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ORIGINAL ARTICLE

Status epilepticus. Diagnosis and treatment

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Abstract

Status epilepticus is defined as more than 30 minutes of either continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures. Since most seizures are brief, status epilepticus treatment protocols have been using a 5 minute threshold definition to minimize neurological adverse outcomes. Status epilepticus is a neurological emergency and its early treatment is related to lower mortality and neurological morbidity. The aim of this article is to review the main aspects of this disease and present didactically the clinical and pharmacological treatment.

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INTRODUCTION

The definition of status epilepticus (SE) remained controversial for many years and even today, conceptually distinct definitions can be found in the literature. SE was first understood as an abnormal neurological condition persisting for a sufficiently prolonged time or recurring at such short intervals that it produced a lasting and invariable epileptic condition[1].

In clinical practice, SE is defined as an epileptic seizure lasting 30 minutes or more or the occurrence of continued epileptic seizures without full recovery of consciousness. The rationale for specifying this duration of 30 minutes is based on prognostic studies, and it is significantly related to increased neurological morbidity and mortality.

Based on its signs and symptoms, SE can be classified into "convulsive" seizures, characterized by evident and abundant motor manifestations, and "nonconvulsive" seizures, characterized by absent or slight motor manifestations[2]. However, epileptic seizures lasting more than 5 minutes have a high risk of reaching a 30-minute duration. Thus, SE can be operationally defined as a continuous epileptic seizure or intermittent seizures without recovery of consciousness lasting more than 5 minutes. In children under the age of 5 years, a seizure should have a duration of 10 minutes to consider it as SE[3].

Although it is not a consensus among authors and the literature presents more than one definition, SE lasting more than 2 hours is called refractory SE. Super-refractory SE occurs when an epileptic seizure lasts more than 24 hours after the onset of anesthetic administration, including cases with SE recurrence during anesthetic treatment withdrawal or interruption[4].

Epidemiology

The use of different conceptual criteria and definitions makes it difficult to assess and compare the prevalence of SE. Data from the 1960s have already shown that SE was one of the most frequent complications in children with epilepsy. A European study showed that up to 27% of children with epilepsy under the age of 16 years had at least one episode of SE and that the risk was greater in the first years after the diagnosis[5].

Severely ill patients admitted to an intensive care environment with decreased consciousness are a particular high-risk group. A study of 236 comatose patients with no motor manifestation suggestive of an epileptic seizure showed that 8% of these individuals met the EEG criteria for the diagnosis of nonconvulsive SE[6]. More recent data show that SE is the most frequent neurological emergency in pediatrics, occurring in 40% of cases in the first 2 years of age[7].

In 12% of cases, SE is the first manifestation of childhood epilepsy. Mortality from this condition is closely associated with the duration and etiology of SE and the time of onset of drug treatment. Febrile SE is the most frequent form of SE in the pediatric population, whereas viral encephalitis is the symptomatic form with the highest incidence. In children with previously diagnosed epilepsy, brain malformations are the most common remote cause of SE[8].

Data on the risk of SE recurrence in childhood are scarce. A prospective study of 95 children with a mean age of 29 months who had their first episode of SE showed a 3% risk of recurrence in cases of febrile SE, 4% in idiopathic cases, 44% in symptomatic cases, and 67% in patients with progressive neurological disorders[9,10].

Etiology

The etiology of SE in pediatrics can be subdivided into (a) acute symptomatic SE, stemming from a recent CNS injury; (b) remote symptomatic SE, stemming from an early and older CNS injury; and (c) cryptogenic SE, when the cause cannot be clearly identified.

The main causes of childhood SE are fever (febrile SE), abrupt interruption of treatment with antiepileptic drugs (AEDs), lack of adherence to treatment, and low serum levels of AEDs in previously diagnosed patients. In febrile SE, seizures rarely remit spontaneously, and a treatment approach with early introduction of AEDs is recommended.

