Research Article

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Etiology, treatment, and outcomes of status epilepticus episodes in the elderly

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Abstract

Objective: Status epilepticus (SE) can cause life-threatening consequences. It is important to determine the etiologic factors of SE and treatment responses in elderly individuals, especially those with certain comorbidities. Based on our databank, these factors were evaluated in patients aged over 60 years.

Methods: We reviewed the data of individuals aged over 60 years who were diagnosed clinically and electrophysiologically as having SE in the same databank. Demographic data of patients, SE subtypes, etiology, treatment responses, and survival of patients were noted.

Results: We evaluated 162 patients aged older than 60 years with SE episodes. The mean age of the patients was 73 years. Seventy-three percent of the patients were female. The types of SE episodes were: nonconvulsive (NCSE) (93 episodes), convulsive SE (56 episodes), and NCSE after convulsive SE (23 episodes). Stroke was the leading cause of the etiologies and accounted for 37% of the SE episodes. The NCSE subtype was more refractory to treatment (p=0.003). The longer duration and refractoriness of the episodes significantly predicted a worse outcome (p=0.0001, p=0.01).

Conclusion: Prolonged SE duration and the refractoriness of SE episodes are risk factors for poor outcomes.

Keywords: Elderly, etiology, outcome, status epilepticus, treatment

INTRODUCTION

Status epilepticus (SE) is functionally defined as continuous seizure activity of at least 5 minutes' duration or separated seizure activity without full recovery of consciousness between episodes (1). Status epilepticus is a clinical entity that is difficult to diagnose without clinical suspicion. Status epilepticus can occur at any age, but the underlying etiology may vary. Early diagnosis and effective treatment may reduce brain injury and death because SE can lead to high morbidity and mortality.

The incidence of SE is higher among adults aged 60 years and over and in children aged under one year. The elderly population is defined as individuals aged over 60 years, and age 16-59 years is accepted as young adults in the literature (2). In the elderly population, SE is 2 to 5 times more common than in young adults (3). Up to 40% of all cases of SE have been reported in people aged over 60 years (4). In about one-third of the elderly population, the first seizure presents as SE (5). The most common definable causes of first seizures or SE in the elderly population include cerebrovascular disease, infections, metabolic alterations, neoplasm, degenerative disease, and trauma (6).

In this study, we retrospectively analyzed the data of SE episodes in patients aged over 60 years in a databank over a 10-year period. We aimed to determine the typical features of SE episodes and tried to reveal their connection with age groups, etiology, duration of SE, type, treatment, refractoriness, and outcomes of patients in the elderly population.

METHODS

The research was conducted in accordance with the Helsinki Declaration and verbal informed consent was obtained from all individuals included in the study.

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In our previous study, we defined the features of SE episodes in young adults (7). We reviewed the data of patients older than 60 years who were clinically and electrophysiologically diagnosed as having SE in the same databank over a 10-year period. The demographic data, SE subtypes, etiology, duration, and response to medical therapy (refractoriness) of these episodes, and survival of the patients were recorded. The patients were divided into two groups as those aged 60-75 years and >75 years. All patients required focused history, neurologic examination, and laboratory investigations to exclude electrolyte imbalances, acid-base disturbances, intoxications, and acute organ failure. Antiepileptic drug (AED) levels were also obtained when available. A minimum of 30 minutes' electroencephalograph (EEG) recording was performed with bipolar montages using digital or analogue EEG devices in all patients (Arc Essentia EEG, Cadwell, USA). All patients underwent computed tomography (CT) of brain (Somatom Emotion 16, Siemens, Erlangen, Germany). Magnetic resonance imaging was performed on patients when needed (Magnetom, Siemens, Erlingen, Germany).

Status epilepticus is classified as convulsive SE (CSE), which can occur with prolonged or repeated tonic-clonic seizures; nonconvulsive SE (NCSE), which is defined as long or repeated absence or complex partial seizures; and subtle SE, which is specified by mental shift and ictal discharges on EEG. Convulsive SE may be converted into NCSE after treatment (8). The transformation of SE subtypes is revealed through EEG follow-up. The etiologic factors for SE have been classified as stroke, metabolic disturbances, systemic infections, central nervous system (CNS) infection, intracranial tumors, withdrawal or change in AEDs, and others (CNS trauma, hypothyroidism, and drugs that can cause SE episodes such as antibiotics and radiocontrast agents). The duration of NCSE is the time from the beginning of the change of a person's level of consciousness until the restoration of mental status after SE treatment. The time between the onset of the convulsions and response to SE treatment is the duration of a CSE episode.

