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Introduction

Status epilepticus (SE) is often referred to the “*maximum expression of epilepsy*.” It is also a very severe expression of an acute brain insult or systemic disturbance leading to excessive hyperexcitation of nervous tissue. But what is status epilepticus? The definition and classification of SE is best understood in its historical context, which is covered extensively in Chap. 1, “History of Status Epilepticus.”

The modern definition and classification of SE dates to the Xth Marseille Colloquium (the 10th European Electroencephalographic Meeting) in 1962, which was completely devoted to status epilepticus. Henri Gastaut, undoubtedly the dominant figure in epilepsy at the time, led the conference, held 2 years before he embarked on a seizure classification system. A total of 103 participants presented 237 cases with both clinical and EEG findings of abnormally prolonged or serially repeated seizures [1]. The proposed definition of SE was intended to be “*etymological*”—now referred to as *semantic* or *conceptual*—consistent with the meaning of the original term *status* in Latin: “*Status epilepticus is a term [used for] a seizure that persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring condition.*” Although there was no duration specified in the definition, Gastaut later proposed 60 min as the defining minimum duration for SE. Though not explicitly stated in the Colloquium report, Gastaut recalled in 1983 that there was a specific hypothesis that there were as many types of status as there were types of epileptic seizures [2]. Gastaut, along with his colleagues at the time, was leading the classification of seizure types. SE was divided into partial, generalized, or unilateral types and basically mirrored the seizure classification [3]. In the 1981 revision, the definition was changed minimally into a

“seizure [that] *persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur.*” Status was classified under the term “prolonged or repetitive seizures (SE)” 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*” [4].

This loose definition, without further explanation of what “fixed and enduring” or “sufficient length” meant, as well as the lack of clinical descriptions (i.e., semiology) of the SE types, was an inherent weakness of the 1970 Classification and its 1981 revision—which was not improved by the proposed diagnostic scheme in 2001 in which SE was classified within the different seizure types [5], and also not in the report of the International League Against Epilepsy (ILAE) Core Group on Classification [6]. In the last ILAE report of 2006, SE was defined “*mechanistically*” (“conceptually” would have been a clearer term), as “*the failure of the natural homeostatic seizure-suppressing mechanisms responsible for seizure termination*” without mentioning a specific time frame for the duration [6].

New Definition and Classification of Status Epilepticus

The previously described concepts, while highly valuable, were imprecise as they did not define the duration of a seizure that was “fixed and enduring” or of “sufficient length,” nor was there a clinical description (semiology) of the types of SE in the classification of 1970 (Table 2.1) or in its 1981 revision. In the report of the ILAE Core Group [6], the clinically used dichotomy of convulsive and nonconvulsive status was abandoned as “lay expressions” (Table 2.2). None of the aforementioned definitions guided clinicians in their treatment decisions or helped to improve outcomes by setting clear standards as to when emergency treatment should be started. In the past, experts suggested that 30 min

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Table 2.1 Clinical classification of status epilepticus per Gastaut 1970 [3]

Continuous seizure types
Generalized SE
Generalized tonic-clonic SE
Clonic SE
Absence SE
Tonic SE
Myoclonic SE
Focal SE
<i>Epilepsia partialis continua</i>
<i>Aura continua</i>
Limbic SE (psychomotor status)
Hemiconvulsive SE with hemiparesis

SE = status epilepticus

Table 2.2 Classification proposal from the 2006 Core Group of the Commission on Classification of the ILAE [6]

I. <i>Epilepsia partialis continua</i> of Kojevnikov
A. As occurs with Rasmussen syndrome
B. As occurs with focal lesions
C. As a component of inborn errors of metabolism
II. Supplementary motor area SE
III. <i>Aura continua</i>
IV. Dyscognitive focal (psychomotor, complex partial) SE
A. Mesial temporal
B. Neocortical
V. Tonic-clonic SE
VI. Absence SE
A. Typical and atypical absence SE
B. Myoclonic absence SE
VII. Myoclonic SE
VIII. Tonic SE
IX. Subtle SE

SE = status epilepticus

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 moved progressively to 20 min and then to 10 min. Lowenstein and colleagues suggested that a generalized tonic-clonic seizure longer than the usual 2–3 min is abnormally prolonged and should be treated as SE [7]. They recommended a time limit for convulsive status of 5 min. This concept opened the door to changing our view of the classical definition of SE.

The Commission of Classification and Terminology of the ILAE (Chair: Dr. Ingrid E. Scheffer) and the Commission on Epidemiology (Chairs: Drs. Ettore Beghi and Dale Hesdorffer) charged a Task Force, chaired by Dr. Daniel H.

Lowenstein and Dr. Eugen Trinka, with clinical researchers and epidemiologists, to revise the classification of SE in 2009. Members were Dr. Hannah Cock (UK), Dr. Hesdorffer (USA), Dr. Lowenstein (USA), Dr. Andrea O. Rossetti (Switzerland), Dr. Scheffer (Australia), Dr. Shlomo Shinnar (USA), Dr. Simon Shorvon (UK), and Dr. Trinka (Austria). This group aimed to achieve a unifying definition and classification of SE serving all purposes [8]. Because current knowledge regarding the pathophysiology and underlying neurobiology of SE is far from complete, the Task Force recognized that a proposed definition should include two dimensions: first, a conceptual approach based on the scientific evidence, and second, an operational frame to guide management.

