Original article

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Short-term outcomes and major barriers in the management of convulsive status epilepticus in children: a study in Georgia

Teona Shatirishvili [1], Tamar Kipiani [1], Giorgi Lomidze [2], Maia Gabunia [3], Nino Tatishvili [1]

[1] M.Iashvili Children Central Hospital - Neuroscience
[2] Institute of Neurology and Neuropsychology - Epilepsy
[3] Neurodevelopment Center - Mental health, Tbilisi, Georgia

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ABSTRACT – *Aim*. Convulsive status epilepticus is the most common childhood neurological emergency in developing countries, where poor healthcare organisation could play a negative role in the management of the condition. Unavailability of second-line injectable anticonvulsants is an additional hindering factor in Georgia. This report reflects the results of the first study aimed at evaluating the epidemiological features of convulsive status epilepticus, as well as identifying obstacles influencing the management of patients with convulsive status epilepticus in Georgia.

Methods. A prospective, hospital-based study was performed. Paediatric patients with convulsive status epilepticus, admitted to the emergency department of a referral academic hospital from 2007 to 2012, were included in the study.

Results. Forty-eight paediatric patients admitted to hospital met the criteria for convulsive status epilepticus. Seizure duration was significantly shorter among the group with adequate and timely pre-hospital intervention. Moreover, patients with appropriate pre-hospital treatment less frequently required mechanical ventilation (p=0.039). Four deaths were detected during the follow-up period, thus the case fatality rate was 8%. Only 31% of patients received treatment with intravenous phenytoin.

Conclusion. The study results show that adequate and timely intervention could improve outcome of convulsive status epilepticus and decrease the need for mechanical ventilation. Mortality parameters were comparable to the results from other resource-limited countries. More than one third of patients did not receive appropriate treatment due to unavailability of phenytoin.

Key words: convulsive status epilepticus, AED unavailability, morbidity, outcome

Correspondence:
Teona Shatirishvili
M. Iashvili Children Central Hospital-Neuroscience,
Ljubljana St. No.2/6,
Tbilisi 0159, Georgia
<teoshatiri@gmail.com>

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Convulsive status epilepticus (CSE) is the most common childhood neurological emergency in developed countries that may lead to neuro-cognitive consequences and/or death (Sadarangani *et al*., 2008). The incidence of CSE reaches 18/100,000 cases per year among the child population (Hesdorffer *et al*., 1998; Coeytaux *et al*., 2000; Chin *et al*., 2006). According to recent data, neurological deterioration after CSE occurs in up to 15% of children (Raspall-Chaure et al., 2006; Novorol et al., 2007). Status epilepticus (SE) is a common medical challenge for patients admitted to hospitals in resource-poor countries, where there is a higher rate of epilepsy and mortality associated with CSE in both adults (11-15%) and children (11-30%) (Raspall-Chaure et al., 2006; Murthy *et al*., 2007; Novorol *et al*., 2007; Winkler *et al*., 2007; Misra *et al*., 2008). Poor healthcare organisation plays a negative role in the management of CSE, which has major limitations regarding inadequate health care infrastructure, delayed admission to the hospital, and inadequate medical intervention during early phase of the condition (Newton, 2009). Georgia is a lower-middle income state and it shares socio-economic features with resource-poor countries, but there are some peculiar factors that could have additional influences on the management of CSE; in particular, a lack of specialised protocols for emergency services could affect pre-hospital management of CSE. Another obstacle is the restricted availability of intravenous second-line antiepileptic drugs (AEDs). There are currently no injectable second-line AEDs officially registered. Buccal midazolam, rectal diazepam, and lorazepam are not accessible for the same reason. Only phenytoin is available in particular cases through personal initiatives of patient relatives or health care workers, who bring injectable phenytoin from abroad. The most prominent barrier, however, could be absence of a consensus for guidelines for the treatment of CSE. Particular hospitals establish their own guidelines and protocols, sharing the experiences of other advanced clinics and internationally-recognised approaches, but the unavailability of essential drugs forces hospitals to adapt these guidelines to their current situations. One such guideline is elaborated at the M. Iashvili Children's Central Hospital which is a referral centre for emergency paediatric patients where most cases of CSE are treated.

