 ± 9.6	4.0 ± 2.8	0.2635
Response to first line treatment	74%	87%	0.6334

NIHSS: NIH stroke scale; NCS: nonconvulsive SE; CS: convulsive SE; MCA: middle cerebral artery; PCA: posterior cerebral artery; numbers: mean ± SD.

however limited number of cases precluded statistical analysis. Moreover, when early- and late-onset groups were analysed separately, a tendency toward a longer delay for treatment in the early-onset group was observed (18.2 ± 15.6 vs. 8.1 ± 7.6 h; *P*: 0.09). The average time-to-treatment was 19.0 ± 17.9 h for 'other' infarcts and 14.1 ± 5.6 h for haemorrhagic lesions. No further analysis was performed due to the limited number of patients in different subgroups.

Twenty-one out of 30 (70%) of the patients, whether in the NCS or CS groups, responded similarly to the first step of SE treatment. Among the others, three patients responded at the 2nd and six patients responded at a higher step or were refractory to treatment. There was no significant difference in the time-to-treatment between the first step responders and higher than the 2nd step responders either in the early-onset NCS group (17.4 ± 15.1 vs. 26.4 ± 16.2 h; *P*: 0.2787) or in the whole group (13.0 ± 13.9 vs. 22.5 ± 17.4 h; *P*: 0. 1762). Despite significant delay in treatment for the NCS patients, no difference in the response to treatment was observed between NCS and CS patients (73.7 vs. 87.5%; *P*: 0.6334).

Furthermore, neither the type of stroke (MCA vs. PCA infarct; 66.7 vs. 100%; *P*: 0.2059), the disability (NIHSS score 17.8 ± 3.6 vs. 16.5 ± 4.8; *P*: 0.5124), and age (73.6 ± 9.3 vs. 75.8 ± 7.3; *P*: 0.6289) had any effect on the response to treatment.

Thirteen out of 30 patients (43.3%) died during hospitalisation, ten with NCS (two with NCS following partial seizures, four with subclinical EEG lateralisation, and four with undetermined NCS) and three with CS (Table 4). No further analysis to determine differences in mortality rates among NCS subgroups was performed due to the small number of patients. Eight of those who died were in the early-onset group and had severe or multiple ischaemic lesions, a large haematoma and underlying chronic medical illnesses. Five patients of the late-onset group had ischaemic lesions and died directly due to their SE, with the exception of one patient in chronic renal failure. Disability (higher NIHSS scores) was significantly associated with higher mortality in the early-onset group (score: 19.6 ± 3.7 vs. 14.2 ± 5.0; *P*: 0.0201) but not in the whole group (score: 18.6 ± 3.3 vs. 15.3 ± 4.8; *P*: 0.0898). Although there was a strikingly high rate mortality within the late-onset NCS subgroup compared to the CS group (80 vs. 20%), this did not reach statistical significance (*P*: 0.2063, OR: 16.000) due to the small sample size. On the other hand, neither the type or localisation of the stroke, timing of SE, delay in time-to-treatment or age significantly affected mortality (Table 5).

Table 4: Timing of SE, type of SE, type of stroke, lesion localisation and correlation with mortality rates.

	Mortality, *n* (%)	*P*
Timing of SE		
Early	8 (40.0)	0.7055
Late	5 (50.0)	
Type of SE		
NCS	10 (45.5)	1.0000
CS	3 (37.5)	
Type of stroke		
Ischaemic	10 (43.5)	1.0000
Haemorrhagic	3 (42.8)	
Lesion localisation		
MCA	2 (22.2)	0.3348
PCA	5 (55.5)	

NCS: nonconvulsive SE; CS: convulsive SE; MCA: middle cerebral artery; PCA: posterior cerebral artery.

Table 5: Relationship between mortality, NIH stroke scale scores, age, and time-to-treatment.

