Seizure xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

25 years of advances in definition, classification and treatment of status epilepticus☆

Eugen Trinka[a,b,c,*], Reetta Kälviäinen[d,e]

[a] Department of Neurology, Paracelsus Medical University Salzburg, and Christian Doppler Medical Centre, Salzburg, Austria
[b] Centre for Cognitive Neurosciences Salzburg, Salzburg, Austria
[c] University for Medical Informatics and Health Technology, UMIT, Hall in Tirol, Austria
[d] Epilepsy Center, Neurocenter, Kuopio University Hospital, Kuopio, Finland
[e] Institute of Clinical Medicine, School of Medicine, Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland

ARTICLE INFO

Article history:
Received 31 October 2016
Accepted 1 November 2016
Available online xxx

Keywords:
Status epilepticus
Classification
Antiepileptic drugs
Benzodiazepines
Anesthetics

ABSTRACT

Purpose: Status epilepticus (SE) requires not only urgent symptomatic treatment with antiepileptic drugs but also rapid identification and treatment of its cause. This narrative review summarizes the most important advances in classification and treatment of SE.
Method: Data sources included MEDLINE, EMBASE, ClinicalTrials.gov, and back tracking of references in pertinent studies, reviews, and books.
Results: SE is now defined as "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 t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures." A new diagnostic classification system of SE introduces four axes: semiology, aetiology, EEG correlates, and age.
For the acute treatment intravenous benzodiazepines (lorazepam, diazepam, clonazepam) and intramuscular midazolam appear as most effective treatments for early SE. In children, buccal or intranasal midazolam are useful alternatives. In established SE intravenous antiepileptic drugs (phenytoin, valproate, levetiracetam, phenobarbital, and lacosamide) are in use. Treatment options in refractory SE are intravenous anaesthetics; ketamine, magnesium, steroids and other drugs have been used in super-refractory SE with variable outcomes.
Conclusion: Over the past 25 years major advances in definition, classification and understanding of its mechanisms have been achieved. Despite this up to 40% of patients in early status cannot be controlled with first line drugs. The treatment of super-refractory status is still an almost evidence free zone.

1. Introduction

Status epilepticus has an estimated incidence of up to 61 episodes per 100,000 per year and an overall mortality of 20% (range 1.9–40%) [1,2]. There has been considerable development in the past 25 years in the understanding of its pathophysiology, causes, clinical features, EEG changes, prognosis and treatment [3,4]. The purpose of this narrative review in the 25-year anniversary issue of "*Seizure—The European Epilepsy Journal*" is to give an update on definition, classification and therapeutic options for patients in SE.

2. Recent advances in the definition and classification of status epilepticus

Status epilepticus is often referred to the "*maximum expression of epilepsy*", but status is also a severe expression of an acute brain insult or systemic disturbance, which leads to excessive hyperexcitation of nervous tissue. The modern definition and classification of status epilepticus has its roots back to the 10th Marseilles Colloquium (the 10th European Electroencephalographic Meeting)

☆ One of the authors of this paper is a member of the current editorial team of Seizure. The supervision of the independent peer review process was undertaken and the decision about the publication of this manuscript were made by other members of the editorial team.

* Corresponding author at: Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University Salzburg, Centre for Cognitive Neuroscience Salzburg, Ignaz Harrerstrasse 79, A-5020 Salzburg, Austria. Fax: +43 572 5534899.
E-mail address: e.trinka@salk.at (E. Trinka).

http://dx.doi.org/10.1016/j.seizure.2016.11.001
1059-1311/

in 1962, which was completely devoted to status epilepticus. Gastaut and co-workers proposed a definition, which was consistent with the meaning of the original term *status* in Latin: "*Status epilepticus is a term whenever a seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring condition*" [5–7]. Although there was no duration specified in the definition, Gastaut later proposed 60 min to define status epilepticus [8]. In the revision of 1981, the definition was minimally changed into a "*seizure*" that "*persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur.*" [9]. Status was classified under the terms "prolonged or repetitive seizures (status epilepticus)"and was divided into partial (e.g., Jacksonian), or generalized (e.g., absence status or tonic-clonic status). "When very localized motor status occurs, it is referred to as *epilepsia partialis continua*". These concepts, while highly valuable, were imprecise, as they did not define the duration of a seizure that was fixed and enduring "or" sufficient length. In the past, experts suggested that 30 min of ongoing seizure activity could be regarded as "fixed and enduring". Over the past two decades the timelines in clinical trials and treatment recommendations were progressively moved to 20 min [10] and to 10 min [11]. Lowenstein et al. suggested in 1999 that a generalized tonic clonic seizure that is longer than the usual two to three minutes is prolonged, and should be treated as SE [12]. The time limit for convulsive status was consequently set to 5 min, which opened the door to change our view on the classical definitions of SE. The Commission of Classification and Terminology of the International League Against Epilepsy and the Commission on Epidemiology charged a Task Force with clinical researchers and epidemiologists to revise the classification of status epilepticus in 2009. The Task force came out in 2015 with the following definition: ***"Status epilepticus 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 t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures"*** [13]. This new definition of SE gives a good guidance, when emergency treatment must be considered. In general, time point t1 is the time when treatment should be started, which is at 5 min for generalized tonic clonic seizures, and at 10 min for focal seizures with or without impairment of consciousness. Time-point t2 marks the time at which neuronal damage or self-perpetuating alteration of neuronal networks may begin, and indicates that SE should be controlled latest by that time; 30 min in case of generalized tonic clonic seizures (Fig. 1).

