ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Etiologies of Convulsive Status Epilepticus in Children

Çocuklarda Konvülsif Status Epileptikus Etiyolojisi

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Abstract

Introduction: Convulsive status epilepticus (CSE) is one of the neurologic emergencies of childhood with varying degrees of impaired consciousness and motor symptoms. The aim of this study was to try to define the etiology of patients with CSE.

Materials and Methods: Children aged 1 month to 18 years with CSE were included in the study. The demographic characteristics of the patients, seizure type, seizure etiology, epilepsy history, drugs used, and complications were recorded.

Results: One hundred forty-five patients who were diagnosed as having were included in the study, 60.7% of whom were male. The seizure type was focal onset in 55.9% of the patients. According to the etiology of CSE, the most common group was found as unknown group (48%), and 72.9% of those had a history of epilepsy. Febrile (17%) and central nervous system infections (8.3%) were found to be the most common in acute etiology, respectively. Pulmonary complications developed most frequently. The mortality rate was 0.7%.

Conclusion: The "unknown etiology" is found as the most common etiology of CSE in children. Febrile seizure and central nervous system infections are common in acute etiologies.

Öz

Giriş: Konvülsif status epileptikus (KSE), değişen derecelerde bilinç bozukluğu ve motor semptomlarla seyreden çocukluk çağının nörolojik acillerinden biridir. Bu çalışmanın amacı, KSE'li hastaların etiyolojisini tanımlamaya çalışmaktır.

Gereç ve Yöntem: Çalışmaya KSE'li 1 ay ile 18 yaş arasındaki çocuklar dahil edildi. Hastaların demografik özellikleri, nöbet tipi, nöbet etiyolojisi, epilepsi öyküsü, kullandığı ilaçlar ve komplikasyonlar kaydedildi.

Bulgular: Çalışmaya %60,7'si erkek olmak üzere 145 hasta alındı. Hastaların %55,9'unda nöbet tipi fokal başlangıçlıydı. KSE etiyolojisinde en sık nedeni bilinmeyen grup (%48) saptandı ve bu grubun %72,9'unda epilepsi öyküsü vardı Akut etiyolojide sırasıyla en sık ateşli (%17) ve merkezi sinir sistemi enfeksiyonları (%8,3) bulundu. En sık pulmoner komplikasyonlar gelişti. Mortalite oranı %0,7 idi.

Sonuç: Çocuklarda KSE'nin en sık etiyolojisi olarak "bilinmeyen etiyoloji" bulunmuştur. Akut etiyolojilerde ateşli nöbetler ve merkezi sinir sistemi enfeksiyonları sık görülür.

Keywords
Status epilepticus, convulsive status epilepticus, epilepsy, etiology

Anahtar kelimeler
Status epileptikus, konvülsif status epileptikus, epilepsi, etyoloji

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Introduction

Status epilepticus (SE) is one of the neurologic emergencies of childhood with morbidity and mortality (1). SE is defined as a single epileptic seizure of >30-min duration or a series of epileptic seizures during which function is not regained between ictal events (2). In 2015 the International League Against Epilepsy (ILAE) defined SE as a condition where the emergence of response mechanisms for seizure termination could be the onset of failure, i.e. t1 time point, and long-term consequences such as neuronal loss depending on the type and duration of seizures at the t2 time point. According to the ILAE, SE is semiologic; It is classified in two main axes: convulsive SE (CSE) with varying degrees of impaired consciousness with the presence of motor symptoms, impaired consciousness without motor symptoms, and nonconvulsive SE (NCSE), which can be diagnosed using electroencephalography (EEG) (3). Infections and prolonged febrile seizures are reported in childhood etiologies of SE (4). The ILAE catagorized the etiology of SE in four large groups; acute (e.g. stroke, intoxication, encephalitis, etc.), remote (e.g. posttraumatic, postencephalitic, poststroke, etc.), progressive (e.g. brain tumor), and unknown (3). In the management of CSE, primarily medical stabilization, diagnosis of the underlying etiology, and rapid treatment of seizures are recommended (5). The aim of this study was to try to define the etiologies of patients admitted to a university hospital with the diagnosis of CSE.