Treatment stages were performed appropriate to previously published guidelines (8, 9). All patients were treated with a 10-mg intravenous diazepam (Diazem; Deva medical, Turkey) bolus followed by 18 mg/kg infusion of intravenous (IV) phenytoin (Epanutin; Pfizer, USA) if no contraindications existed. If this treatment was found unsuccessful, IV infusion of 10 mg/kg phenytoin was used. The cessation of convulsive activity in a patient or SE activity on EEG was defined as successful treatment. Refractory SE (RSE) is often defined as continuous seizure activity after the initiation of a first-stage (early) (IV benzodiazepines) and one second-stage AED (mostly phenytoin, valproate, levetiracetam or phenobarbital) (Depakin; Sanofi, Paris, France, Keppra; UCB Pharma, Bruccels, Belgian) (10, 11). After failure of second-stage (established) antiepileptic drugs, third-stage (refractory) drugs which include anesthetic agents were applied (12). The decision of the choice of drug was based on the comorbidities of the patient, the etiology of SE, and patient age. The clinical and EEG response was evaluated in all patients after treatment and if the patient did not return to normal consciousness level in CSE after appropriate treatment, EEGs were performed to exclude evolvement to NCSE. Response to treatment was evaluated in two ways. In CSE, treatment response was evaluated as discontinuation of clinical convulsions and was evaluated as regaining consciousness or cessation of ongoing abnormal activity on EEG in patients with NCSE. At least 1 EEG was performed; EEG was repeated in the event of clinicial detorioration. The outcome of patients with SE was classified as either death or survival related to SE episodes and other causes.

Statistical Analysis

The correlations between various demographic data were assessed using the Chi-square and Fisher's exact test where appropriate. After testing for normal distribution of the data, the study population was divided into two groups based on different age groups. Demographic features of patients and descriptive features of SE episodes, and treatment responses of SE episodes were assessed between the different age groups using one-way analysis of variance (ANOVA). The Statistical Package for the Social Sciences (SPSS, version 15.0, Inc.; New York, USA) was used for all statistical analyses. A p value <0.05 was considered significant.

RESULTS

We analyzed 270 patients with SE episodes in our database. A total of 270 patients had 298 episodes of SE. The patient cohort included inpatients from our hospital and patients referred to our clinic. We evaluated 162 patients (172 episodes of SE) aged over 60 years. One hundred eighteen women (73%) and 44 men (27%) were included in the study group. The mean age of the participants was 73 years. Nine patients had more than one SE episode. Three SE episodes were detected in one patient and two SE episodes were detected in 8 patients. Eight of the 9 patients with repeated SE episodes were women. One hundred ten SE episodes (64%) were detected in the 60-75 age group and 62 SE episodes (36%) were detected in the 76-93 age group. Thirty-two (20%) patients already had a diagnosis of epilepsy.

Of the 172 SE episodes, 93 (54%) episodes were NCSE, 56 (33%) episodes were CSE, and the 23 (13%) episodes were CSE to NCSE according to the clinical and EEG follow-up. The mean duration of the SE episodes in both age groups was 18 (range 1-168) hours. The duration of SE episodes did not vary significantly between the age groups (p=0.461). The subtypes of SE did not vary significantly between the age groups (p=0.363, p=0.113, p=0.403). However, there was a tendency for the older group to be classified under NCSE type (p=0.113).

When we reviewed the etiologies of SE episodes in all age groups, stroke was the most common cause of SE, occuring in 64 (37%) of total SE episodes, followed by metabolic disturbances in 31 (18%), systemic infection in 23 (11%), CNS tumors in 18 (13%), withdrawal or change of AEDs in 6 (3%), CNS infection in 5 (3%), other causes in 10 (6%), and unknown causes in 15 (9%) of total SE episodes. The 'other causes' group consisted of head trauma (n=5), toxicity (n=4), and acute surgery (n=1). The different etiologies of SE episodes according to age groups are shown in Table 1. When we looked at the first 3 causes of SE episodes, there was an evident female predominancy. When we divided the group as patients aged between 60 and 75 years and those aged over 75 years, we found no differences regarding etiologies (p=0.247).

Table 1. Demographic features and types and etiologies of status epilepticus episodes in different age groups in the elderly population

	1st group (60-75 years)	2nd group (76-93 years)	p
Female/male	74-28	44-16	
Status type			
CSE	39	17	0.363
NCSE	54	39	0.113
CSE-NCSE	17	6	0.403
Pre-existing epilepsy	9	23	0.138
Dead	25	14	0.976
Etiology			
Stroke	35	29	0.051
Systemic infection	14	9	0.740
CNS tumor	15	3	0.070
CNS infection	3	2	0.852
Metabolic	19	12	0.733
AED withdrawal	4	2	0.888
Others	7	3	0.682
Unknown	13	2	0.055

CSE: convulsive status epilepticus; NCSE: nonconvulsive status epilepticus; CNS: central nervous system; AED: antiepileptic drug

Table 2. Types and duration of SE episodes, mortality rate, age groups in refractory and nonrefractory SE episodes in the elderly

