Status Epilepticus in Children: Experience in a Portuguese Tertiary Hospital

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Purpose: Status epilepticus (SE) is a life-threatening neurological emergency, frequently diagnosed in pediatric patients. We aimed to characterize our pediatric cases of SE in an 11-year period according to the 2015 International League Against Epilepsy report.

Methods: Clinical electronic records were retrospectively reviewed. All pediatric SE cases admitted from January 2010 to December 2020 were included, excluding neonates. SE was considered refractory if it persisted despite the administration of two appropriate antiseizure medications at acceptable doses.

Results: We included 102 episodes, 55 (53.9%) in boys. The median age was 2.5 years (interquartile range, 1.3 to 5.0). Most episodes were classified as SE with prominent motor features (92.2%), and the most frequent etiological classification was acute symptomatic cause (84.3%). A benzodiazepine was used as the first-line antiseizure medication in 99 (97%) cases, of which diazepam was preferred (93%). The preferred second-line medication was phenytoin (65.7%). Midazolam was the most frequently responsible for termination of SE when given in a continuous infusion (47%). Episodes of SE were classified as refractory in 81 (79.4%) cases. Episodes of >60 minutes were more frequent in patients diagnosed with epilepsy (P=0.036), focal motor SE (P<0.001), and non-convulsive SE (P=0.037). The in-hospital mortality rate was 2.9%.

Conclusion: Most of our findings are in accord with the current literature. Epilepsy, non-convulsive SE, and focal motor SE were associated with prolonged duration (>60 minutes), which reinforces the significance of the underlying neurological disease and semiological standardization in pediatric SE.

Keywords: Status epilepticus; Epilepsy; Seizures; Pediatrics

Introduction

Status epilepticus (SE) is a life-threatening neurological emergency, one of the most frequently found in pediatric settings, with an annual incidence of 10 to 73 per 100,000 children [1]. It is a major cause of admission to pediatric intensive care units (PICUs) globally [1].

Our understanding of the pathophysiology of SE has advanced...
significantly in recent years. However, this has not straightforwardly translated to clinical practice and guidelines [2]. In 2015, the International League Against Epilepsy (ILAE) reviewed some clinical aspects and proposed a new definition and classification for SE [3]. The definition states that SE is 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 (after time point 1)... that can have long term consequences (after time point 2)” [3]. For convulsive status epilepticus (CSE), it was suggested that time point 1 is 5 minutes, while time point 2 is 30 minutes [3]. This is extremely important because the timing of antiseizure medication (ASM) is a major determinant for preventing brain injury from excitotoxicity and cell death [4]. The new classification of SE has clinical and epidemiological meaning, and it involves four axes: semiology, etiology, correlates in electroencephalography (EEG), and age [3]. Globally, several research groups have applied these updates by ILAE in their observational studies of SE in children [5-7].

There is not a complete consensus regarding the treatment of SE, and it may vary according to local guidelines [8]. In our country, Portugal, a review of the approach to CSE in children and adolescents was published in 2020 by the Portuguese Society of Neuropediatrics [9]. To our knowledge, no observational studies from Portugal have previously applied the latest definition and classification by ILAE.

Therefore, the aim of our study was to characterize clinically and demographically all pediatric cases of SE admitted to our tertiary hospital in an 11-year period. We also aimed to describe the classification of all cases according to the 2015 ILAE report.

Materials and Methods

1. Subjects
The study included all cases of pediatric SE admitted to the urgent care clinic, emergency room, or PICU of our tertiary institution from January 2010 to December 2020. We searched for cases with a discharge code of SE according to the International Classification of Diseases, 10th Revision (ICD-10) and included cases of SE with prominent motor features and non-convulsive status epilepticus (NCSE) with clinical descriptions in accordance with the new definition in the 2015 ILAE report [3]. The diagnosis of NCSE was confirmed by EEG, applying the modified Salzburg criteria [10].

Cases with an initial ICD-10 code of SE were excluded when they could not be diagnosed with SE from a review of the clinical record. Neonates were also excluded from this study, due to their specific characteristics.