Acute disorders that affect the CNS directly or indirectly are relatively frequent causes of SE. These include neonatal birth injury, viral encephalitis, bacterial meningitis, fluid and electrolyte disorders, and traumatic brain injury[1,7,8,11].

Some drugs used routinely in pediatrics may also induce epileptic seizures and SE, e.g., penicillin and other beta-lactam antibiotics, lidocaine, aminophylline, N-acetyl cysteine, metronidazole, opioids, theophylline, imipenem, isoniazid, clozapine, cyclophosphamide, and propoxyphene.

With the technological development of neuroimaging methods, particularly high-definition magnetic resonance imaging, disorders of cortical development, previously underdiagnosed, are increasingly being associated with cases of childhood SE. In the case of neonatal SE, it is important to emphasize the potential presence of inborn errors of metabolism[1,7,8,11].

Classification and Pathophysiology

Theoretically, there would be as many types of SE as there are types of epileptic seizures because any convulsive or nonconvulsive seizure could be prolonged and assume a lasting and invariable nature.

Typical absence status is the classical nonconvulsive SE theoretical model, with a pathophysiology strongly related to the exacerbation of inhibitory phenomena by synchronous neuron inhibition. The pathophysiological mechanism involved is GABAB receptor-mediated hyperpolarization through the opening of T-type calcium channels, followed by cyclic neuron depolarization. The neurotransmitter GABA binds to its specific receptor on the postsynaptic membrane, causing the opening

of potassium channels via the G protein, hyperpolarization of the postsynaptic membrane, and subsequent opening of T-type calcium channels. The latter causes calcium influx, triggering the release of more GABA, enabling the beginning of a new inhibition cycle[12,13]. It remains unclear whether this feedback inhibition model using thalamocortical connections is capable of causing permanent nerve injury[14].

The pathophysiology of convulsive SE is not yet fully understood, although studies in animal models show that, in addition to systemic changes (hypoxia, hypercapnia, hypoglycemia, decreased cerebral blood flow, and hyperthermia), long-lasting abnormal electrical activity itself is able to cause irreversible neuronal damage, particularly in the entorhinal cortex, hippocampus, amygdala, Purkinje cells, and thalamic nuclei.

Physiopathogenic and injury mechanisms are related to excitotoxicity mediated by AMPA and NMDA glutamate receptors, which cause an increase in neuronal calcium influx; mitochondrial dysfunction; intracellular activation of certain enzymes, such as lipases, proteases, endonucleases, and nitric oxide synthase; production of free radicals; and release of fatty acids. Permanently injured neurons release excitatory neurotransmitters, especially glutamate, maintaining this process[15,16].

Although all cases feature a failure in the control mechanisms of excitatory phenomena, the reasons why some SE become refractory or super-refractory are not yet completely understood. One of the most recently identified mechanisms related to the progression of SE is the presence of receptors along the axon membrane with highly dynamic features, undergoing receptor externalization and internalization during the course of a seizure.

Thus, with the progression of SE, receptors for inhibitory neurotransmitters (GABA) are progressively internalized, whereas receptors for excitatory neurotransmitters (glutamate) are expressed on the surface of the axon membrane, which perpetuates the ictal phenomenon[17].

Two other important mechanisms involved in the maintenance of the ictal phenomenon and neuronal cell death during SE are failure in the mitochondrial system, which triggers cell necrosis and apoptosis, and inflammatory phenomena that can alter the permeability of the blood–brain barrier and, consequently, the local potassium flux and neuronal excitability[18,19].

Treatment[1,21-23]

SE is a medical emergency in which neurological mortality and morbidity are closely related to the effectiveness and time of onset of the treatment. Thus, it is essential that not only the seizure but also the systemic effects and complications arising from SE be identified early and monitored.

