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Original Article

Status Epilepticus Type, Etiology, and Treatment: One-year Data

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Abstract

Objective: This study aimed to review the demographic characteristics, type, and etiology of status epilepticus (SE) cases followed in our hospital for a period of 1 year and to reveal the factors affecting the prognosis of the patients.

Methods: Patients diagnosed with SE among the patients who applied to the emergency department of our hospital within a 1-year period (August 2018 and August 2019) and who were consulted to us because of epileptic seizures or changes in consciousness and behavior while being followed up in the services or intensive care unit were retrospectively screened.

Results: A total of 51 patients, 28 female (54.9%) and 23 male (45.1%), were included in our study. Twenty-eight patients were under or equal to the age of 60, and 23 patients were over the age of 60. Twenty-one patients had convulsive SE, 18 patients had non-convulsive SE (NCSE), and 14 patients were transitioning from convulsive SE to NCSE. Causes of SE were; lack of anti-seizure drugs (ASD) in 9 patients, intracranial mass in 9 patients, infection in 8 patients, and cerebrovascular event in 6 patients. Refractory SE cases were mostly observed in patients who developed SE due to lack of ASD and infection. In addition to first-line treatment with benzodiazepines, intravenous (IV) phenytoin, levetiracetam, valproic acid, and oral topiramate and lacosamide treatments were used. It was observed that 26 patients who developed refractory SE were treated with IV midazolam, propofol, or thiopental infusion. It was observed that 2 patients died because of refractory seizures.

Conclusion: SE is an important condition that requires rapid treatment and can be fatal. In this cross-sectional study, the demographic characteristics and etiological causes of SE cases registered in our center were presented, and the characteristics of refractory SE cases were also mentioned.

Keywords: Status epilepticus, refractory status epilepticus, etiology, treatment

INTRODUCTION

Status epilepticus (SE) is an epileptic emergency that has a time-dependent relationship with the risk of morbidity and mortality. It has different forms and a wide variety of etiologies. SE is practically divided into two main groups: convulsive and non-convulsive SE. The most widely accepted definition for convulsive SE (CSE) is either 5 minutes or more of continuous seizure activity or two or more separate seizures with no full recovery of consciousness between them.[1] A common definition of non-convulsive SE (NCSE) is electrographic seizure activity lasting more than 30 min in the absence of visible convulsions. The definition of SE proposed by the Neurocritical Care Society is defined as clinical and/or electrographic seizure activity of 5 min between seizures or recurrent seizure activity without improvement.[1] SE is one of the most important emergencies in neurology, and one out of every three patients is unresponsive to first-line treatment.[2] Refractory SE refers to clinical or electrographic seizures that persist after an adequate dose of initial benzodiazepine and an acceptable second-line therapy. In super-refractory SE, seizures continue to recur 24 h or more after the initiation of anesthetic therapy.[1,2]

The 2015 classification of the International League Against Epilepsy (ILAE) proposes a highly functional approach to subtypes by addressing 4 axes [semiology, etiology, electroencephalography (EEG) correlates, and age].[3]

It is important to initiate effective treatment without delay in SE patients. Benzodiazepines are effective agents used in first-line therapy. Phenytoin has been used as a second-line therapy for many years. In refractory SE cases, anesthetic agents are used.

In this study, we aimed to review the SE type, demographic characteristics, and etiologies of SE cases and treatment approaches, followed in our hospital in the emergency room, intensive care unit, neurology clinics, and other services within a 1-year period, and to indicate the prognosis of the patients.

METHODS

Our study was planned as a single-center, cross-sectional study. Among the patients who were consulted to us because of epileptic seizures or changes in consciousness and behavior while being followed up in the emergency room, neurology service and other services, or intensive care unit within 1 years (between August 2018 and August 2019), the patients who were diagnosed with SE were included in the study retrospectively.

In terms of being more practical in our study, we divided SE into three groups: CSE, NCSE, and those transitioning from CSE to NCSE. EEG recordings of the patients were made, and EEG follow-ups were continued to evaluate whether there was a transition from CSE to NCSE.

To reveal the underlying etiology, a detailed anamnesis was taken from the patient's relatives or follow-up doctor. For the etiology, it was noted whether there was a history of anti-seizure drug (ASD) withdrawal, metabolic disorder, accompanying infection or stroke, intracranial mass, previous diagnosis of epilepsy or mesial temporal sclerosis (MTS), recent antibiotic use, and a history of exposure to hypoxia for a long time. To reveal the etiology, biochemical analyses, infectious panel, and autoimmune encephalitis panel were sent for the patients deemed necessary. Necessary imaging tests were performed for intracranial pathologies.