2. Research design
We conducted a single-center retrospective study of accessible electronic medical records to describe demographic features and clinical characteristics, as well as management, responsiveness to treatment, and in-hospital outcomes.

3. Variables
The following data were collected for each patient: age and sex; year of admission; previous seizures or SE episodes, epilepsy, and other underlying neurological diseases; circumstances of the event, including place of occurrence and inter-hospital or intra-hospital transfer; clinical features, including duration, semiology, and etiology according to the 2015 ILAE report; antiseizure management including selected ASM (before and after admission) and administration routes; and responsiveness to treatment; and in-hospital outcome (survival).

Semiology was described according to the presence or absence of prominent motor symptoms, and the degree of impaired consciousness [3]. Etiology was determined based on medical history, symptoms, physical examination, and laboratory tests. Etiologies were divided into known (symptomatic) and unknown (cryptogenic). Symptomatic etiologies included acute, remote, and progressive disorders, as well as SE in defined electroclinical syndromes [3]. The duration of SE was clinically assessed and included information from observers about seizure duration before admission. The total duration of SE was categorized as <30, 30–60, and >60 minutes. Regarding responsiveness to treatment, SE was classified as refractory if it persisted despite the administration of two appropriate ASMs at acceptable doses [5].

4. Ethics
This study was approved by the Ethics Committee of São João University Hospital Center, Porto, Portugal (No. CE-28-2023). Written informed consent by the patients was waived due to a retrospective nature of our study.

5. Statistical analysis
Data collection and statistical analysis were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA). Categorical variables were described as absolute and relative frequencies, continuous variables with a symmetric distribution by mean ± standard deviation, and continuous variables with an asymmetric distribution by median with interquartile range (IQR). The chi-square test and Fisher exact test were applied to compare categorical variables, and the independent t-test and Mann-Whitney U test were used for symmetric and asymmetric continuous variables, respectively. A P < 0.05 was considered statistically significant.
**Results**

1. **Demographics and clinical characteristics of the cohort**

The study cohort included 102 episodes of SE in 99 patients (one patient had two episodes; another patient had three episodes). Fifty-five (53.9%) episodes occurred in boys. Patients' age ranged from 36 days to 16 years, with a median age of 2.5 years (IQR, 1.3 to 5.0). Episodes of SE occurred at home in 66 cases (64.7%), at the hospital in 22 cases (21.6%), and at unspecified locations in 14 cases (13.7%). Patients were transferred from other hospitals in 64 cases (62.7%) and from other departments of our hospital in 10 cases (9.8%); they came directly from home in 28 cases (27.5%).

The clinical description is summarized in Table 1. Fifty-two patients (52/99; 52.5%) were diagnosed with epilepsy, and six of them (11.5%) had a history of previous SE episodes. In the group of patients with epilepsy, a diagnosis of epilepsy was established prior to admission in 26 patients (50%), during the hospital stay in eight patients (15.4%), and after discharge in 18 patients (34.6%). In 19 episodes (18.6%), patients had additional neurological disorders, such as chromosomal aberrations and intracranial tumors, which condition the presence of epilepsy. Regarding semiology, most episodes were classified as SE with prominent motor features (94/102; 92.2%). The most frequent etiological classification was an acute symptomatic cause (86/102; 84.3%), and an infectious etiology was the most common cause of SE (79/102; 77.5%). All patients with an unknown cause of SE were older than 2 years, and this association was statistically significant (P=0.045).