Materials and Methods

Study Design

The study was planned at University Hospital, which has a pediatric emergency unit, pediatric intensive care center and pediatric neurology clinic between January 2012 and December 2017. The hospital is a reference hospital serving a population of approximately six million people. Children aged 1 month to 18 years who were diagnosed as having CSE were included in the study. The diagnosis of CSE was taken as recurrent seizure activity in which the seizure lasted longer than 30 minutes or when consciousness is not regained between seizures (2). Due to the study period in which the data were collected, the old definition was used instead of the new status epilepticus definition defined by IlAE in 2015. Those diagnosed as having CSE were included and their electronic files were reviewed retrospectively. The demographic characteristics of the patients, seizure types, duration of seizure, etiologies of seizures, concomitant diseases, epilepsy history, antiepileptic drugs (AEDs) used, cranial imaging, EEG reports, length of hospital stay and status were recorded. The file data of patients were scanned meticulously by two pediatric neurologists, and the etiological classification was made retrospectively according to the ILAE classification. The same patients who presented with the diagnosis of CSE at different times during the study period were included as a single case. The treatment of the patients was arranged according to the treatment protocol for CSE of our clinic. According to this protocol; in our country, intravenous (i.v.) preparations are available in the first step, benzodiazepines (diazepam, midazolam), if there is no response, phenytoin infusion, i.v. midazolam infusion and pentobarbital coma in the last step.

Statistical Analysis

The SPSS package program was used for statistical evaluation. Descriptive statistics of evaluation results; are given as numbers and percentages for categorical variables and mean, standard deviation, minimum and maximum for numerical variables. The conformity of the data to normal distribution was checked using the Kolmogorov-Smirnov test. Comparisons of numerical variables between two independent groups were made using Student's test when normal distribution conditions were met, and the Mann-Whitney U test when they were not. Comparisons of numerical variables between more than two independent groups were made using one-way analysis of variance (ANOVA) when normal distribution conditions were met, and the Kruskall Wallis test when they were not. Differences between the ratios of categorical variables in independent groups were tested using chi-square analysis. Statistical significance level was accepted as $p<0.05$.

Ethics Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee (18-1005).

Results

One hundred forty-five patients who were diagnosed as CSE were included in the study. Of the patients,

Table 1. The descriptive data of patients are shown in the table		
Age (mean ± SD) (month)	73.5±55.6 (min: 3 - max: 214)	
Gender (n=145)	n	%
Girls	57	39.3
Boys	88	60.7
Epilepsy history		
Yes	83	57.2
No	62	42,8

39.3% were girls (n=57) and 60.7% were boys (n=88). The frequency of CSE was found to be significantly higher in boys (p=0.01). The mean age of the patients was 73.5 ± 55.6 months. The median age of girls was 52 (min: 3, max: 204) months, and the median age of boys was 59 (min: 3, max: 214) months. There was no difference between the median ages of girls and boys (p=0.44). Descriptive data of the patients are shown in Table 1 and Table 2. The seizure type was defined as focal in the files of 81 (55.9%) patients, and the seizure type of the other patients was unknown; they

Table 2. Seizure characteristics of the patients are shown in the table		
	n	%
Seizure Type		
Focal Onset	81	55.9
Generalize/Unknown Onset	64	44.1
Etiology Group		
1-Unkown	70	48.3
2-Acute		
Febrile Status	25	17.2
Central nervous system infection	12	8.3
Inappropriate use or discontinuation of AEDs	8	5.5
Electrolyte Disorder	6	4.1
Substance Intake	1	0.7
3-Remote (Hypoxic Ischemic Injury, poststroke, Congenital brain malformation)	9	6.2
4- Progressive		
Neurometabolic Disease	8	5.5
Brain tumor	3	2.1
Progressive myoclonic epilepsies	3	2.1
EEG (Epileptiform discharge)	57	39.3
MRI (Abnormal)	64	44.1
Treatments Received		
Benzodiazepine (midazolam/diazepam)	145	100
Phenytoin	117	80.7
Midazolam infusion	74	51.0
Pentobarbital	6	4.1
Number of Patients Developing Complications	26	17.9
(More than one complication developed in a person)		
Evolving Complications		
Pulmonary Complications	18	12.4
Cardiac Complications	14	9.7
Gastrointestinal complications	8	5.5
Urinary Complications	7	4.8
Death	1	0.7
AEDS: Antiepileptic drug		

did not have clear and consistent information about the generalization or onset. There was a previous history of epilepsy in 57.2% of the patients. The most common group was found as unknown (48%) according to the etiology of CSE. Febrile (17%) and central nervous system infections (8.3%) were the most common acute aetiology, respectively. Neurometabolic disorders (5.5%) were the most common in the progressive group. When compared according to age, the mean age of children with focal epileptic seizures was found to be significantly higher than in children with generalized seizures (p=0.013) (Table 3). When the etiologies according to age were compared, the mean and median age of the acute group was younger, but it was not statistically significant.