	Survivor[a]	Dead[a]	*P*
NIHSS scores	15.3 ± 4.8	18.6 ± 3.3	0.0898
Early SE group	14.2 ± 5.0	19.6 ± 3.7	**0.0201**
Age (years)	74.5 ± 9	72.4 ± 9	0.5294
Time-to-treatment (hours)	17.7 ± 14.1	17.2 ± 13.1	0.9306

[a] Mean ± SD; NIHSS: NIH stroke scale.

DISCUSSION

This study emphasises once more that stroke is an important factor in the aetiology of SE, as demonstrated by the 24.8% incidence in our series of 121 patients with SE. Furthermore, independent of the timing of SE onset, NCS was more frequent among these patients, challenging the issue of diagnosis in an acute stroke setting. Several points are worth discussing in this aspect.

Type of status epilepticus

The type of SE associated with stroke is unfortunately not mentioned in most studies[7, 8, 19–21]. In others,

however, CS is either reported to be exclusively present[18] or more frequent compared to NCS[17]. In the present study, NCS was the predominant type in the early-onset group (85%) and was as frequent as CS (50%) in the late-onset group. These high rates emphasise once more the importance of NCS in patients with cerebrovascular disease and the necessity of a high degree of suspicion in order to allow accurate diagnosis.

Type and localisation of stroke

Although different studies have affirmed that poststroke seizures were mostly related to haemorrhagic[6,8,10] or ischaemic stroke[12], recently published large stroke series failed to demonstrate a relation between stroke type and seizure or SE occurrence[17,21]. The present study could not demonstrate an association between early-onset SE and stroke type, however the absence of haemorrhagic stroke in the late-onset SE group was noteworthy. Previous reports have associated cortical lesions[15,26,27] or carotid territory lesions[20,28] with poststroke seizures. However, two recent studies denied any relation between localisation and SE occurrence[17,21] and one study could only correlate SE to lobar lesions[18]. Similarly, no particular site was associated with early-onset SE in our study, but PCA infarcts were significantly more frequent in the late-onset group. However, the limited number of patients precludes further comment.

Outcome

We observed an overall good response to the first step of SE treatment in all patients. This study failed to demonstrate other factors influencing the response to treatment (age, stroke severity localisation, or type of SE). The prominent delay in time-to-treatment within the early-onset NCS group did not, surprisingly, influence the response to treatment or the mortality. However, this delay could still be important in regards to neurobehavioural sequelae or a lower quality of life of survivors. Our study design did not include such data and this area may be worth investigating.

The mortality among our patients (44.8%) is apparently higher than the rates given in recent studies that ranged between 8 and 38%[3,29]. However, these studies included all aetiologies of SE together and were generally of CS. Two recent studies dealing with SE in stroke patients reported mortality rates of 48.3[17] and 53%[21], respectively. Moreover, similarly high mortality rates were demonstrated among SE patients associated with organic brain disease[30] or stroke[31] as compared with those patients with no underlying pathology, emphasising the possible synergistic effect of SE and a destructive brain lesion. Similarly, Claassen *et al*. determined that acute symptomatic seizures were independent predictors of mortality[32]. We found no association between mortality and SE timing or type, stroke type or localisation, age or delay to treatment. However, we found stroke severity to be associated with increased mortality in the early-onset group. Several reports point to the possible deleterious role of early seizures or SE in stroke patients[33–35]. Moreover, Labovitz *et al*.[18] pointed out a possible relationship between stroke severity or NIHSS scores and mortality. Velioğlu *et al*.[21] also suggested an association of SE with increased disability but not mortality in a stroke setting.

CONCLUSIONS

The results of our study suggest that NCS could be important in the acute stroke setting further increasing neuronal injury and hence morbidity. Therefore, patients with severe stroke would benefit from an EEG in any case of unexplained changes in consciousness. Moreover, patients having a history of severe ischaemic stroke (especially in MCA and PCA territories) should be thoroughly investigated if consciousness or behaviour change suddenly in order not to miss a NCS. Consequently, the potential association of late SE with certain stroke localisation's may require further prospective studies.

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