2. **Management and outcome**

Sixty-eight (66.7%) episodes occurred in patients admitted to the PICU, while the remaining 34 (33.3%) were admitted to the emergency room or ED. Before admission to our hospital, SE treatment was started in 40 cases (39.2%). In 14 cases (13.7%), the ASM start time was recorded, with a median interval of 17.5 minutes (IQR, 13.8 to 30) after the beginning of SE; all 14 of these cases were CSE. The first ASM used was a benzodiazepine (BZD) in 99 (97%) cases, of which diazepam was the preferred BZD (93%) versus midazolam (7%). All cases in which a non-BZD was the first-line ASM were patients with known epilepsy. Overall, rectal route was preferred for the administration of the first BZD in 65 (65.7%) cases, followed by the intravenous route in 33 (33.3%) cases; intramuscular midazolam was administered in one patient. Before reaching the hospital, the first BZD route was rectal in 67.5% of patients, intravenous in 30% and intramuscular in 2.5%. In the hospital, the first BZD route was rectal in 69.5% of patients and intravenous in 30.5%. There were no statistically significant differences between the administration routes (with vs. without peripheral venous access) and the start of treatment prior to or after admission (P=0.957). A second bolus of BZD was administered in 76 of 99 cases (76.8%), with the same BZD in 68 cases (89.5%). A second bolus of BZD was more frequently administered in patients with episodes of SE occurring at home or other locations outside a hospital (83.6%), but this difference was not statistically significant.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td>Additional neurological disorders</td>
<td>19 (18.6)</td>
</tr>
<tr>
<td>Chromosomal aberration/congenital malformation</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Intracranial tumor</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Neurodegenerative disease</td>
<td>2 (10.5)</td>
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<tr>
<td>Metabolic disorder</td>
<td>2 (10.5)</td>
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<tr>
<td>Head trauma</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Autoimmune disorder</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Mitochondrial disease</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Cortical dysplasia</td>
<td>1 (5.3)</td>
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**Semiology according to the 2015 ILAE classification**

- With prominent motor features: 94 (92.2%)
- Convulsive SE: 75 (79.8%)
- Generalized: 70 (93.3%)
- Focal onset evolving into bilateral: 5 (6.7%)
- Focal motor: 17 (18.1%)
- Tonic status: 2 (2.1%)
- Without prominent motor features: 8 (7.8%)
- Non-convulsive SE with coma: 6 (7.5%)
- Non-convulsive SE without coma: 2 (2.1%)

**Etiology according to the 2015 ILAE classification**

- Acute: 86 (84.3%)
- Infection: 79 (91.9%)
- Intracranial hemorrhage: 2 (2.3%)
- Anoxia/hypoxia: 2 (2.3%)
- Drug intoxication: 1 (1.2%)
- Autoimmune encephalitis: 1 (1.2%)
- Electrolyte imbalance: 1 (1.2%)
- Progressive: 1 (1.2%)
- Electroclinical syndromes: 7 (6.9%)
- Dravet syndrome: 3 (42.9%)
- Epilepsy with myoclonic absence: 1 (14.3%)
- West syndrome: 1 (14.3%)
- Landau-Kleffner syndrome: 1 (14.3%)
- Panayiotopoulos syndrome: 1 (14.3%)
- Unknown cause: 8 (7.8%)

ILAE, International League Against Epilepsy; SE, status epilepticus.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Microcephaly (4), Cornelia de Lange-like syndrome</td>
<td>1 (1.2%)</td>
</tr>
</tbody>
</table>
| Chromo plexus tumors (2), meningioma (1); Leukoencephalopathy with vanishing white matter (2), Metachromatic leukodystrophy (1), biotinidase deficiency (1); Acute disseminated encephalomyelitis (2), Mitochondrial complex II, IV, and V deficiency (1); Neonatal stroke (1), Polymicrogyria (1); Carbamazepine intoxication (1), Hyponatremia (1), Intracranial tumor (1); Infection as possible trigger (4), discontinuation of antiseizure medication as possible trigger (3).
The preferred second-line ASMs were phenytoin in 67 cases (65.7%) and propofol in eight cases (7.8%). The preferred third-line ASMs were a continuous infusion of midazolam in 24 cases (23.5%) and bolus of phenobarbital in 19 cases (18.6%). The mean number of ASMs used to terminate SE was 3.8 ± 1.1. Midazolam was the ASM most frequently responsible for the termination of SE when given in continuous infusion (47%), followed by propofol (13.7%). Episodes of SE were classified as refractory in 81 cases (79.4%). The duration of SE was 5 to 30 minutes in six cases (6.2%), 30 to 60 minutes in 73 cases (75.3%), and more than 60 minutes in 18 cases (18.6%). In five patients (4.9%), the duration of SE was not recorded. Prolonged episodes (lasting more than 60 minutes) were significantly more frequent in patients with a diagnosis of epilepsy (P=0.036) and in patients with focal motor SE (P<0.001) and NCSE (P=0.037) (Table 2). The in-hospital mortality rate was 2.9%.