This article reflects the results of the first study aimed to establish some epidemiological features, as well as to assess the influence of hindering factors on management, course and short-term outcome of CSE in paediatric patients under the adapted guideline.

Patients and methods

We evaluated data of consecutive paediatric patients admitted to the emergency department of the M. Iashvili Children's Central Hospital (referral academic hospital) from March 2007 to March 2012. All patients aged one month to 18 years that met criteria for CSE were included in the study. The demographic data and detailed medical history was obtained in all cases. The short-term outcome of CSE was evaluated after 30 days from admission. The outcome was assessed as death, neurological deterioration, or no consequence. In patients under the age of 6 months, the evaluation was performed with the Bayley screening test; the Age and Stage Questionnaire (ASQ) was used for patients from 6 months to 5 years old; and patients above the age of 5 years were evaluated with "The functional independence measure for children (WeeFIM)". Home videos and parent interviews were used to compare the patients' previous neurological status with the condition after CSE to determine new neurological sequelae.

Definitions

CSE was defined as continuous generalised tonic-clonic seizure activity or two or more seizures without full recovery of consciousness during the interictal period, lasting longer than 30 minutes (Novorol *et al*., 2007).

An "appropriate" treatment was defined as treatment using one dose of a benzodiazepine (BZD) in the pre-hospital setting and one dose of a BZD in the hospital setting. If there was no pre-hospital administration of a BZD, "appropriate treatment" was defined as the use of two doses of a BZD in the hospital setting.

An "inappropriate treatment" was defined as the use of more than one dose of BZD in the pre-hospital setting (both at home or paramedic) or use (pre-hospital and/or at hospital) of BZD more than twice (if continuous BZD was administered because of unavailability of injectable phenytoin, treatment was considered as "inappropriate").

"Timely" intervention was defined as a treatment starting within 10 minutes of the seizure onset; otherwise, intervention was defined as "delayed".

Children with a medical history of CSE were defined as having "recurrent" CSE.

The duration of CSE was defined as the time period from clinically manifested seizures to the end of CSE.

The aetiology of CSE was summarised into five categories according to Shinnar's classification:

idiopathic/cryptogenic SE, remote symptomatic SE, febrile SE, acute symptomatic SE, and progressive encephalopathy (Shinnar, 2006).

Treatment protocol

The treatment protocol was based on the North Central London Epilepsy Network for Children & Young People Guideline, The Management of Convulsive Status Epilepticus (published in April 2005 and reviewed in 2007 and 2010) (Guidelines Steering Group and Epilepsy Interest Group, 2005), and on the National Institute for Health and Clinical Excellence (NICE) clinical guideline (NICE, 2012).
The implementation of some recommendations reflected in the guidelines was not possible, thus we adapted the guidelines taking into account the current state of availability of essential medications (see *supplementary figure* showing the adapted guidelines). The basic difference between the adapted and the original protocol is the continuous administration of BZD when second-line injectable AEDs are not available. In these cases, the continuous administration of BZD is a "last chance" measure before thiopentone is used.

Statistical analysis

Descriptive statistics were used. Pearson's chi square test was used to identify associations between the categorical variables (Fisher's Exact test was used where appropriate). The Mann-Whitney test was used to identify differences between two means. Two-sided probabilities of less than 0.05 were considered statistically significant. Case fatality rate (CFR) was estimated as the number of known deaths in the cohort during follow-up, divided by the number of people in the cohort. The statistical analysis was performed with SPSS, version 21.0 (SPSS, Chicago, Illinois, USA).

Ethical issues

The study protocol was scrutinised and approved by the M. Iashvili Children Central Hospital Research Ethics Committee. All patients were included in the study only after signed agreement was obtained from their parents or legal proxies.