While IV diazepam was used as the first-line treatment in SE, IV levetiracetam, IV valproic acid, IV phenytoin, oral lacosamide, and topiramate were used as the second-line treatment protocol. In cases with refractory SE, midazolam, propofol, thiopental infusion, or a combination of these drugs were administered as general anesthetic agents in the intensive care unit. The death notification system (DNS) was used to determine the prospective life expectancy of the patients, and mortality rates were recorded.

Statistical Analysis

In our current study, where 1-year data was discussed and 53 SE events of 51 patients were analyzed, the patients were categorized as CSE, NCSE and those who transitioning from CSE to NCSE. When each group was divided into subgroups such as demographic characteristics, etiology, and mortality, statistical analysis could not be performed due to the small number of patients included in these subheadings, and the current findings were summarized in tables and graphs.

RESULTS

A total of 51 patients, 28 female (54.9%) and 23 male (45.1%), registered in our SE database between August 2018 and August 2019 were included in our study.

MAIN POINTS

- Status epilepticus (SE) requires early intervention, has a high morbidity and mortality rate if treatment is delayed, and can be overlooked, especially in patients hospitalized in the intensive care unit.
- In our study, the most common causes of SE included withdrawal or missed dose of anti-seizure medication, intracanial mass, and infections.
- In addition, refractory SE was most frequently associated with the discontinuation or missed dose of anti-seizure medication.

Demographic analysis: The ages of the patients were between 19 and 89 years; the mean age was 55 years and the median value was 57 years. Twenty-eight patients were under or equal to the age of 60, and 23 were over the age of 60 years. A total of 53 SE data were available due to recurrence in 2 of 51 patients. Of these, 21 were patients with CSE, 18 with NCSE, and 14 with transition from CSE to NCSE. Seven patients had a previous diagnosis of epilepsy. While 4 of these patients had CSE, 3 had transitioned from CSE to NCSE (Table 1, Figure 1).

The mean age at CSE was 46.1 years, the mean age at NCSE was 64.3 years, and the mean age of those who transitioned from CSE to NCSE was 57.5 years (Table 1).

Status epilepticus etiology: The reason for developing SE in nine patients was the withdrawal of ASD. Of these, 3 were due to ASD missed by the patient, 3 were due to decreased oral intake, and 3 patients were due to cessation or reduction of ASD because of seizure-free follow-up. Of these patients, 6 had CSE, 2 had NCSE, and 1 had transitioned from CSE to NCSE (Figure 2).

Nine patients who developed SE due to intracranial mass were associated with postoperative complications. One patient developed SE due to a primary intracranial mass after radiotherapy

Table 1. Demographical data and etiology according to SE types

	CSE	NCSE	CSE >>> NCSE
Gender (F/M)	8/13	13/3	7/7
Mean age	46.1	64.3	57.3
Etiology			
ASD	6	2	1
ICM	5	3	1
Infection	2	5	1
PDE	4	3	-
CVD	1	3	2
Metabolic disorder	1	1	2
Antibiotic usage	-	4	-
Idiopathic	1	1	2
MTS	-	1	-
Arrest	1	-	-

SE: Status epilepticus, CSE: Convulsive status epilepticus, NCSE: Non-convulsive status epilepticus, ASD: Anti-seizure drug, ICM: Intracranial mass, PDE: Previous diagnosis of epilepsy, CVD: Cerebrovascular diseases, MTS: Mesial temporal sclerosis, F/M: Female/male

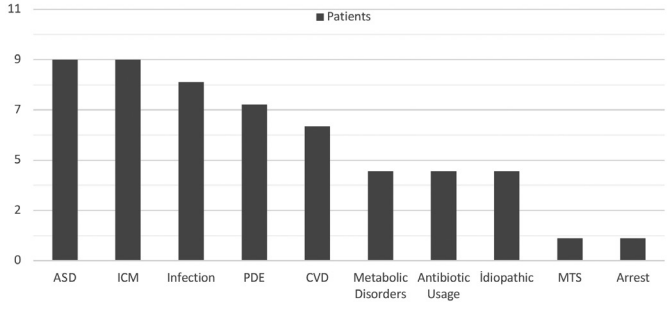

Figure 1. Frequencies of status epilepticus etiologies

ASD: Anti-seizure drug, ICM: Intracranial mass, PDE: Previous diagnosis of epilepsy, CVD: Cerebrovascular diseases, MTS: Mesial temporal sclerosis

and 2 patients developed SE due to intracranial metastasis. Of these patients, 5 had CSE, 1 had NCSE, and 3 were transitioning from CSE to NCSE (Figure 2).