The latest treatment protocols divide SE treatment into three stages. In “stage 1” (early status epilepticus), treatment should be administered with benzodiazepines. If the SE persists even after the use of these drugs, the patient enters “stage 2” (established status epilepticus) and should be treated with specific AEDs, including phenytoin, phenobarbital, and sodium valproate. If the SE persists for more than 2 hours after the use of these medications, it reaches “stage 3” (refractory status epilepticus), when general anesthesia is recommended until the EEG shows a burst/suppression pattern or the SE is under control both clinically and in the EEG[1,4,22].

For didactic purposes, we can divide the therapeutic approach toward SE into seven steps:

Step 1: Clinical determination of seizure etiology[1]

- Brief neurological examination, preferably before the start of drug treatment.
- Collection of basic information: past history of epilepsy, interrupted or irregular use of AED, recent history of traumatic brain injury, suspicion or clinical picture suggestive of metabolic disorders, CNS infection, or drug toxicity.

Step 2: Primary tests and examinations[1]

- Seizure in the pediatric emergency department: complete blood count; glucose, sodium, potassium, calcium, and magnesium levels; and arterial blood gases.
- Seizure with an uncertain duration or lasting over 30 minutes: liver enzymes (AST and ALT), amylase, urea, and creatinine.
- Signs or suspicion of CNS infection: cerebrospinal fluid collection only after the epileptic seizure is controlled and the patient is completely stable.
- Suspected acute or subacute CNS structural lesion: emergency neuroimaging examination, preferably head computed tomography.
- Specific cases and/or suspicion of toxicity: toxicology test and serum AED.

Step 3: General treatment measures[1]

- Always use a bed or gurney with raised sides in order to prevent falls and accidents.
- If necessary, insert an oropharyngeal cannula between the patient’s teeth to prevent tongue laceration, and frequently suction his or her mouth to reduce the risk of aspiration pneumonia.
- Frequently monitor the main vital signs: heart rate, respiratory rate, blood pressure, and temperature.
- Keep airways clear and, if necessary, administer oxygen through a mask with a flow rate of 2-3 liters/minute.
- Insert a venous catheter, avoiding central catheters in case the motor manifestations of SE are exacerbated, owing to the high risk of iatrogenic pneumothorax.

Step 4: Pharmacological measures[1]

First-line drugs:

Without a venous catheter: rectal diazepam (0.5 mg/kg - maximum dosage: 10 mg); oral midazolam (0.5 mg/kg

- maximum dosage: 10 mg); intranasal midazolam (0.2 mg/kg - maximum dosage: 10 mg); intramuscular midazolam (0.2 mg/kg - maximum dosage: 10 mg). An additional dose can be administered after 5 minutes[21].

With a venous catheter: diazepam (0.3 mg/kg - maximum dosage: 10 mg); midazolam (0.2 mg/kg - maximum dosage: 15 mg). An additional dose can be administered after 5 minutes[21].

Second-line drugs:

Phenytoin (15 to 20 mg/kg, intravenous - maximum infusion rate: 1 mg/kg/min, up to 50 mg/min). An additional dose of 10 mg/kg can be administered after 15 minutes[20].

Phenobarbital (20 mg/kg, intravenous - maximum infusion rate: 2 mg/kg/min, up to 100 mg/min). An additional dose of 20 mg/kg can be administered after 15 minutes[20].

Sodium valproate (20-40 mg/kg, intravenous, infused in 10 minutes[20]).

Third-line drugs:

From this stage of treatment, the patient should preferably be admitted to an intensive care unit and continually monitored by EEG.

Continuous midazolam: rapid intravenous infusion (0.1-0.3 mg/kg) followed by maintenance intravenous infusion (0.05-0.4 mg/kg/h)[1,20-22]. Its main advantage is the rapid onset of action and significant antiepileptic effect. However, benzodiazepines have an early tolerance and are associated with a high risk of seizure recurrence after the treatment is discontinued[22].

