https://doi.org/10.52418/moldovan-med-j.64-2.21.02
UDC: 616.853.9-053.2

Refractory status epilepticus – a major problem for the practitioners

*[1,5]Cornelia Calcii, [1,5]Svetlana Hadjiu, [2,5]Mariana Sprincean, [1,6]Ludmila Feghiu, [1]Nadejda Lupusor, [1,5]Ninel Revenco, [3,4,6]Stanislav Groppa

[1]Department of Pediatrics, [2]Department of Molecular Biology and Human Genetics, [3]Department of Neurology No 2
[4]Laboratory of Neurobiology and Medical Genetics
Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, the Republic of Moldova
[5]Institute of Mother and Child, Chisinau, the Republic of Moldova
[6]The National Center of Epileptology, Chisinau, the Republic of Moldova

Authors' ORCID iDs, academic degrees and contributions are available at the end of the article

*Corresponding author: cornelia.calcii@usmf.md
Manuscript received June 22, 2020; revised manuscript March 18, 2021; published online April 28, 2021

Abstract

Introduction: Status epilepticus (SE) is a life-threatening neurological emergency requiring immediate medical intervention and is associated with high mortality and morbidity. The aim of this research was evaluation of clinical and etiological profile of refractory status epilepticus (RSE) among children aged between 1 month and 18 years.
Material and methods: The study was done between January 1, 2017 and December 24, 2019. All children with the age limits mentioned above, who presented convulsive SE, subsequently with development in refractory status epileptic (RSE), were included in the study. Patients were investigated and evaluated according to a standard protocol. Subsequently, the characteristics of children with RSE and those without an evolution in RSE were compared.
Results: 55 children, out of whom 32 boys with SE were enrolled in the study, of which 20 children (36%) developed RSE. Central nervous system (CNS) infections were the most common causes of SE and development of RSE (51% in SE and 53% in RSE, $p > 0.05$). Noncompliance of antiepileptic medication served as the second cause for evolution of RSE. The overall mortality rate was 10.9%, the chances of death in RSE (20%) being higher than in SE (5.7%). The unfavorable prognosis was seven times higher in children with RSE, compared to children who developed SE.
Conclusions: In the management of CNS infections, pediatricians should be aware of the high risk of developing RSE. In addition, the possibility of developing RSE should be considered and promptly managed in an intensive care unit in order to reduce the risk of mortality and morbidity of this severe neurological condition.
Key words: refractory status epilepticus, childhood epilepsy, CNS infection.

Cite this article
Calcii C, Hadjiu S, Sprincean M, Feghiu L, Lupusor N, Revenco N, Groppa S. Refractory status epilepticus – a major problem for practitioners. *Mold Med J.* 2021;64(2):12-15. https://doi.org/10.52418/moldovan-med-j.64-2.21.02.

Introduction

Status epilepticus (SE) is a life-threatening neurological emergency requiring immediate medical intervention and is associated with high mortality and morbidity. The incidence of SE in children is reported to be of 10-40 children per 100000 people. SE is the most common pediatric neurological emergency [1, 2], being a condition resulting from the loss of the mechanisms responsible for ending of convulsive access or by initiating mechanisms that cause an abnormal convulsive response (after Time 1) [3, 4]. SE is a condition that can lead to long-term consequences (after Time 2), including neuronal death, neuronal injury, alterations of neural networks depending on the type and duration of the attacks [4]. The practical approach suggests that any seizure or series of seizures, lasting more than five minutes, could be considered as SE, most children requiring pharmacotherapy for control of seizures [3, 4]. Recently, Tinka et al. proposed a new definition for focal SE: a duration of 10 minutes of seizures (without the return of consciousness between seizures) and 60 minutes for possible long-term consequences [4]. At the same time, and experimental data support the idea that prolonged seizures cause neuronal damage, therefore the drug intervention is considered critical in such cases [5, 6].

