Annals of Medical Research

DOI: 10.5455/annalsmedres.2019.02.092 2020;27(2):682-7

Original Article

Clinical features associated with convulsive status epilepticus in patients with epilepsy

Asli Ece Cilliler , Bulent Guven

University of Health Sciences, Ankara Dışkapı Yıldırım Beyazıt Research and Training Hospital, Department of Neurology, Ankara, Turkey

Abstract

Aim: Status epilepticus (SE) is an important and distinct problem with its high morbidity and mortality. The need for early identification of SE to predict the course and prognosis of epilepsy have led us to investigate the clinical features associated with SE in patients with epilepsy in this study.

Material and Methods: The information of the patients with epilepsy recorded comprised demographic features, type and etiology of seizures, age of onset of epilepsy, frequency of seizures, mono- or polytherapy treatment, history of convulsive SE, triggering factors for SE and brain magnetic resonance imaging findings. The data also included patients' family history of epilepsy and history of febrile seizures, mental retardation.

Results: A total of 610 patients with epilepsy (291 men, 319 women) were included in the study. It was found that 49 (8%) of the patients had at least one convulsive SE. Univariate logistic regression analysis showed that earlier onset of epilepsy, symptomatic/cryptogenic etiology, mental retardation, frequency of seizures ≥1/month, treatment with polytherapy, and abnormalities in neuroimaging are associated with SE (p=0.001, p<0.001, p<0.001, p<0.001, p<0.001 and p<0.001, respectively). In multivariate logistic regression analysis; mental retardation (SE 0.380; 95% CI 0.186-0.825; p=0.014) and polytherapy (SE 0.392; 95% CI 0.158-0.735; p=0.006) were found to be independent factors related with SE. It was determined that 69% of patients had a triggering factor for SE and infection (65%) was the most common among these.

Conclusion: The results of this study showed that there is a clear relationship between the occurrence of SE and mental retardation and treatment with polytherapy in patients with epilepsy. Symptomatic/cryptogenic etiology, early onset of epilepsy, high frequency of seizures and presence of abnormalities in neuroimaging are also associated with SE. Identification of these risk factors of SE will be helpful to initiate the appropriate treatment within a short time after diagnosis.

Keywords: Epilepsy; status epilepticus; risk factors

INTRODUCTION

Status epilepticus (SE) is one of the most important neurological emergencies that especially affect young children and older adults (1-4). Although there are many different definitions for SE, continuous seizures lasting than 5 minutes or more, having two or more seizures without incomplete recovery of consciousness is accepted as SE. SE is recently defined as a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (5). The pathophysiological changes underlying SE are partially understood. Hypersynchronous hyperexcitability state of SE depends on complex interaction between mechanisms on both synaptic and network level (6-9).

While it is regarded as the most severe form of epilepsy; SE can be seen as the prominent symptom of systemic or central nervous system disorders caused by structural, metabolic, infectious, inflammatory, toxic or genetic origin (5,10). Annual incidence of SE has been reported to be 10-41/100000 (1,2,4,9,11-13). The incidence of SE appears to peak at ages older than 50 years and younger than 10 years (12). Although previous studies reported a greater incidence of SE in males (1,2,11), it is recently suggested that the rates for both sexes are more similar than previously thought (13).

Received: 02.02.2020 **Accepted:** 20.02.2020 **Available online:** 25.02.2020

Corresponding Author: Bulent Guven, University of Health Sciences, Ankara Dışkapı Yıldırım Beyazıt Research and Training Hospital, Department of Neurology, Ankara, Turkey **E-mail:** bulentcanguven@gmail.com

It has been reported that approximately 15-20% of patients with epilepsy have a history of SE at least once in their lifetime and 12% of patients present with SE at onset (1,14-16). SE is associated with an overall mortality of 20% (14). A greater case mortality rate was reported in the elderly and in patients with refractory SE (13). It has been suggested that three major factors are responsible for increased risk of mortality and morbidity associated with SE; underlying cause, advanced age and SE duration (14). Acute symptomatic causes of convulsive SE are generally more common and have been associated with higher morbidity and mortality rates (1,2,9,13).

Convulsive SE is a time-sensitive emergency and requires immediate treatment. SE is a life-threatening condition due to recurrent and prolonged seizures as well as is important for the development of neuronal damage and pharmacoresistance. SE modifies neurotransmission and susceptibility to AEDs over time. It has also long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures (5,6,9).