		RSE episodes (n=58)	Non-RSE episodes (n=114)	p
Age (years)	60-75	32	78	0.087
	76-93	26	36	
SE episode subtype	CSE	13	43	0.064
	NCSE	41	52	0.003
	CSE-NCSE	4	19	0.097
SE episode duration (hour)	0-3	17	40	0.554
	3-24	30	60	
	24-48	7	7	
	>48	4	7	
Mortality		23	17	0.001

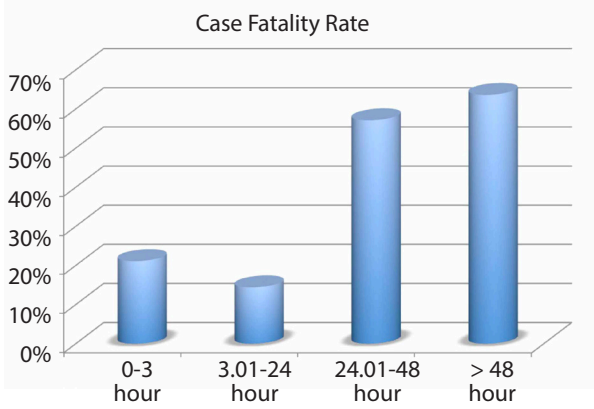
RSE: refractory status epilepticus; CSE: convulsive status epilepticus; NCSE: nonconvulsive status epilepticus

Nineteen SE episodes were detected in 9 patients with repeated SE episodes. Of the 19 SE episodes, 15 (79%) episodes were NCSE, 2 (10.5%) episodes were CSE, and the 2 (10.5%) episodes were CSE to NCSE according to the clinical and EEG follow-up. When we reviewed the etiologies of SE episodes in patients with repeated SE episodes, stroke was the cause of 10 episodes, followed by metabolic disturbances in 3, CNS tumors in 2, CNS infection in 2, and withdrawal of AEDs in 2 episodes. Stroke (n=8) and CNS tumors (n=8) were the leading causes of SE episodes in patients with preexisting epilepsy diagnoses (n=32). Systemic infection (n=5), withdrawal of AEDs (n=5), metabolic disturbances (n=2), CNS infection (n=1), other causes (n=3) were detected in the remaining 16 patients.

All SE episodes were treated with a 10-mg IV diazepam bolus and one of the stage-two drugs (mostly phenytoin, valproate, levetiracetam or phenobarbital) and 56% of episodes (n=114) responded to treatment. In the remaining episodes (n=58), stage-three drugs were administered to the patients. Thity-four percent of SE episodes remained refractory despite appropriate treatment. Although patients aged 76-93 years were more refractory to treatment, the difference was not statistically significant (p=0.123). Fifty-six percent of the NCSE cases were responsive and 44% were resistant. The NCSE subtype was more refractory to treatment and this difference was statistically significant (p=0.003). Nine refractory episodes were seen in 35 patients with epilepsy syndrome but this was not statistically significant. The relation of age, SE episodes subtype, SE duration and mortality rate with refractory and nonrefractory SE are summarized in Table 2.

It is widely accepted that it is important to recognize SE and initiate treatment as early as possible to avoid refractory sta-

Figure 1. The association between the duration of status epilepticus and case fatality rate (p=0.0001)



tus. Therefore, we divided the duration of the SE episodes into four group as follows: 0-3 hours, 3.01-24 hours, 24.01-48 hours, and >48 hours. There were no statistically significant differences between the age groups and SE episode durations (p=0.461), and there was no statistically significant difference between the duration of SE episodes and refractoriness (p=0.554).

Thirty-nine (24%) patients died in hospital. When we examined this group, 26 (68%) patients were in the NCSE subtype, 10 (24%) were in the CSE subtype, and 3 (8%) patients were in the transformation group from the CSE to NCSE subtype. Death was observed with stroke (n=17), infection (n=6), CNS tumors (n=3), metabolic disturbances (n=10), in the AED withdrawal group (n=1), and the acute surgery group (n=2). The occurrence of death in SE episodes did not vary significantly between the sexes (p=0.976). The duration of SE in patients who died was longer and this difference was statistically significant (p=0.0001) (Figure 1). Death was observed more frequently in patients with refractory RSE episodes and this difference was statistically significant (p=0.001). Outcome did not differ significantly according to etiology (p=0.248), age (p=0.976), and sex (p=0.420).

DISCUSSION

The incidence of SE is higher in two different age groups. Apart from children aged less than one year, in the elderly, those aged over 60 years, SE is 2 to 5 times more common than in young adults (3). Also, the incidence of SE episodes in older age groups is at least two times higher than in the general population (13). In our study, 58% of SE episodes were detected in individuals aged over 60 years; 60% of the entire cohort was aged over 60 years. In a population-based study conducted in Richmond, Virginia, the authors found that the incidence of SE in the elderly was 86 persons/year, and the incidence of SE in adults was 27 persons/year in the same cohort (3). In another population-based study conducted in Rochester, Minnesota, the incidence of SE was 6 persons/year in adults and 62 persons/year in the elderly population (6).