In children, the incidence is higher compared to that in adults; however, the mortality rate of adult patients is higher, around 20%, and in children under 10 years of age, it can be up to 2.6% [7, 8]. Early diagnosis and prompt treatment significantly reduce mortality and are key steps in SE management [9]. After initial supportive treatment (ABC via intravenous [I/V] access), seizure control with Lorazepam I/V is recommended as a first-line treatment [10, 11]. Alternatives to Lorazepam include intravenous administration of Midazolam or Diazepam. If I/V access

is not achieved, Midazolam may be administered orally, intranasally or intramuscularly. Diazepam may also be administered rectally [12, 13]. First-line drugs control the seizures and they are obtained in 80% of children in the first 30 minutes [14]. If the patients continue to have seizures, additional treatment should be given rapidly [15]. Most experts recommend fosphenytoin as a second-line therapy, although there are supporters in favor of the use of other alternative antiepileptic drugs (AED), such as phenobarbital, valproic acid or levetiracetam [16]. While most of the causes of SE are due to epilepsy, in case of SE in children primary causes can be considered atypical febrile seizures, neuroinfections, cerebral hypoxia and innate errors of metabolism [17].

Refractory epileptic status (RSE) is a more severe variant of SE. Currently, the accepted definition of RSE is the persistence of seizures despite the administration of two adequate anticonvulsants in acceptable doses and is estimated in approximately 10-40% of patients with SE. RSE has been shown to be associated with a higher mortality rate and more long-term neurological consequences. Based on the fact that RSE is a major emergency and on the fact that there are no studies on RSE in the Republic of Moldova, this research was carried out with the aim of improving knowledge on the etiology and evolution of RSE among children with SE, to prevent unfavorable prognosis, including mortality.

Material and methods

This study is a part of a larger research, carried out within the project "Integration of epileptogenic mechanisms in order of creating a network of multimodal diagnosis and treatment of epilepsy". The study is retrospective and descriptive (preliminary data attributed to the project). The group of patients included in the study was selected from children admitted to the Departments of Neurology of the Institute of Mother and Child Health Care during the years 2017-2019. SE was defined as a continuous seizure lasting more than five minutes and/or multiple seizures between which the state of consciousness was not regained within at least 30 minutes. The age of the patients included in the study ranged from one month to 18 years. Newborns and children with undocumented SE were excluded from the research. The medical records were reviewed to make an analysis of the data, type of seizures (focal versus generalized), data on epilepsy, as a precursor disease to the installation of SE, analyzed antiepileptic drags (AED) used daily by patients, serum levels of AED at the time of admission (therapeutic or sub-therapeutic), neuroimaging examinations performed, EEG data, possible etiological causes, mortality rate. Continuous data is presented as a median interval; some is presented as a percentage. A *p* value of less than 0.05 was considered significant.

RSE was defined as SE, in which seizures persisted despite the administration of two adequate anticonvulsants at acceptable doses. Unfavorable prognosis included death of the patient, persistent vegetative state or severe disability. In subjects with previously diagnosed epilepsy were collected data about the type of seizures, duration of disease, especially drawing attention to non-compliance and / or other changes in the dosage of drugs. The standard management of SE consisted of two doses of Diazepam, followed sequentially by intravenous phenytoin and intravenous phenobarbital. In severe cases, Propofol infusion was done. After seizure control, neuroimaging and EEG examinations were performed. In the case, if the child had fever, the lumbar puncture was performed (Glasgow Scale > 7 points). The children were monitored daily with appropriate examinations. All data were analyzed using Epi Info software. Different characteristics and results obtained in children with SE and children with RSE were compared.

Results

Of the 55 children (32 boys) with SE, the evolution of SE to RSE was recorded in 20 children (36%). The average age of patients was 6.5 years. There have been documented 6 (10.9%) cases of children who developed a recurrent SE. At the time of admission, the number of children with pre-existing seizures who did not receive routine AED was 9% (5 cases), and 32 children (58.1%) received two or more AED daily. The results of serum AED were evaluated in 77.3% of children, of whom 51.6% children had subtherapeutic levels of AED.

Diazepam was the most common medication given as emergency therapy, used both in children with pre-existing seizures and in those with "*de novo*" SE (62.5% vs 51.1%; p >0.05). The second-line anticonvulsant therapy was phenytoin (45.2% vs 51.1%; p >0.05). Phenobarbital infusion was used in 7.3% of children with pre-existing seizures and in none of the children with "de novo" SE. In 36.3% of cases, endotracheal intubation was required, mainly in the children with RSE (28.5% vs. 60%, p >0.05).