Discussion

To our knowledge, the present study is the first observational study in Portugal that summarizes the epidemiological and clinical characteristics of SE in a pediatric cohort while applying the most recent ILAE guidelines. It represents the real-life decisions of general pediatricians and pediatric intensivists in the difficult management of pediatric SE during the past 11 years. Furthermore, our results are not limited to common practices in our hospital, since we also reviewed data from many patients in whom treatment was initiated before admission or who were transferred from other national health institutions. Most of our findings are in accord with the current literature.

Concerning demographic features, previous studies reported a higher prevalence of SE in boys and preschool children, with median ages ranging from 1.9 to 4.5 years, similar to our results (median age, 2.5 years; IQR, 1.3 to 5.0) [1,5,11-13].

In clinical aspects such as etiology and semiology, we also obtained some expected findings, which were more easily compared to the existing literature due to the standardization provided by the 2015 ILAE guidelines. According to several papers, acute symptomatic etiology is the most common cause of pediatric SE [1,11,14]. Unlike a study performed by Chiarello et al. [5] in a unit with primarily hematological-oncological disorders, our data set included only three patients with a personal history of brain tumor, even though our hospital is a regional referral center, and only one patient displayed an episode of SE on account of progressive etiology. This may be due to two factors: prophylactic ASM and early treatment were given to patients with brain tumors, which stopped seizures from evolving to SE, and some patients with brain tumors and SE could have lacked a discharge ICD-10 code for SE and therefore were missed in our research.

The prevalence of unknown (cryptogenic) etiology has mixed results in the literature, which may be due to the characteristics of the populations studied, namely the percentage of patients with a statistically significant (P=0.065). More than two boluses of BZD were administered in five cases (5/99; 5%).
previous diagnosis of epilepsy. Interestingly, some researchers have noticed that unknown causes of SE were more prevalent in children older than 2 years, which we also verified [5,15]. The association between etiology and age was detailed by Shinnar et al. [15], who documented significant differences in the distribution of causes between the first and second year of life, with a rapid decrease in the frequency of acute symptomatic cases and a higher proportion of cryptogenic and remote symptomatic cases in the older children.

CSE, particularly the generalized subtype, was the most frequent semiological classification, which also agrees with many published works [1,5,12,16]. Nonetheless, recent studies have focused on NCSE, especially in the PICU. NCSE is the result of a prolonged electrographic seizure leading to non-convulsive clinical symptoms [5]. In the literature, it accounts for only 6% of the cases, but diagnosis requires a high index of suspicion, since cognitive or behavioral changes are often difficult to notice [1]. In the present study, we were able to confirm the diagnosis of NCSE in 7.8% of our patients, and it was associated with prolonged SE (>60 minutes). Focal motor SE was also associated with episodes >60 minutes. These findings reinforce the importance of semiology and its standardization in pediatric SE.

Rectal diazepam was the preferred first-line BZD, both before arrival at the hospital and at the hospital. Some studies performed in pediatric cohorts have not shown the superiority of any BZD [14]. In a Cochrane review, intravenous lorazepam and intravenous diazepam led to more rapid seizure cessation, but in the absence of intravenous access, buccal midazolam or rectal diazepam were considered acceptable first-line ASMs [17]. Although phenytoin was the most frequently selected second-line ASM, as in previously published studies [12], it was followed by propofol as the second most used. Although propofol is not usually selected as a second-line ASM because of its safety profile, it is very effective in seizure cessation, particularly in refractory cases, and it can be used in the emergency room, especially with support from the PICU team [8]. Midazolam in continuous infusion was the preferred third-line ASM and was most frequently responsible for the termination of SE, as has also been reported in the literature [4].