Early identification of risk factors associated with SE will allow physicians predict the clinical course of epilepsy and initiate the appropriate treatment within a short time after diagnosis without waiting the progression of disease. In this study our objective is to investigate the risk factors associated with SE in patients with epilepsy.

MATERIAL and METHODS

The study included 610 patients who were followed up in the epilepsy outpatient clinic between 2009 and 2017. Data were obtained by reviewing patients' file records and interviewing with patients. Patients who had inadequate file information, in whom seizure type was not differentiated accurately and who had systemic disease were excluded from the study. In addition, patients were excluded if they had conditions with a high or low risk of seizure recurrence and SE such as Lennox-Gastaut Syndrome, West syndrome, and benign childhood epilepsy with centrotemporal spikes.

The information recorded comprised demographic features, type and etiology of seizures, age of onset of seizures, frequency of seizures, mono- or polytherapy treatment, history of convulsive SE, the presence of additional factors (sleeplessness, hunger, infection, emotional stress and drug discontinuation) that can trigger SE and brain magnetic resonance imaging (MRI) findings. The data also included patients' family history of epilepsy and history of febrile seizures, mental retardation.

The type of seizure was evaluated and classified according to the ILAE criteria as focal, generalized, or focal to bilateral tonic-clonic seizures (17). The etiology of epilepsy was determined as idiopathic, cryptogenic, or symptomatic. Brain MRI was evaluated as abnormal if there was a lesion that could be considered as the cause of epilepsy. The occurrence of a non-provoked seizure history among first and second-degree relatives of the patient was accepted as a positive family history. The frequency of seizures was determined by the number of seizures prior to SE (<1 / month, ≥1/month).

The study was carried out according to the Helsinki Declaration and was approved by the Institutional Ethics Committee. All patients participating in the study provided written informed consent.

Statistical Analysis

Statistical analyses were performed using statistical software (Statistical Package for the Social Sciences, version 23.0 for Windows, SPSS Inc., Chicago, IL, U.S.A.). Descriptive statistics for continuous variables were expressed as the mean±SD. Numbers of cases and percentages were used for categorical data.

The best predictors that had an effect on status epilepticus were analyzed by a univariate logistic regression method. Any variable with a p value less than 0.05 in the univariable test was accepted as a candidate for the multivariable model. Multivariate logistic regressions were performed on univariate variables with a p value <0.05 to determine their effect on status epilepticus. The standard error (SE) and 95% confidence intervals (CI) were also calculated for each independent variable. Statistical significance was defined as p<0.05.

RESULTS

A total of 610 patients (291 men, 319 women) with a mean age of 30.5±12.1 years were included in the study. Convulsive SE history was found in 49 (8%) of the patients. It was found that 69.4% of the patients had a triggering factor for SE and infection was the most common among these factors (64.7%). MRI abnormalities detected were namely; cortical dysplasia in 9 (26.5%), hippocampal sclerosis in 6 (17.7%), focal encephalomalacia in 6 (17.7%), giant arachnoid cyst in 4 (11.8%), leukomalacia due to perinatal injury in 2 (5.9%), arteriovenous malformation in 2 (5.9%), corpus callosum agenesis in 1 (2.9%), pachygyria in 1 (2.9%), double cortex in 1 (2.9%), tuberosclerosis in 1 (2.9%) and encephalomalacia due to autoimmune encephalitis sequel in 1 (2.9%). Demographic and clinical characteristics of the patients are shown in Table 1.

The univariate logistic regression analysis showed that factors related to SE were; early onset of epilepsy, symptomatic/cryptogenic etiology, mental retardation, seizure frequency ≥1/month, treatment with polytherapy, and lesions in brain MRI that may be considered as the cause of epilepsy (p=0.001, p<0.001, p<0.001, p<0.001, p<0.001 and p<0.001, respectively). In the multivariate analysis, mental retardation and treatment with polytherapy were found to be independent factors associated with SE (p=0.014 and p=0.006, respectively) (Table 2).