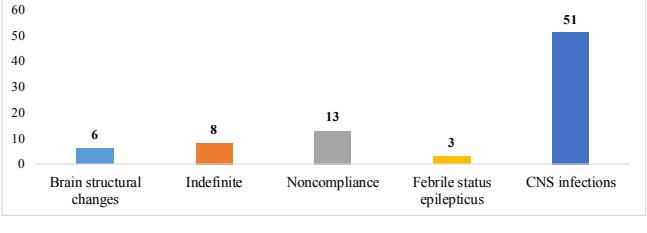

Fig. 1. Etiological factors for convulsive SE in children (n=35), (%)

The gender and type of seizures did not differ significantly between these 2 groups (tab. 1). Electroencephalography (EEG) was performed in 82% of all children admitted with SE. Of these, 72% showed changes on the EEG route. Among children with RSE, EEG was performed in 98% of cases, an abnormal route of EEG was recorded in 85% of cases.

Being admitted to the hospital, children were analyzed for possible causes for the onset of SE. Thus, CNS infection was considered an etiological cause for both SE and RSE (51% in SE and 53% in RSE, respectively) (fig. 2).

Another cause for SE and RSE development was non-compliance with doses and regimes of AED administration, with no statistical difference between groups (p > 0.05).

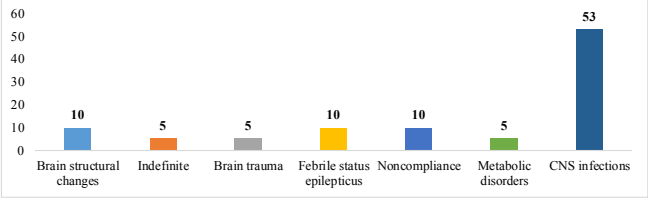

Fig. 2. Etiological factors recorded in RSE (n=20), (%)

The proportion of patients with pre-existing epilepsy, the duration of the disease before SE development and the etiology of epilepsy (genetic / structural) were not significantly different between the two groups (p > 0.05). Most patients (85%) developed generalized seizures. The risk of evolution in RSE was not significantly different for febrile children (PR =1.2; 95% CI : 0.34–3.9; p >0.5), children with pre-existing epilepsy (PR = 0.7; 95% CI : 0.18–2.7, p > 0.6), children with developmental disorders (PR = 1.25; 95% CI: 0.29–5.4; p > 0.8), focal seizures (PR = 5.12; 95% CI: 49–53.2, p > 0.17), (tab. 1).

Table1. General characteristics of children with SE and RSE

Characteristics	SE (n=35), %	RSE (n=20), %
Median age (years)	7.5	5.5
Sex boys girls	18 (32.7%) 17 (30.9)	14 (70%) 6 (30%)
Mean weight (kg)	42	34
Fever association	57.1	70
Pre-existent epilepsy (%)	27.2	25
Intubation (%)	28.5	60
EEG performed on admission (%)	82	98
Pathologic EEG course	68.9	54.7
Neuroimagistic exam at admission (%)	62.6	85.2
Pathological neuroimagistic exam (%)	43.4	62.6
Disorders of children's neurodevelopment (%)	38.1	75
State of shock at admission to the hospital	42.8	25

Six children (10.9 %) died, CNS infection being the most common cause of death (80.2%). The death rates in children with RSE (20%) were higher than those with SE (5.7%). The unfavorable prognosis was seven times higher in children with RSE, compared to children who developed SE (PR= 7.0; 95% CI:1.6–22.3).

Table 2. The outcome of SE

Description	SE (n=35),%	RSE (n=20), %
Death	2 (5.7)	4 (20)
Persistent vegetative state	1 (2.8)	1 (5)
Persistent disability	2 (5.7)	5 (25)
Moderate disability	10 (28.5)	2 (10)
Good reabilitation	18 (51.4)	4 (20)

Discussion

In this observational study based on the hospitalization of 55 children with convulsive SE (including 20 with RSE) at the Hospital of Mother and Child Health Care, we found out that CNS infections were the most common etiological cause in both groups of patients. Most studies in developing countries report CNS infections as the most common etiology of SE. Among pediatric studies, CNS infections are also the most common RSE etiologies [18].