Results

In total, 48 patients met the criteria for CSE during the study period. The mean age of patients was 5.4 years (SD: 5.5). Fourteen (29.2%) patients were 2 years or younger. Twenty-six (54%) individuals were male. The majority of patients (85%) resided in the capital city.

Table 1. Aetiological factors of Convulsive Status Epilepticus among 48 patients.

Aetiology	n (%)
Acute symptomatic	11 (23)
Viral encephalitis	3
Bacterial meningitis	1
Tuberculous meningitis	1
Haemorrhagic stroke after rupture of arteriovenous malformation	1
Sinus thrombosis	1
Ischaemic stroke	1
Posterior reversible encephalopathy	1
AED withdrawal	1
Aspiration syndrome	1
Febrile CSE	10 (21)
Idiopathic/cryptogenic CSE	16 (33)
Progressive encephalopathies	5 (10)
Dravet syndrome	2
Migrating partial epilepsy of infancy	1
Congenital disorder of glycosylation CDG type 1	1
Urea cycle disorder	1
Remote symptomatic	6 (13)

In 33% of patients, an idiopathic/cryptogenic aetiology of CSE was detected. The second most frequent aetiology was acute symptomatic, which was revealed in 11 (23%) cases. For more details on the distribution of aetiological factors, see *table 1*.
Recurrent CSE manifested in 11 (23%) patients. In four (8%) patients, CSE was the first presentation of epileptic seizures. Twenty-one (44%) individuals had previous diagnosis of epilepsy. New neurological deficits were revealed in eight (17%) patients of the entire cohort. The nature of the new neurological consequences in the entire cohort were as follows: diffuse persistent hypotonia (one case), focal neurological deficit (hemiparesis) (one case), cranial nerve palsy (one case), cognitive impairment (one case), and loss of previously reached developmental milestones (four cases).
Thirty-one (65%) patients received "appropriate" pre-hospital treatment. The seizure duration in these cases was significantly shorter, compared with the

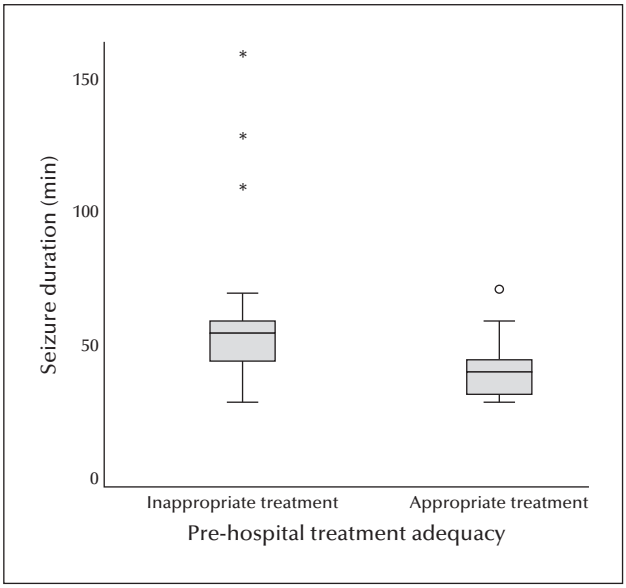

Figure 1. Seizure duration and adequacy of pre-hospital treatment.