Table 1. Demographic and disease characteristics of patients with epilepsy with and without status epilepticus

Characteristics	Patients without SE (n=561)	Patiens with SE (n=49)
Age (years)	30.6±12.2	29.4±11.6
Gender (female/male)	295 (52.6)/266 (47.4)	24 (49)/25 (51)
Epilepsy duration (years)	13.2±10.3	18.6±11.5
Age at onset (years)	17.4±13	10.6±12.7
Seizure type		
Focal	109 (19.4)	5 (10.2)
Generalized	337 (60.1)	30 (61.2)
Focal to bilateral tonic clonic seizures	115 (20.5)	14 (28.6)
Etiology		
Idiopathic	374 (66.7)	14 (28.6)
Symptomatic/cryptogenic	187 (33.3)	35 (71.4)
Mental retardation	97 (17.3)	26 (53.1)
History of febril seizures	128 (22.8)	17 (34.7)
Family history of epilepsy	100 (17.8)	5 (10.2)
Seizure frequency before SE		
<1/month	344 (61.3)	17 (34.7)
≥1/month	217 (38.7)	32 (65.3)
Presence of triggering factor for SE	-	34 (69.4)
Triggering factors		
Sleeplessness	-	4 (11.8)
Hunger	-	1 (2.9)
Infection	-	22 (64.7)
Emotional stress	-	1 (2.9)
AED withdrawal	-	6 (17.6)
Brain MRI abnormalities	189 (33.7)	34 (69.4)
Treatment type		
Monotherapy	382 (68.1)	12 (24.5)
Polytherapy	179 (31.9)	37 (75.5)

Data are presented as mean ± SD or number (%)
SE: Status epilepticus, AED: Antiepileptic drug, MRI: Magnetic resonance imaging

Table 2. Univariate and multivariate logistic regression analyses of factors related with status epilepticus in patients with epilepsy

	β	SE	95% CI	*p*	β	SE	95% CI	*p*
Age (years)	-0.009	0.013	0.967-1.017	0.501				
Gender Male (ref. female)	0.144	0.298	0.644-2.072	0.628				
Age at onset (years)	-0.055	0.016	0.917-0.977	**0.001**	-0.006	0.016	0.963-1.026	0.705
Seizure type Generalized	0.663	0.495	0.735-5.125	0.181				
(ref. focal) Focal to bilateral tonic clonic	0.976	0.538	0.925-7.616	0.070				
Etiology Idiopathic (ref. symptomatic/cryptogenic)	-1.609	0.329	0.105-0.381	**<0.001**	-1.308	0.834	0.053-1.386	0.117
Mental retardation No (ref. yes)	-1.688	0.307	0.101-0.338	**<0.001**	-0.937	0.380	0.186-0.825	**0.014**
History of febril convulsion No (ref. yes)	-0.586	0.317	0.299-1.035	0.064				
Family history of epilepsy No (ref. yes)	0.647	0.485	0.738-4.935	0.182				
Seizure frequency <1/month ref.≥1/month)	-1.093	0.312	0.182-0.618	**<0.001**	-0.438	0.347	0.327-1.274	0.207
Brain MRI abnormalities No (ref. yes)	-1.495	0.323	0.119-0.422	**<0.001**	0.506	0.838	0.321-8.567	0.546
Treatment type Monotherapy (ref. polytherapy)	-1.884	0.344	0.077-0.298	**<0.001**	-1.077	0.392	0.158-0.735	**0.006**
					Cox & Snell R2 = 0.096Nagelkerke R2 = 0.223			

Bold indicates statistical significance
MRI: Magnetic resonance imaging, Ref.: reference, SE: Standard error. CI: Confidence interval

DISCUSSION

Presence of mental retardation and treatment with polytherapy was found to be independent risk factors for the occurrence of SE in patients with epilepsy in this study. We also found that symptomatic etiology, early onset of epilepsy, more frequent seizures, and presence of abnormality in neuroimaging are also associated with the occurrence of SE.

Symptomatic epilepsy is defined as epilepsy that arises from the effects of an epileptic lesion, whether that lesion is focal or a defect in metabolism causing widespread injury to the brain. Cryptogenic syndromes involve a presumptive lesion that is otherwise difficult or impossible to uncover during evaluation. Patients with symptomatic or cryptogenic epilepsy generally fare less well than patients with idiopathic epilepsy for seizure control and prognosis (18). The changed structure and function of the central nervous system led to hyperexcitability as the main cause of epilepsy. In our study, it was determined that seizures with symptomatic or cryptogenic etiology were more common in patients who had SE compared to those without. In a similar direction, patients with SE had more common abnormalities in neuroimaging. It was reported in a study that one third of patients with SE have a structural etiology (19). In patients with refractory epilepsy, it is not surprising to detect structural or acquired abnormalities in brain MRI more frequently than other epilepsy patients.