Despite the recognition of the need for urgent ASM administration, the timing of drug administration remains a significant barrier in pediatric SE. The 2015 ILAE guidelines indicate that the minimum time for starting emergency treatment of SE is 5 minutes for CSE [3]. In our study, the timing of the start of ASM was rarely listed in the clinical records. From the available data, we obtained a median interval of 17.5 minutes between the beginning of SE and ASM in CSE, which is longer than the recommended timing. The circumstances of the occurrence of SE, such as the place of the event (particularly in new-onset SE without at home rescue diazepam), may interfere with the urgent administration of an ASM, and studies on this topic should systematically review this issue.

The longer SE goes untreated, the more likely it is to become BZD-resistant and require anesthetic doses for cessation (refractory SE) [4]. In animal models, this seems to be associated with reuptake/decreased surface expression of the BZD-specific gamma-aminobutyric acid receptor subunit γ2 [4]. Refractory SE occurs in 29% to 43% of SE cases, according to the literature [6]. In our study, we found a very high percentage of refractory SE (79.4%). A more recent standardized protocol for the management of pediatric SE has been available in our hospital since 2019, and it suggests using midazolam or diazepam as first-line drugs (the administration routes differ between prehospital or hospital initiation of treatment); levetiracetam, valproate sodium, phenytoin, or phenobarbital as second-line drugs; and midazolam, thiopental, or propofol in continuous intravenous infusion as third-line drugs. It would be interesting to compare the therapeutic management of SE and outcomes in our hospital before and after the implementation of this protocol. In fact, we suspect that some changes in choices of ASM may have occurred after protocol implementation, such as levetiracetam replacing phenytoin as the preferred second-line drug. However, we should note that very prolonged SE (>60 minutes) was significantly associated with a diagnosis of epilepsy. It is known that patients with more severe epilepsy may not respond as well to the standard dosing/dose sequence of ASMs [18]. This raises a question regarding whether management is inappropriately homogeneous when protocols are applied, as has been discussed in previous studies [18].

The main limitation of this study is its retrospective and mainly descriptive nature. Patients were identified based on ICD-10 codes and confirmed by a clinical review; therefore, diagnoses could have been missed. ICD-10 codes are recorded by pediatricians at discharge, and sometimes the cause of SE is coded as the final diagnosis (e.g., infection) and the associated diagnoses are omitted. Intensive care pediatricians may be more likely to systematically codify SE compared to general pediatricians in the ED, which might explain why we obtained a higher proportion of cases admitted in the PICU than we excepted. For that reason, refractory cases may have been overestimated, but we also received many patients transferred from other hospitals, which are usually more severe cases. Temporal variables may lack accuracy due to post-management documentation in electronic records by medical doctors. Our results may have been influenced by treatment prior to admission, and we lacked information on the timing of ambulance arrival, duration of transport, and other prehospital data. Semiology was analyzed...
based on medical descriptions, which may have been influenced by experience. We did not obtain complete information about EEG in seizure monitoring, only for diagnostic purposes in NCSE. It would be interesting to evaluate EEG patterns in future studies to better characterize NCSE. Outcomes were not fully explored in this article. The observed in-hospital mortality rate was consistent with mortality rates reported in pediatric cohorts in developed countries [7]; however, neurodevelopmental outcomes were not reviewed, which could be particularly important given the high percentage of prolonged SE in our sample.

In summary, most of our findings are in accord with the current literature, including the most frequent demographic features (boys and preschool children), etiological and semiological classification (acute symptomatic etiology and CSE), and the selection of ASMs (the preferred ASMs were rectal diazepam as first BZD, phenytoin as second-line therapy, and midazolam with a continuous infusion as third-line treatment). The standardization provided by the 2015 ILAE guidelines allowed an easier comparison with other recent studies. Epilepsy, NCSE, and focal motor SE were associated with prolonged SE (>60 minutes), which reinforces the importance of the underlying neurological diseases and semiological standardization in pediatric SE.

This paper reports high percentages of patients with refractory SE. A standardized protocol for the management of pediatric SE has been available in our hospital since 2019, and hopefully, it will allow a more rapid recognition and initial treatment.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Author contribution

Conceptualization: AR. Data curation: MJS and TCM. Formal analysis: CGM, RR, and AR. Methodology: CGM and RR. Writing -original draft: CGM. Writing - review & editing: MJS, TCM, RR, and AR.

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