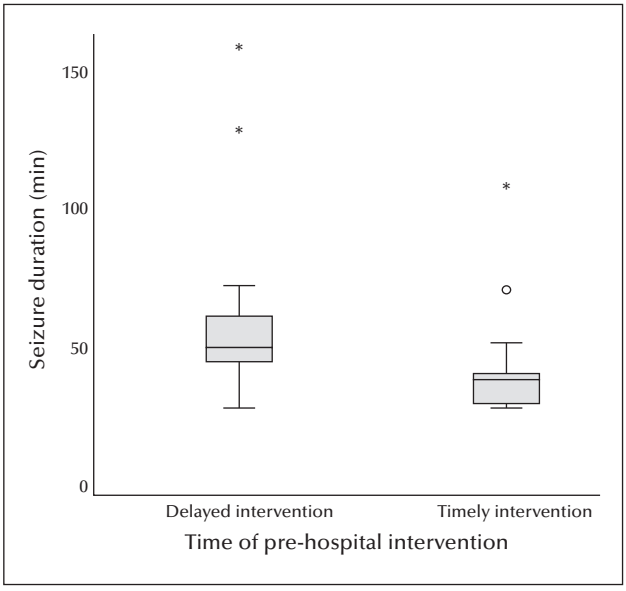

Figure 2. Seizure duration and time of intervention.

"inappropriate" group ($p<0.001$) (*figure 1*). After excluding all outliers from calculation, the difference remained statistically significant.

In total, 25 (52%) patients received timely medical intervention. The minimal time from seizure onset to BZD administration at pre-hospital setting was five minutes. The seizure duration in the timely intervention group was significantly shorter compared to those with delayed intervention ($p<0.001$) (*figure 2*).

Thirteen (27%) patients required mechanical ventilation; of these, eight cases were given excessive BZDs in pre-hospital settings, four individuals had inadequate hospital treatment (due to unavailability of injectable phenytoin), and one patient was treated adequately. Patients with adequate pre-hospital treatment (Pearson Chi-Square: 5.32; df: 1; Fisher's Exact Test: $p=0.039$) less frequently required mechanical ventilation. We did not, however, find association between use of artificial ventilation and increased morbidity or mortality.

For second-line treatment, phenytoin was used only in 15 (31%) patients, and in five of these patients, phenytoin became available only after multiple doses of BZD were used. In the remaining 33 (69%) patients, treatment was carried out only with continuous BDZ or thiopentone infusion after initial BDZ treatment. Phenytoin use was not associated with neurological outcomes or with mortality.

The short-term mortality was assessed 30 days after hospitalisation and detected in four cases; the CFR was therefore 8%. Of the four death cases, two were associated with acute symptomatic aetiology. For more details on the clinico-epidemiological characteristics of the lethal cases, see *table 2*.

Discussion

In this study, we attempted to establish some epidemiological features of CSE among the child population and to assess whether objective obstacles can affect management of the condition.

Data from recent studies suggest that idiopathic/cryptogenic aetiology is more frequently associated with CSE. Acute symptomatic aetiology was the second most frequent cause, with central nervous system infection predominating. In a study authored by Murthy *et al*. (2007), acute symptomatic aetiologies accounted for 54% of all cases. A similar high frequency of acute symptomatic aetiology was reported in studies from developing countries where CNS infections manifested within 28-67% of the aetiological spectrum, especially in the paediatric population (Kwong *et al.,* 1995; Murthy and Yangala, 1999; Mhodj *et al*., 2000; Campanille *et al*., 2001; Garzon *et al*., 2003; Hui *et al*., 2003; Kravljanac *et al*., 2011). Similar results were observed in our study, where one third of cases with idiopathic or cryptogenic aetiology were detected. Acute symptomatic cases were detected in 23% and CNS infections accounted for 11% of cases.

According to our results, the majority of patients had a favourable outcome with unchanged neurological status. Neurological deterioration after CSE developed in eight patients with a morbidity rate of 17%.

Data from Alldredge and colleagues (Alldredge *et al*., 1995) support the idea that pre-hospital treatment with rectal or intravenous diazepam shortens the duration

Table 2. Clinico-epidemiological characteristics of patients with fatal outcomes.

	Age at death (years)	Sex	Seizure duration (min)	Aetiology of CSE	Cause of death	Intervention
Case 1	1.2	Male	30	Haemorrhagic insult in patient with leukaemia	Underlying disease	Inappropriate and delayed pre-hospital treatment
Case 2	2	Female	120	Migrating partial epilepsy of infancy	Cardiac arrest during seizure	Inappropriate and delayed pre-hospital treatment
Case 3	13	Female	70	Rupture of arteriovenous malformation	Underlying disease	Appropriate and timely pre-hospital and hospital treatment
Case 4	7	Male	35	Encephalitis	Underlying disease	Appropriate and timely pre-hospital and hospital treatment

of SE and simplifies the subsequent management of these patients in the emergency department. The results of our study are in agreement, indicating that adequate pre-hospital treatment could contribute to the rapid cessation of CSE.