The finding that mental retardation was predictive for SE is an important observation in our study. It was reported in previous studies that 20% of patients with mental retardation have also epilepsy and the incidence of epilepsy increases as the severity of mental retardation increases (20,21). On the other hand, it was also suggested that approximately 25% of patients with epilepsy have mental retardation. (20,22). Some studies have shown

that frequency and prognosis of epilepsy is poorer in patients with mental retardation than the general epilepsy population and the frequency of sudden unexpected death is higher in these patients. (20-22). Mental retardation probably implies a more diffuse and severe brain injury and can be accepted as a marker for symptomatic epilepsy, which is associated with a relatively poor prognosis.

In our study, it was determined that patients with SE are significantly younger than the patients without at the onset of epilepsy. The incidence of SE is higher in young children (1-3,15,23). As is expected, seizures are likely to start earlier in patients with symptomatic/cryptogenic epilepsy and mental retardation.

We found that more than one seizure per month is a significant factor to occur SE on univariate analysis. Repeated seizures have been shown to produce neuronal loss and mossy fiber sprouting in the hippocampus, which in turn can reinforce their production, forming excitatory recurrent circuits (24,25). Our findings also indicated a strong and independent relationship between SE and polytheraphy. It may be thought that the occurrence of SE may be easier in patients with drug-resistant epilepsy treated with two or more AEDs, as previously reported that refractory epilepsies are associated with history of SE (19,26-28). On the other hand, SE modifies AED sensitivity over time and pharmacoresistance may develop (6,9).

Features associated with the development of SE in our study are also risk factors for drug-resistant epilepsy. Mental retardation/developmental delay (26-30), younger age at the onset of epilepsy (29,30), symptomatic/cryptogenic epilepsies (29-31), high frequency of seizures (29,31,32), and presence of abnormality in neuroimaging (26) were identified as risk factors for drug-resistant epilepsy. Mental retardation, symptomatic epilepsy, early age at epilepsy onset, and abnormal neuroimaging findings were reported to increase risk for drug-resistant epilepsy in one metaanalysis (33). In another metaanalysis, while symptomatic epilepsy was found to be a strong risk factor for drug-resistant epilepsy, age of onset of disease was not found to be a risk factor. It was reported that there is a substantial heterogeneity between studies in mental retardation and high initial seizure frequency (34).

Our study has some limitations. Because of the retrospective design of the study, it is possible that there may be data loss due to the fact that file records were the main source of information. Another limitation is that the data evaluated belong to both child and adult periods. Problems that may arise from this have been partially addressed by excluding patients with childhood epilepsies that are known to have a good or bad prognosis.

CONCLUSION

The results of this study showed that there is a clear relationship between the occurrence of SE and mental retardation and treatment with polytherapy in patients with epilepsy. Symptomatic/cryptogenic etiology, early onset of epilepsy, high frequency of seizures and presence of abnormalities in neuroimaging are also related with SE. Since there is a cause and effect relationship between these characteristics, early identification of at least one of these risk factors in clinical practice will be helpful to predict the clinical course of the disease in patients with epilepsy, especially at risk of SE.

Competing interests: The authors declare that they have no competing interest.
Financial Disclosure: There are no financial supports.
Ethical approval: The study was carried out according to the Helsinki Declaration and was approved by the Institutional Ethics Committee.

Aslı Ece Cilliler ORCID: 0000-0002-5006-1157
Bulent Guven ORCID: 0000-0002-4816-9257

REFERENCES

1. Coeytaux A, Jallon P, Galobardes B, et al. Incidence of status epilepticus in French-speaking Switzerland: (EPISTAR). Neurology 2000;55:693-7.
2. Hesdorffer DC, Logroscino G, Cascino G, et al. Incidence of status epilepticus in Rochester, Minnesota, 1965-1984. Neurology 1998;50:735-41.
3. Chin RF, Neville BG, Peckham C, et al. NLSTEPSS Collaborative Group. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet 2006;368:222-9.
4. Leitinger M, Trinka E, Giovannini G, et al. Epidemiology of status epilepticus in adults: A population-based study on incidence, causes, and outcomes. Epilepsia 2019;60:53-62.
5. Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56:1515-23.
6. Sánchez Fernández I, Goodkin HP, Scott RC. Pathophysiology of convulsive status epilepticus. Seizure 2019;68:16-21.
7. Burman RJ, Raimondo JV, Jefferys JGR, et al. The transition to status epilepticus: how the brain meets the demands of perpetual seizure activity. Seizure 2020;75:137-44.
8. Nelson SE, Varelas PN. Status Epilepticus, refractory status epilepticus, and super-refractory status epilepticus. Continuum (Minneap Minn) 2018;24:1683-707.
9. Betjemann JP, Lowenstein DH. Status epilepticus in adults. Lancet Neurol 2015;14:615-24.
10. Neligan A, Shorvon SD. Frequency and prognosis of convulsive status epilepticus of different causes: a systematic review. Arch Neurol 2010;67:931-40.
11. Knake S, Rosenow F, Vescovi M, et al. Status Epilepticus Study Group Hessen (SESGH). Incidence of status epilepticus in adults in Germany: a prospective, population-based study. Epilepsia 2001;42:714-8.
12. Dham BS, Hunter K, Rincon F. The epidemiology of status epilepticus in the United States. Neurocrit Care 2014;20:476-83.