The task force also came out with a new classification, built on four axes [13]: (i) semiology, (ii) etiology, (iii) EEG correlates, and (iv) age. The backbone of the classification is the semiology. The various clinical forms of status epilepticus are differentiated along two taxonomic criteria: *motor activity* and *impairment of consciousness* falling into two major groups: [1] status epilepticus with prominent motor symptoms, including all convulsive forms, and [2] those without prominent motor symptoms representing the non-convulsive forms of status epilepticus (NCSE) (see Table 1). Each group can be divided again according to the degree of impairment of consciousness, which is highly clinically relevant. Comatose NCSE represents a life threatening condition that requires urgent and consequent treatment, whereas NCSE proper without coma occurs most often in the form of absence status or focal status with impairment of consciousness (older terms for this conditions were "psychomotor status" or "complex partial status epilepticus") [13,14]. The etiology of status is divided into two groups: (i) known or symptomatic and (ii) unknown or cryptogenic. The symptomatic group can be subdivided into acute symptomatic, remote symptomatic and progressive symptomatic. The new classification also provides a list of known causes of status as an appendix to the classification, which can be updated periodically as new information emerges. Status epilepticus often

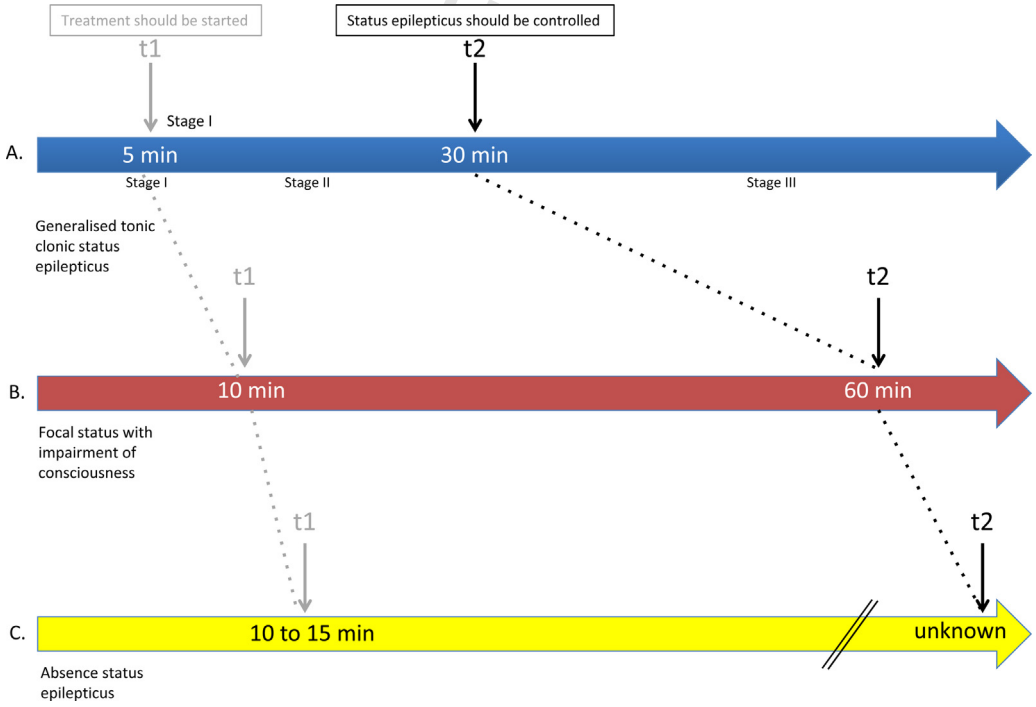

Fig. 1. Operational dimensions with t1 indicating the time that emergency treatment of SE should be started and t2 denoting the time at which long term consequences may be expected. Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity. Time (t2), when a seizure may cause long-term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits). For generalized tonic clonic status the stages have been added (stage I 5–10 min; stage II 10–30 min; stage III 30–30 min) [13].

Please cite this article in press as: E. Trinka, R. Kälviäinen, 25 years of advances in definition, classification and treatment of status epilepticus, Seizure: Eur J Epilepsy (2016), http://dx.doi.org/10.1016/j.seizure.2016.11.001