Thiopental: intravenous infusion of 100-250 mg in 20 seconds, followed by additional rapid 50mg infusions every 2-3 minutes until the SE is under control both clinically and in the EEG[1,21-23].

Pentobarbital: rapid intravenous infusion of 5-7 mg/kg, with a maximum infusion rate of 50 mg/min, followed by additional infusions of 1-5 mg/kg every 2-3 minutes until the SE is under control both clinically and in the EEG. Maintenance dose: 0.5 to 5 mg/kg/h[1,20-22].

The main advantages of using thiopental or pentobarbital are their significant antiepileptic effectiveness, relative safety, and long time of experience. On the other hand, these drugs present zero-order kinetics, which makes drug toxicity common, and their rapid redistribution may cause accumulation in the body and a prolonged half-life[22].

Propofol: rapid intravenous infusion (2 mg/kg), followed by maintenance intravenous infusion (5-10 mg/kg/h). Its main advantages are significant antiepileptic effectiveness, minimal interaction with other drugs, and rapid onset and end of action, allowing for greater control of potential side effects. Although propofol can lower blood pressure and heart rate, these effects are less frequent and less intense compared with those caused by continuous infusion of midazolam, thiopental, and pentobarbital[22].

Ketamine: rapid intravenous infusion (1.5 mg/kg), followed by maintenance intravenous infusion (0.01-0.05 mg/kg/h). Although ketamine is frequently used to treat SE, consistent studies on its effectiveness and safety in the pediatric population are scarce. However, it has a significant neuroprotective effect because it is a potent glutamate antagonist[1,20-22].

Lidocaine: rapid intravenous infusion (1-2 mg/kg), followed by maintenance intravenous infusion (6 mg/kg/h)[20].

The maintenance doses of these anesthetics should be titrated, in order to maintain control of the SE both clinically and in the EEG or until the EEG shows a burst/suppression pattern. There is no reliable evidence in the literature regarding which anesthetic is the most effective to control childhood SE, for how long should it be maintained, or how to reduce and discontinue it after the SE is under clinical and EEG control[1].

In case of failure of these anesthetics, there is no reliable data on the effectiveness of other treatments. High doses (up to 30 mg/kg/day, via enteral feeding tubes) of topiramate, targeted temperature management, levetiracetam, lacosamide, steroids, immunotherapy, and ketogenic diet can also be used as alternative treatment options[21,22].

Although steroids and adrenocorticotropic hormone have been used for many years to treat SE, little is known about their mechanisms of action and effectiveness. In super-refractory SE, the presence of antibodies against neuronal elements, such as voltage-gated potassium channels, has been demonstrated, which could explain the effectiveness of immunotherapy in some cases[23].

Ketogenic diet has been used in the treatment of medically refractory epilepsy since the 1920s. However, its prescription for super-refractory SE is controversial, lacking well-defined protocols. The first case series of patients with SE successfully treated with ketogenic diet was published in 2003[24]; few sound studies on this topic have been conducted since[21,22].

In experimental studies, such as the pilocarpine model in rats with SE, targeted temperature management reduced both the total duration of SE and neuronal apoptosis, suggesting that its use may be neuroprotective and improve neurological prognosis[25,26].

SE is one of the main and most frequent emergencies in pediatric emergency departments. Therefore, clinical protocols should be used routinely in these units in order to standardize care and reduce neurological mortality and morbidity.

REFERENCES

1. Liberalesso P. Manual de Diagnóstico e Tratamento das Epilepsias na Infância. 1ª ed. Curitiba: UTP; 2010.
2. Gastaut H. Classification of status epilepticus. In: Delgado-Escueta AV, Wasterlain CG, Treiman DM, Porter RJ, eds. Status Epilepticus: Mechanisms of brain damage and treatment. Advances in Neurology. New York: Raven Press; 1983. p. 15-35.