When the patients were compared according to their etiology, the frequency of generalized seizures was higher in those who had seizures for acute etiologic reasons, and the frequency of focal seizures was found to be higher in seizures of unknown etiology (p=0.001) (Table 4). Epilepsy history was more common in the remote, unknown and progressive groups (88.9%, 72.9%, and 71.4%, respectively), where as it was found as 26.9% in the acute group. Seventy-four patients who were started on midazolam infusion were evaluated as refractory status epilepticus, and 6 patients who were started on pentobarbital were evaluated as super refractory status epilepticus.

No relationship was found between the development of complications and etiology. Complications developed in 17,9% of the patients. The most common complications were pulmonary and cardiac complications, respectively. One patient who developed CSE due to Herpes simplex encephalitis died.

Discussion

This study is a long-term study with the highest number of cases among the publications on childhood CSE reported from Turkey in the literature. One hundred forty-five patients who were diagnosed as having CSE were included in the study. In our study, the male sex

Table 3. The comparison of the data of the patients according to the age of patients is shown in the table

	Mean ± SD	Median	Min.	Max.	p
Gender**					
Girls	69.1±57.7	52	3	204	0.258
Boys	76.4±54.3	59	3	214	
Seizure Type**					
Focal Onset	84.3±58.4	80	3	214	0.013
Generalize/Unknown Onset	60.0±49.0	44	6	206	
Epilepsy History**					
Yes	81.1±57.8	80	3	214	0.063
No	63.4±51.2	47	3	204	
ILAE Etiology **					
Unkown	78.6±55.4	76	3	214	0.234
Known	68.9±55.7	48	3	206	
ILAE Etiology **					
Unkown	78.6±55.4	76	3	214	0.631
Acute	66.8±55.1	45	3	204	
Remote	73.8±49.8	72	10	186	
Progressive	73.4±64.3	60,5	3	206	
Complication Development **					
Yes	72.8±54.2	60	6	206	0.953
No	73.7±56.1	58	3	214	

* Normally distributed, ** Non-normal distribution

Table 4. The comparison of the data of the patients according to the etiology of epilepsy is shown in the table									
	Unkown[a]		Acute[b]		Remote[c]		Progressive[d]		p
Seizure Type	n	%	n	%	n	%	n	%	
Focal Onset	48	68.6	19	36.5	6	66.7	8	57.1	0.005
Generalize/Unknown Onset	22	31.4	33	63.5	3	33.3	6	42.9	
	p(a-b)=0.001, p(a-c)=1.000, p(a-d)=0.536, p(b-c)=0.142, p(b-d)=0.278, p(c-d)=1.000								
Epilepsy History									
Yes	51	72.9	14	26.9	8	88.9	10	71.4	<0.001
No	19	27.1	38	73.1	1	11,1	4	28.6	
	p(a-b)<0.001, p(a-c)=0.435, p(a-d)=1.000, p(b-c)=0.001, p(b-d)=0.006, p(c-d)=0.611								
Drugs used									
Benzodiazepine	70	100.0	52	100.0	9	100.0	14	100.0	0.075
Phenytoin	55	78.6	44	84.6	7	77.8	11	78.6	0.848
Midazolam infusion	36	51.4	22	42.3	4	44.4	12	85.7	0.037
Pentobarbital	2	2.9	2	3.8	0	0.0	2	14.3	0.229
Complication Development									
Yes	8	11.4	11	21.2	3	33.3	4	28.6	0.179
No	62	88.6	41	78.8	6	66.7	10	71.4	
	p(a-b)=0.031, p(a-c)=0.029, p(a-d)=0.051, p(b-c)<0.001, p(b-d)<0.001, p(c-d)=1.000								
TOTAL	70	100.0	52	100.0	9	100.0	14	100.0	
Evaluate on column percentage									

ratio was found to be high, similar to the literature. (6-12). Although the etiological classifications were similar, they were different from each other in the studies performed until the etiological classification proposal on CSE of the ILAE in 2015.