In our study, half of patients received timely pre-hospital service. The reason for this could be a relatively effective ambulance service network in the capital city, where the majority of the patients from the study cohort resided. Also, it should be mentioned that chronic epilepsy patients mostly have a BZD solution at home, and family members frequently perform the first intramuscular injection to patients.

Chin and colleagues demonstrated that the risk of respiratory depression is greater with more than two doses of BZD in the pre-hospital setting, and treatment delay and the choice of second-line emergency AED also contribute to respiratory failure (Chin et al., 2004). The data from Stewart and colleagues (Stewart *et al.*, 2002) support the suggestion that multiple doses of BZD increase the risk of respiratory depression. We identified an increased need for artificial ventilation among patients receiving inappropriate treatment in the pre-hospital setting. According to Spatola and colleagues (Spatola *et al.*, 2013), orotracheal intubation had no significant effects on the outcome of CSE (including mortality). This is in agreement with our results, in which the use of artificial ventilation was not associated with increased mortality.

Current estimates of case fatality associated with CSE in childhood range between 2.7% and 5.2% (Chin *et al.*, 2006). Mortality rates of 5% to 8% are reported for children who are admitted to paediatric intensive care units (Alldredge *et al.*, 1995). The results of our study show the case fatality rate to be 7%, which is comparable with hospital series from other studies.

Limitations

There are some potential limitations to the present study. The study was carried out in a referral hospital, where an experienced team provides the management of CSE. However, some other clinics with less expertise were also involved in the treatment of CSE, where mortality and morbidity rates may be higher. The data may have been subjected to recall bias, especially regarding intervention timing and seizure duration.

It should be mentioned that the time limit regarding the definition of CSE excluded cases from the study with seizures that lasted less than 30 minutes. We may therefore consider that only those cases with complicated physiological inhibitory mechanisms of seizure suppression were included in the study which would contribute to the general epidemiological data of CSE.

Conclusion

As the study results show, the restricted availability of injectable second-line anticonvulsants, buccal midazolam, and rectal diazepam leads to obstacles for appropriate management of CSE in Georgia, but it seems that this has no major effect on morbidity and mortality. We did not find unavailability of phenytoin to be linked to poor outcome, however, the reason for this could be the fact that, in five cases, phenytoin became available only after multiple doses of BZD

were administered (these cases were considered as "inappropriate hospital treatment"). This may have biased the effectiveness of phenytoin on disease course and might explain the failure of significant improvement of the disease course after phenytoin use.

In the other hand, unavailability of injectable phenytoin leads to repeated use of BZDs and to increased need for mechanical ventilation. This should be alarming for decision makers, prompting them to ensure universal availability of second-line injectable AEDs throughout the country. The adapted guideline seems to be an adequate instrument for the treatment of CSE for the current situation. Emphasis should be taken to improve pre-hospital intervention that can shorten seizure duration. Further population-based studies are needed to obtain more precise data on epidemiological characteristics, risk factors, and burden of CSE in Georgia. □

Supplementary data.
Summary didactic slides and supplementary figure are available on the www.epilepticdisorders.com website.

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None of the authors have any conflict of interest to disclose.

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TEST YOURSELF

(1) What are the main aetiological factors for convulsive status epilepticus in children?

(2) What was the nature of the new neurological consequences in the entire cohort of our study?

(3) Describe the basic difference between the adapted (please see *supplementary figure*) and the original treatment protocol for CSE?

(4) What are the results of delayed treatment strategy and use of multiple doses of BZD in the treatment of convulsive status epilepticus according to our results?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".