Of the cases that developed SE due to infection, 2 were due to meningoencephalitis, 2 were due to aspiration pneumonia, and 4 were due to systemic infection. Of these, 2 were CSE, 4 were NCSE, and 2 were patients with transition from CSE to NCSE (Figure 2).

SE developed after cerebrovascular disease (CVD) in 6 patients and due to metabolic causes in 4 patients. Of the CVD patients, 1 had CSE, 3 had NCSE, and 2 had a transition from CSE to NCSE (Figure 2).

It was noted that antibiotic-associated SE developed in 4 patients three of whom were related to cefepime and 1 of them was related to linezolid. All 4 of these patients had NCSE (Figure 2).

Four patients presenting with SE for the first time were recorded. One patient developed MTS and one patient developed SE due to hypoxia after arrest. While the MTS patient was NCSE, the patient who developed post-arrest hypoxia was in myoclonic status (Figure 2).

Refractory SE cases (n=26) mostly occurred in SE due to ASD disruption and infection. Refractory SE was observed in more than 50% of SE cases with a known history of epilepsy and CVD (Table 2, Figure 3).

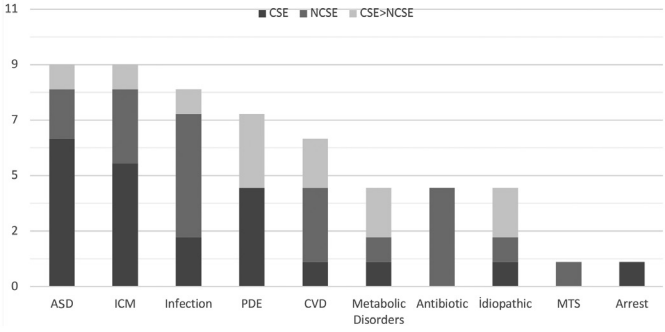

Figure 2. Status epilepticus types according to etiologies

ASD: Anti-seizure drug, ICM: Intracranial mass, PDE: Previous diagnosis of epilepsy, CVD: Cerebrovascular diseases, MTS: Mesial temporal sclerosis

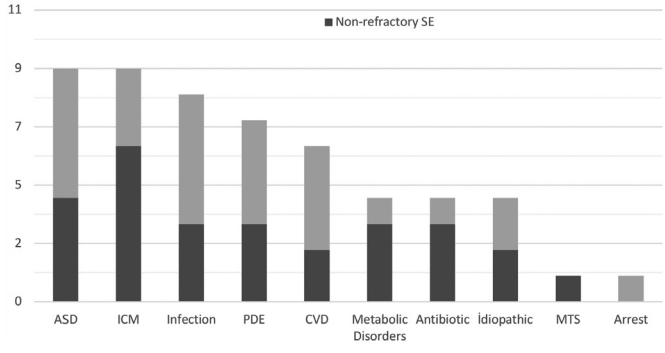

Figure 3. Refractory and non-refractory status epilepticus according to etiologies

ASD: Anti-seizure drug, ICM: Intracranial mass, PDE: Previous diagnosis of epilepsy, CVD: Cerebrovascular diseases, MTS: Mesial temporal sclerosis, SE: Status epilepticus

Status epilepticus treatment: In our study, first-line treatment (23 IV diazepam, 12 IM midazolam) was applied in 35 of 53 SE events. In 31 patients, second-line or third-line treatment was initiated. Agents frequently used in second-line treatment were levetiracetam (n=41), phenytoin (n=15) and valproic acid (n=10). Apart from these, high-dose oral topiramate or lacosamide treatment was applied (n=2). More than one second-line treatment agent was administered in 14 of the SEs that could not be stopped with a single agent. Second-line treatment was initiated in 18 patients with long SE duration at the time of admission, and success was achieved in 10 of them. In the remaining 8, third-line treatment was initiated. Twenty-six patients were evaluated with refractory SE, and midazolam was preferred as the primary anesthetic agent. Despite this, propofol and then thiopental infusion were administered to 2 cases whose seizures continued or electrophysiological seizure activity continued on EEG. It was learned from the DNS records that 18 of 51 patients were exitus (35.29%). Eleven were female patients.