In our study, the most common CSE etiologic group was unknown group (48.3%). Similarly, in a study in Georgia (n=48), the rate of the most frequent etiology group, unknown, was found as 33% (13). When we look at the literature, our rate is quite high. However unlike our study, acute symptomatic causes and especially febrile CSEs in this group are reported as the etiology of CSE in childhood. As the etiology of CSE in a limited number of studies conducted in childhood; the most common were acute central nervous system infections in India (n=73) (7), Iran (n=135) (6), Turkey (n=27) (14), Honduras (n=47) (12) and Pakistan (n=73) (15) and prolonged febrile seizures were found in London, England (n=226) (16). In this study, although prolonged febrile seizures were the most common among acute etiologies, they ranked second among all etiological causes. The history of epilepsy in studies in the India and Iran ranged from 10-30% (6,7). In our study, the history of epilepsy was quite high (57.2%). The fact that the hospital where this study was conducted was the reference hospital where complex and difficult cases were sent, and the sending of patients with epilepsy in their medical history may be a factor. In addition, the fact that prolonged febrile seizures in our country can be treated more frequently by pediatricians in state hospitals may be another factor. Similar to our study, the remote group was found to be the most common in a population study in which patients from all age groups were recruited in a university hospital in Italy, where neurology patients were frequently referred, and 40% of the patients had a history of epilepsy. In the literature, it is reported that 10% of children with epilepsy have their first seizures as SE and 60% have no neurologic deficits before the SE episode (1). In our study, 72.9% of the unknown etiology group had a history of epilepsy and 27.1% had their first seizure as SE. In our study, patients with a history of epilepsy were classified in the unknown group because there were no structural, metabolic, or inappropriate use or discontinuation of AEDs. In a large population study conducted in Germany (n=467),

patients with SE were divided into three groups as non-refractory SE, refractory SE and super-refractory SE, and the rate of epilepsy history in these groups was 35.5%, 24.8% and 10% respectively. The rates of the unknown group were reported as 33.7%, 18.4%, and 21.7%, respectively (17). In the present study, the history of epilepsy may have been higher than in the literature, because the hospital was a reference center. However, the real question is whether the high rate of epilepsy caused the rate of the unknown group to be so high; we do not know the answer to this question yet. On the other hand, the rate of epilepsy history was high in the remote and progressive groups. Although the management and treatment of CSE differs between medical centers, the initial treatment is similar all over the World with the use of benzodiazepines (18). Benzodiazepines were also used in this study. SE, in which seizure activity continues despite the administration of AEDs with two different mechanisms, is called refractory SE and drugs that are constantly administered to stop seizures are required regardless of seizure duration and coma induced by anesthetic agents such as ketamine, pentobarbital and propofol is the most common form of treatment (18). Pentobarbital was used in six patients.

The mortality rate was found as 0.7%. In the literature, the mortality rate from CSE has been reported as between 3% and 14% (6-7,13,16-17). It has been reported that acute symptomatic events such as encephalitis and meningitis have the highest mortality (19). Similarly, a patient with encephalitis died in this study. The etiology of CSE, which causes mortality, needs to be understood more clearly. General population studies may show predominantly febrile or acute symptomatic etiology. We believe that more population studies should be supported to generalize treatment planning of countries because these etiologies show high mortality. On the other hand, what causes CSE in patients with epilepsy who have not structural problems and who regularly use routine medications is an important problem. For medical professionals dealing with epilepsy; there seems to be a need for clinical studies to reveal the causes of CSE in children with diagnosed epilepsy who are under treatment. The mechanism of the condition that makes the seizure activity continuous and does not respond to AEDs may be solved with neurophysiologic studies.

Study Limitations

One of the important limitations of this study is that it is retrospective, and the old definition was used instead of the new status epilepticus definition defined by ILAE in 2015. Prospective studies are needed according to the new definition of status epilepticus.

Conclusion

The "unknown etiology" is found as the most common etiology of CSE in children. Febrile seizure and central nervous system infections are common in acute etiologies. The frequency of CSE is higher in boys than girls.

Ethics

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee (Uludag University Faculty of Medicine Clinical Research Ethics Committee - 18-1005).

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

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