3. Lowenstein DH, Bleck T, Macdonal RL. It's time to revised the definition of status epilepticus. Epilepsia. 1999;40(1):120-2.
4. Shorvon SD, Trinka E. The 5th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures. Epilepsy Behav. 2015;49:1-3.
5. Sillanpää M, Shinnar S. Status epilepticus in a population-based cohort with childhood-onset epilepsy in Finland. Ann Neurol. 2002;52(3):303-10.
6. Towne AR, Waterhouse EJ, Boggs JG, Garnett LK, Brown AJ, Smith JR Jr, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology. 2000;54(2):340-5.
7. Chin RF, Neville BG, Peckham C, Bedford H, Wade A, Scott RC; NLSTEPSS Collaborative Group. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. Lancet. 2006;368(9531):222-9.
8. Singh RK, Stephens S, Berl MM, Chang T, Brown K, Vezina LG, et al. Prospective study of new-onset seizures presenting as status epilepticus in childhood. Neurology. 2010;74(8):636-42.
9. Shinnar S, Pellock JM, Berg AT. An inception cohort of children with febrile status epilepticus. Epilepsia. 1995;36(Suppl 4):31.
10. Shinnar S, Maytal J, Krasnoff L, Moshe SL. Recurrent status epilepticus in children. Ann Neurol. 1992;31(6):598-604.
11. Foreman B. Hirsch LJ. Epilepsy emergencies: diagnosis and management. Neurol Clin. 2012;30(1):11-41.
12. Ong J, Kerr DI. Recent advances in GABAB receptors: from pharmacology to molecular biology. Acta Pharmacol Sin. 2000;21(2):111-23.
13. Fountain NB, Lothman EW. Pathophysiology of status epilepticus. J Clin Neurophysiol. 1995;12(4):326-42.
14. Boggs JG. Mortality Associated with Status Epilepticus. Epilepsy Curr. 2004;4(1):25-7.
15. Meldrum BS, Brierley JB. Prolonged epileptic seizures in primates. Ischemic cell change and its relationship to ictal physiological events. Arch Neurol. 1973;28(1):10-7.
16. Meldrum BS, Horton RW. Physiology of status epilepticus in primates. Arch Neurol. 1973;28(1):1-9.
17. Smith KR, Kittler JT. The cell biology of synaptic inhibition in health and disease. Curr Opin Neurobiol. 2010;20(5):550-6.
18. Cock HR, Tong X, Hargreaves IP, Heales SJ, Clark JB, Patsalos PN, et al. Mitochondrial dysfunction associated with neuronal death following status epilepticus in rat. Epilepsy Res. 2002;48(3):157-68.
19. Friedman A, Dingledine R. Molecular cascades that mediate the influence of inflammation on epilepsy. Epilepsia. 2011;52(Suppl 3):33-9.
20. Coan AC, Montenegro MA, Guerreiro MM. Crises epilépticas e o estado de mal epiléptico. In: Rodrigues MM, Vilanova LCP, eds. Tratado de Neurologia Infantil. São Paulo: Atheneu; 2016. p. 51-65.
21. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016;16(1):48-61.
22. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain. 2011;134(Pt 10):2802-18.
23. Vezzani A, Balosso S, Aronica E, Ravizza T. Basic mechanisms of status epilepticus due to infection and inflammation. Epilepsia. 2009;50(Suppl 12):56-7.
24. Francois LL, Manel V, Roussele C, David M. Ketogenic regime as anti-epileptic treatment: its use in 29 epileptic children. Arch Pediatr. 2003;10(4):300-6.
25. Yu L, Zhou Y, Chen W, Wang Y. Mild hypothermia pretreatment protects against pilocarpine-induced status epilepticus and neuronalapoptosis in immature rats. Neuropathology. 2011;31(2):144-51.
26. Marchi N, Fan Q, Ghosh C, Fazio V, Bertolini F, Betto G, et al. Antagonism of peripheral inflammation reduces the severity of status epilepticus. Neurobiol Dis. 2009;33(2):171-81.