DISCUSSION

In our study, which included our one-year SE data, we found that there were more female patients and CSE was slightly higher than NCSE, and the most common etiologies were anti-seizure medication deficiency and infection. In another feature we obtained from our data, we found that CSE was more common in SE cases due to ASD deficiency and intracranial mass, whereas NCSE was more common in SE cases due to infection and antibiotic use. The mortality rate due to SE was approximately 35% in our study.

In our study, which analyzed 53 SE events of 51 patients, our finding of female superiority with a rate of 54.9% was similar to a study conducted in Italy and the study by Leitinger et al.[4,5] In our study, CSE was higher in males and NCSE was higher in females (Table 1). The incidence of SE has a bimodal distribution, increasing in the first year and in the elderly.[6] Alroughani reported that the mean age of 42 NCSE patients was 61.8 years, while

Table 2. Refractory and non-refractory SE frequencies according to variables

	Refractory SE n=26	**Non-refractory SE n=27**
Mean age	49.96	59.85
Gender		
F/M	13/13	15/12
SE type		
CSE	12 (46.15%)	9 (33.33%)
NCSE	7 (26.9%)	11 (40.74%)
CSE >>> NCSE	7 (26.9%)	7 (25.92%)
Etiology		
ASD discontinuation	5 (19.23%)	4 (14.81%)
ICM	3 (11.53%)	6 (22.22%)
Infection	4 (15.38%)	4 (14.81%)
PDE	4 (15.38%)	3 (11.11%)
CVD	4 (15.38%)	2 (7.4%)
Mortality	2	-

SE: Status epilepticus, CSE: Convulsive status epilepticus, NCSE: Non-convulsive status epilepticus, ASD: Anti-seizure drug, ICM: Intracranial mass, PDE: Previous diagnosis of epilepsy, CVD: Cerebrovascular disease, F/M: Female/male

some studies showed a significant increase in the incidence of SE over the age of 50.[4,7] In our study, we found the mean age of SE to be 55 years, for CSE to be 46.4 years, and for NCSE to be 64.3 years. The mean age of NCSE patients was higher than that of other SE types (Table 1).

In our 53 SE records, we found our rate of CSE to be 39.6%, which was higher than that of NCSE (33.9%), and we found the most common etiology as anti-seizure medication discontinuation, while the second most common cause was intracranial mass. In NCSE cases, the most common etiologic event was infection, whereas the second cause was associated with antibiotic use. It has been reported in the literature that NCSE is observed in 25-50% of cases with SE.[7] Leitinger et al.[4] in their retrospective study of 221 first-episode SE cases reported, CSE as 65.6% and NCSE as 34.4%. In this study, the most common cause of SE was CVD (45.2%), followed by trauma (16.7%). In a study by Fountain[8], the most common cause of CSE in adults is a decrease in ASD levels and a history of central nervous system damage. Stroke, metabolic abnormalities, hypoxia, systemic infection, anoxia, trauma, overuse of drugs, central nervous system infections, and central nervous system bleeding are listed as acute causes of SE.[9] Among the chronic causes of SE are low serum levels of ASD, distant symptomatic causes such as tumor, stroke, and trauma, alcohol abuse, and idiopathic respectively.[9] Acute symptomatic causes for CSE are much more common, and the relationship between mortality and morbidity is higher.[9] In a study by Ozdilek et al.[10], SE attacks of 88 patients aged 16-50 years were analyzed, and the most common etiology of SE was found to be dose changes of anti-seizure medication at a rate of 31%. In the study conducted by Sünter et al.[11], in which 162 patients over 60 years of age who had an SE attack were evaluated, the most common cause of SE was found to be 37% of stroke, while the second most common cause was metabolic abnormalities at a rate of 18%.