The unfavorable prognosis was seven times higher in children with RSE, compared to children who developed SE. The proportion of generalized seizures varies from 63% to 96% in pediatric studies, similar to our conclusions (85%) [19].

About 1/4 of the subjects in the study had a previously established diagnosis of epilepsy, the conclusion corresponds to similar studies on RSE (16–29%) [20]. In the same way, we were able to perform the EEG exam only in 82% of patients with SE and in 98% of RSE. Neuroimaging was performed in 62.6% of patients with SE and 85.2% with RSE, with pathological changes in 43.4% of patients with SE and 62.6 with RSE, data correlate with previous studies [20].

Non-compliance with AED dosing regimens was an important cause of SE in this study (13%), subtherapeutic levels constituting 51.6%, similar to previous reports in adults (20–27%) [21]. A meta-analysis of paediatric RSE reported a mortality rate of 16%; more recent studies report rates up to 3.7% [22]. Studies in the adult population report mortality rates of 5–35% in RSE [23]. Our study reported a mortality rate of 10.9%, predominantly in the case of RSE.

Conclusions

1. The high proportion of RSE in patients with CNS infections, high rate of mortality in children with RSE and high rates of remote unfavorable prognosis are the highlights in the management of these cases.
2. Early identification of RSE in intensive care unit and emergency care service could reduce mortality in this group of children.
3. Since most patients with RSE have various CNS infections as an etiologic cause, antibacterial treatment should be initiated from the very first minutes of RSE.
4. During the management of children with CNS infections, treating physicians should be aware of the high risk of developing of RSE, and this risk should be managed in an intensive care unit in order to reduce mortality and morbidity due to this severe neurological condition.
5. In addition to infections, another important etiologic cause of RSE was noncompliance with the AED; a situation that could be avoided by improving physician-patient compliance.

References

1. Newton CR, Neville BG. Paediatric neurology: advances on many fronts. Lancet Neurol. 2009;8(1):14-15. doi: 10.1016/S1474-4422(08)70276-X.
2. Singh RK, Stephens S, Berl MM, et al. Prospective study of new-