13. Lv RJ, Wang Q, Cui T, et al. Status epilepticus-related etiology, incidence and mortality: A meta-analysis. Epilepsy Res 2017;136:12-7.
14. Trinka E, Höfler J, Zerbs A. Causes of status epilepticus. Epilepsia 2012;53:127-38.
15. Fountain NB. Status epilepticus: risk factors and complications. Epilepsia 2000;41 Suppl 2:S23-30.
16. Logroscino G, Hesdorffer DC, Cascino G, et al. Mortality after a first episode of status epilepticus in the United States and Europe. Epilepsia 2005;46 Suppl 11:46-8.
17. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512-21.
18. Britton JW. Antiepileptic drug withdrawal: literature review. Mayo Clin Proc 2002;77:1378-88.
19. Yildiz EP, Gunes D, Bektas G, et al. Predictive factors of drug-resistant epilepsy in children presenting under 2 years of age: experience of a tertiary center in Turkey. Acta Neurol Belg 2018;118:71-5.
20. Shankar R, Rowe C, Van Hoorn A, et al. Under representation of people with epilepsy and intellectual disability in research. PLoS One 2018;13:e0198261.
21. Doran Z, Shankar R, Keezer MR, et al. Managing anti-epileptic drug treatment in adult patients with intellectual disability: a serious conundrum. Eur J Neurol 2016;23:1152-7.
22. Devinsky O, Asato M, Camfield P, et al. Delivery of epilepsy care to adults with intellectual and developmental disabilities. Neurology 2015;85:1512-21.
23. Shinnar S, Pellock JM, Moshé SL, et al. In whom does status epilepticus occur: age-related differences in children. Epilepsia 1997;38:907-14.
24. Dalby NO, Mody I. The process of epileptogenesis: a pathophysiological approach. Curr Opin Neurol 2001;14:187-92.
25. Sperk G, Drexel M, Pirker S. Neuronal plasticity in animal models and the epileptic human hippocampus. Epilepsia 2009;50 Suppl 12:29-31.
26. Wirrell E, Wong-Kisiel L, Mandrekar J, et al. Predictors and course of medically intractable epilepsy in young children presenting before 36 months of age: a retrospective, population-based study. Epilepsia 2012;53:1563-9.
27. Seker Yilmaz B, Okuyaz C, Komur M. Predictors of intractable childhood epilepsy. Pediatr Neurol 2013;48:52-5.
28. Callaghan BC, Anand K, Hesdorffer D, et al. Likelihood of seizure remission in an adult population with refractory epilepsy. Ann Neurol 2007;62:382-9.
29. Voll A, Hernández-Ronquillo L, Buckley S, et al. Predicting drug resistance in adult patients with generalized epilepsy: A case-control study. Epilepsy Behav 2015;53:126-30.
30. Geerts A, Brouwer O, Stroink H, et al. Onset of intractability and its course over time: The Dutch study of epilepsy in childhood. Epilepsia 2012;53:741-51.
31. Berg AT, Shinnar S, Levy SR, et al. Early development of intractable epilepsy in children: a prospective study. Neurology 2001;56:1445-52. Erratum in: Neurology 2001;57:939.
32. Hitiris N, Mohanraj R, Norrie J, et al. Predictors of pharmacoresistant epilepsy. Epilepsy Res 2007;75:192-6.
33. Kalilani L, Sun X, Pelgrims B, et al. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsia 2018;59:2179-93.
34. Xue-Ping W, Hai-Jiao W, Li-Na Z, et al. Risk factors for drug-resistant epilepsy: A systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e16402.