Antibiotic groups, including penicillin, cephalosporin, carbapenem, and quinolones, have reported to cause seizures. Benzyl penicillin lowers the seizure threshold more than synthetic penicillins.[12] Among cephalosporins, cefazolin lowers the seizure threshold at a high rate, but SE has also been reported with ceftriaxone, cefotaxime, ceftazidime, and cefepime.[12] Imipenem is more convulsant than meropenem. Among quinolones, the convulsant effect of trovafloxacin is higher than that of levofloxacin, and SE has been reported with ciprofloxacin, ofloxacin, and gatifloxacin.[12] In our study, cefepime was found to be the most common among those who developed antibiotic-associated SE. NCSE has been reported, especially in patients with renal failure, after the use of ceftazidime, ceftriaxone, and cefepime.[13]

The incidence of refractory SE in patients with SE is between 23% and 43%.[2,9] In the study of Atmaca et al.[14], 59 SE cases were prospectively followed for 2 years, and the rate of refractory SE was found to be 25.4%. While retrospective studies reported the mortality rate of refractory SE between 16% and 23%, the mortality rate of refractory SE was 39% in a prospective study. The mortality rate of non-refractory SE was 11%.[14] SE developing with acute brain injury has an easier risk of transforming into refractory SE. If the etiology includes head trauma, brain infections such as encephalitis, brain tumors, and strokes, refractory SE may be more resistant to treatment. In our study, the rate of refractory SE was found to be 49.05%, and the most common etiology in patients who developed refractory SE was a decrease in the level of ASD, infections, and CVD. Ağan Yıldırım and Sünter.[2] analyzed the data of 290 patients with SE and found the rate of refractory SE to be 38%. In this study, when the etiology of refractory SE was examined, it was determined that acute causes predominated in 66.7%.[15] Sünter et al.[16] in a study of 38 patients who had SE due to an intracranial mass, 40% of the attacks were found to be refractory SE.

Benzodiazepines constitute the first-line treatment option for SE, although IV lorazepam is the first choice in international treatment algorithms. However, because it is not available in our country, treatment is started with IV diazepam. However, considering that its effect will decrease rapidly, treatment with longer-acting ASD should be continued. Phenytoin, fosphenytoin as well as IV valproic acid, levetiracetam, and phenobarbital are also among the options.[9,17] In a study by Kellinghaus et al.[18], first-line treatment success was reported as 21% in generalized CSE patients, 16% in non-generalized CSE patients, and second-line treatment success was reported as 46% for generalized CSE and 38% for non-generalized CSE. However, in this study, it was not overlooked that drug doses were used below the first-line doses recommended in the guidelines. In fact, benzodiazepines were not used as first-line therapy in 15% of patients.[18] In the literature, the success rate of first-line therapy is reported to be 55.5% for CSE and 14.9% for subtle SE.[19]

Considering the treatment response rates in our study, those who responded to second-line treatment were found to be 45.28%.

Midazolam, propofol, thiopental, and pentobarbital are the most commonly used anesthetic agents as third-line therapy in patients who develop refractory SE.[20,21] They act via the $GABA_A$ receptor. In a meta-analysis, the probability of having a seizure was 4% in patients treated with EEG suppression mostly provided by pentobarbital, compared with 53% in patients treated clinically and electrographically with midazolam or propofol. Here, while the probability of hypotension due to pentobarbital use was 76%, this rate was 29% in the other group.[21]

Midazolam (n=24) was the primary treatment in 26 patients with refractory SE, followed by propofol and then thiopental (n=2) treatment. Aggressive treatment should be considered in these patients because of the high risk of death, neuronal damage, and serious long-term morbidity.

Eighteen (35.29%) of 51 patients died in our study, 11 of them were female patients, and 2 of these patients were followed up with refractory SE. One of these two patients was being followed up with CSE and the other with NCSE, and the underlying causes in these patients were hypoxia after cardiopulmonary arrest and infection, respectively. It was determined that the remaining 16 patients in the follow-up with the DNS died because of other causes.

Study Limitations

The limitation of our study is that it was a study in which a certain percentage of patients were handled, covering a 1-year period, no data on SE durations were given, and the EEG characteristics of the patients could not be mentioned.

CONCLUSION

SE is an important condition that requires rapid treatment and can be mortal. In this cross-sectional study, which included our one-year SE data, we found that there were more female patients and CSE was slightly higher than NCSE. We found that CSE were more common in SE cases due to ASD deficiency and intracranial mass, while NCSE was more common in SE cases due to infection and antibiotic use. The mortality rate due to SE was approximately 35% in our series.

Ethics

Ethics Committee Approval: The Marmara University Faculty of Medicine Clinical Research Ethics Committee approved the study (number: 09.2023.182, date: 06.01.2023).

Informed Consent: The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and informed consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: D.Ç., H.İ., K.A., İ.M., Concept: K.A., İ.M., Design: K.A., İ.M., Data Collection or Processing: H.İ., B.B., Analysis or Interpretation: D.Ç., H.İ., B.B., Literature Search: D.Ç., Writing: D.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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