Unlike CSE, NCSE is a difficult condition to diagnose in patients aged over 60 years. This is due to the comorbidities frequently found in this group of patients, the medication they use, and concurrent age-related problems. It can be difficult to diagnose NCSE because of its heterogeneous presentation. Only with suspicion of this condition and the availability of emergency EEG monitorization, the correct diagnosis can be made (14, 15). We showed that 54% of episodes were NCSE, and 23 (13%) episodes were NCSE after CSE according to clinical and EEG follow-up. This high rate can be related to the availability of continuous EEG monitorization in our center. In a study that assessed 63 patients aged over 70 years who were hospitalized for SE, Canouï-Poitrine et al. found that 83% had complex partial NCSE, and the remaining 17% patients demonstrated CSE immediately or secondarily generalized SE (16). In the elderly population, there is a dominant presentation of NCSE (17).

The outcome of SE depends on age, etiology, clinical presentation, and immediate and appropriate treatment (2). Although stroke is the most common etiology of SE episodes among the elderly, infection is more commonly seen in children, and history of epilepsy or withdrawal of various drugs are commonly seen in adults (6, 13, 18, 19). In the present study, stroke was the most common (37%) etiologic cause in patients aged over 60 years.

Age is an independent predictor of mortality in SE. De Lorenzo et al. found that the mortality rate was about 13% in young adults, reaching 38% in older adults aged 60-79 years, and was found as up to 50% after the age of 80 years (17). Other factors associated with mortality in the elderly population are seizure duration, underlying structural lesions, de novo SE, and severity of SE refractoriness (20, 21). In the present study, the mortality rate was 24% and NCSE was the leading subtype (68%). We found that outcome was related to the duration of SE but was not related to etiology of SE episodes or increased age.

In the present study, patients in both age groups were mostly women (73%), as in other older patient NCSE series (22-24). In our study, there was an evident female predominancy among the first 3 causes of SE episodes. It should be considered, however, that women have greater longevity than men in Turkey. These two conditions may be the reason for the female predominancy among our elderly population with SE.

According to our database, most (72%) of the SE episodes were treated successfully with first-line treatment in patients younger than 60 years old. The median duration of SE episodes was reported as 9 hours. Ozdilek et al. found that first-line treatment success was related to the short duration of SE episodes (7). In our study, 34% of SE episodes were found to be refractory to first-line treatment. In our cohort, refractoriness was higher among the elderly population, similar to other author's results (3, 11). In our young cohort, withdrawal of AEDs was the leading cause, whereas in the elderly cohort, stroke was found as the leading cause. The NCSE subtype was more frequently seen in the elderly cohort, and CSE was more frequently seen in the young cohort (2, 25). With respect to refractoriness, 28% of SE episodes remained refarctory to first-line treatment in the young cohort and 34% of SE episodes remained refractory in the elderly cohort. Death occurred in 14% of the patients in the young cohort and in 24% of patients in the elderly cohort.

In our study, a total of 34% of SE episodes remained refractory to first-line treatment and 66% of SE episodes were treated successfully. Also, patients aged between 76 and 93 years were more refractory to first-line treatment. The success of first-line treatment is mostly related to episode duration

and patient age (26). In general, RSE accounts approximately 23-48% of all cases of SE. In a previous study, Agan et al. reported that 38% of SE episodes were refractory to first-line treatments. They found that age, female sex, SE type, SE duration, and acute etiology were associated with refractoriness, whereas EEG patterns were not (27). In addition, female sex and acute etiology were shown to be the only significant independent predictors of refractoriness.

The current study includes a large number of elderly patients with SE and provides detailed information. However, the study has some limitations because it does not give information about EEG patterns. We have the opportunity to provide EEG monitorization to our patients on weekdays, but we have some limitations on weekends. Cessation of ongoing abnormal activity in EEG was accepted as a response to treatment in patients with NCSE and at least 1 EEG was performed, but we did not have the possibility to continue EEG monitorization. In addition, the number of NCSE episodes may be found high because the EEG data evaluation was performed without considering the new criteria of NCSE-type EEG patterns (28).

Status epilepticus is an emergency situation that needs to be treated immediately. There is a higher incidence of SE in the older age group and it commonly has a nonconvulsive presentation. Continued EEG monitoring is important in the diagnosis of this pattern. Stroke is the main etiology for SE in this age group. It is important to initiate treatment in the early phase because prolonged SE duration and the refractoriness of SE episodes cause poor outcomes.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

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