onset seizures presenting as status epilepticus in childhood. Neurology. 2010;74(8):636-642. doi: 10.1212/WNL.0b013e3181d0cca2.
3. Chamberlain JM, Okada P, Holsti M, et al. Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. JAMA. 2014;31001/jama.2014.2625.
4. 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(10):1515-1523. doi: 10.1111/epi.13121.
5. Tasker RC, Goodkin HP, Sánchez Fernández I, et al. Refractory status epilepticus in children: intention-to-treat with continuous infusions of midazolam and pentobarbital. Pediatr Crit Care Med. 2016;17(10):968-975. doi: 10.1097/PCC.0000000000000900.
6. Modi AC, Guilfoyle SM, Mann KA, Rausch JR. A pilot randomized controlled clinical trial to improve antiepileptic drug adherence in young children with epilepsy. Epilepsia. 2016;57(3):e69-75. doi: 10.1111/epi.13289.
7. Sánchez Fernández I, Jackson MC, Abend NS, et al. Refractory status epilepticus in children with and without prior epilepsy or status epilepticus. Neurology. 2017;88(4):386-94. doi: 10.1212/WNL.0000000000003550.
8. Sinha S, Prashantha DK, Thennarasu K, Umamaheshwara Rao GS, Satishchandra P. Refractory status epilepticus: a developing country perspective. J Neurol Sci. 2010;290(1-2):60-5. doi: 10.1016/j.jns.2009.11.007.
9. Tripathi M, Vibha D, Choudhary N, et al. Management of refractory status epilepticus at a tertiary care centre in a developing country. Seizure. 2010;19(2):109-11. doi: 10.1016/j.seizure.2009.11.007.
10. Gulati S, Kalra V, Sridhar MR. Status epilepticus in Indian children in a tertiary care center. Indian J Pediatr. 2005;72(2):105-8. doi: 10.1007/BF02760691.
11. Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia. 1993;34(4):592-6. doi: 10.1111/j.1528-1157.1993.tb00433.x.
12. Lacroix J, Deal C, Gauthier M, Rousseau E, Farrell CA. Admissions to a pediatric intensive care unit for status epilepticus: a 10-year experience. Crit Care Med. 1994;22(5):827-832. doi: 10.1097/00003246-199405000-00019.
13. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975;1:480-4. doi: 10.1016/s0140-6736(75)92830-5.
14. Mishra D, Sharma S, Sankhyan N, et al. Consensus guidelines of management of childhood convulsive status epilepticus. Indian Pediatr. 2014;51(12):975-90. doi: 10.1007/s13312-014-0543-4.
15. Kang DC, Lee YM, Lee J, Kim HD, Coe C. Prognostic factors of status epilepticus in children. Yonsei Med J. 2005;46(1):27-33. doi: 10.3349/ymj.2005.46.1.27.
16. Singhi S, Banerjee S, Singhi P. Refractory status epilepticus: role of continuous diazepam infusion. J Child Neurol. 1998;13(1):23-6. doi: 10.1177/088307389801300104.
17. Watemberg N, Segal G. A suggested approach to the etiologic evaluation of status epilepticus in children: what to seek after the usual causes have been ruled out. J Child Neurol. 2010;25(2):203-211. doi: 10.1177/0883073809337032
18. Kravljanac R, Jovic N, Djuric M, et al. Outcome of status epilepticus in children treated in the intensive care unit: a study of 302 cases. Epilepsia. 2011;52(2):358-363. doi: 10.1111/j.1528-1167.2010.02943.x.
19. Dragoumi P, Tzetzi O, Vargiami E, et al. Clinical course and seizure outcome of idiopathic childhood epilepsy: determinants of early and long-term prognosis. BMC Neurol. 2013;13:206. doi: 10.1186/1471-2377-13-206.
20. Brophy GM, Bell R, Claassen J, et al; Neurocritical Care Society Status Epilepticus Guideline Writing Committee. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1):3-23. doi: 10.1007/s12028-012-9695-z.
21. Sánchez Fernández I, Abend NS, Arndt DH, et al. Electrographic seizures after convulsive status epilepticus in children and young adults: a retrospective multicenter study. J Pediatr. 2014;164(2):339-346. doi: 10.1016/j.jpeds.2013.09.032.
22. Neligan A, Shorvon SD. Frequency and prognosis of convulsive status epilepticus of different causes: a systematic review. Arch Neurol. 2010;67(8):931-940. doi: 10.1001/archneurol.2010.169.
23. Gaillard WD, Chiron C, Cross JH, et al. Guidelines for imaging infants and children with recent-onset epilepsy. Epilepsia. 2009;50(9):2147-2153. doi: 10.1111/j.15281167.2009.02075.x.

Authors' ORCID iDs and academic degrees
Cornelia Calcii, MD, PhD, Associate Professor – https://orcid.org/0000-0002-2608-2417
Svetlana Hadjiu, MD, PhD, Professor of Neurology – https://orcid.org/0000-0001-5281-3626
Mariana Sprincean, MD, PhD, Associate Professor – https://orcid.org/0000-0002-3619-1924
Nadejda Lupusor, MD – https://orcid.org/0000-0002-0877-8998
Ludmila Feghiu, MD – https://orcid.org/0000-0002-1425-1885
Ninel Revenco, MD, PhD, Professor of Pediatrics – https://orcid.org/0000-0002-5229-7841
Stanislav Groppa, MD, PhD, Academician, Professor of Neurology – https://orcid.org/0000-0002-2120-2408

Authors' contributions
CC drafted the first manuscript; SH conducted/performed the laboratory work; MS interpreted the data, LP collected the data; FL collected the data; NR conceptualized the project and designed the research; SG conducted the laboratory work, revised the manuscript critically. All the authors approved the final version of the manuscript.

Funding
It was provided by *Nicolae Testemitanu* State University of Medicine and Pharmacy and Mother and Child Institute. The trial was the authors' initiative. The authors are independent and take responsibility for the integrity of the data and accuracy of the data analysis.

Ethics approval and consent to participate
No approval was required for this study.

Conflict of Interests
There is no known conflict of interests and financial or non-financial support associated with this publication.