A classification refers to the way in which items are organized and should be based ideally on the underlying neurobiology to form natural classes or entities [9]. Again, knowledge of the different types of SE and its underlying mechanisms are, at best, marginal so any classification would be a compromise between a conceptual, scientific (drawing on what is known) classification and a pragmatic empirical classification [10]. The Task force issued 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*” [8].

There are two novel aspects included in this definition: First, conceptually, SE does not represent only a “failure of seizure suppressing mechanism,” as maintained in 2006. Recent advances in the basic understanding of SE have made it clear that there is likely a multitude of simultaneous, parallel processes underlying SE, suggesting that initiation of perpetuating mechanisms seems to be at least as important as failure of suppressing mechanisms. Second, the two time-points, t1 and t2, are highly relevant clinically (Fig. 2.1): time-point t1 indicates when a seizure is abnormally prolonged and unlikely to stop spontaneously in a given time. There is good evidence from clinical research that this is at 5 min for generalized tonic-clonic seizures [11–14]. There is some evidence that t1 is at about 10 min in focal seizures with or without impairment of consciousness [14]. Thus, in general, t1 is the time when treatment should be started. In individual patients there may be some variability based on prior history and comorbidities. Time-point t2 marks the time at which neuronal damage or alteration of neuronal networks may begin, highlighting the need for aggressive treatment to prevent SE from reaching this stage. Again, as knowledge is incomplete, but given the experimental evidence indicating irreversible brain damage after

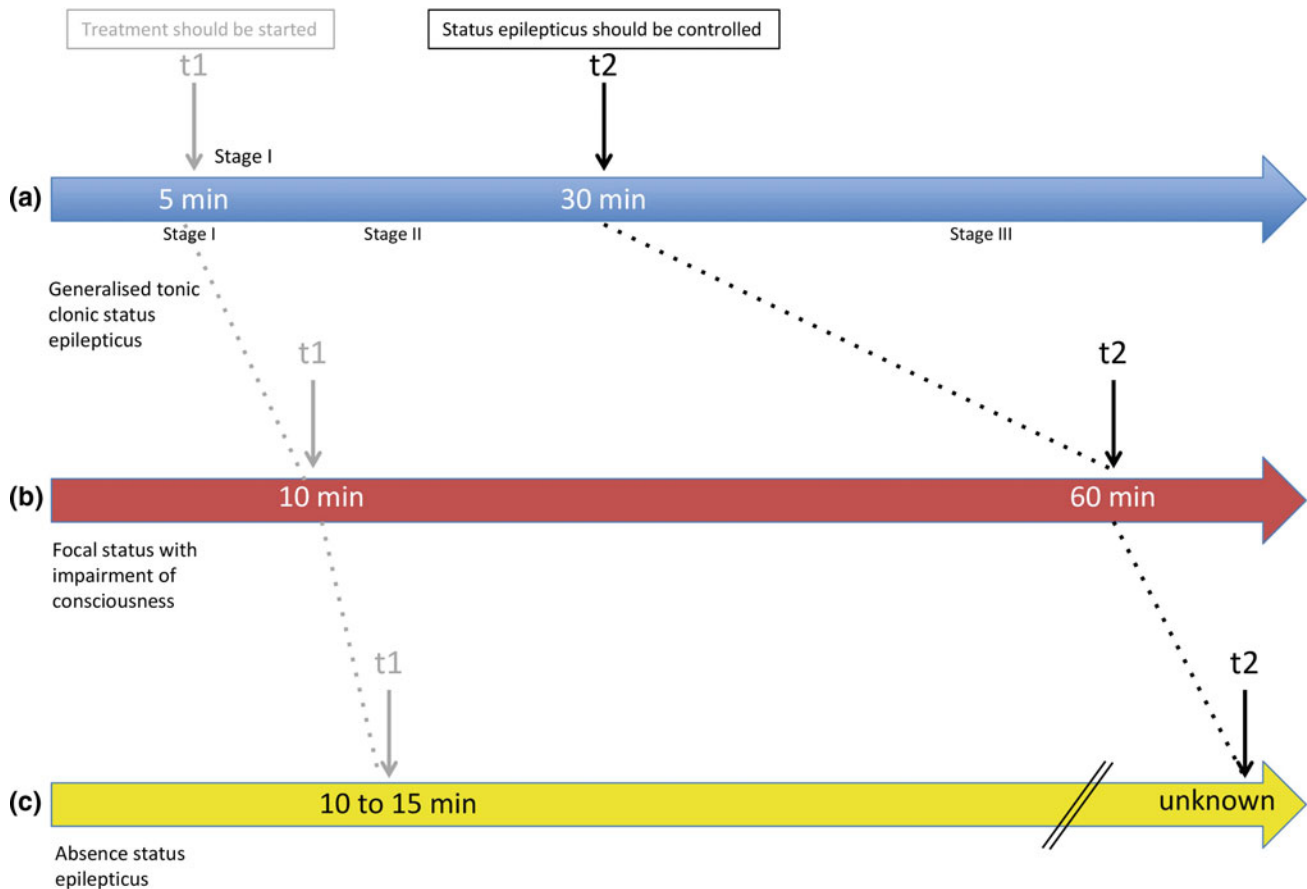


Fig. 2.1 Operational dimensions with t_1 indicating the time that emergency treatment of status epilepticus should be started and t_2 denoting the time at which long-term consequences may be expected. Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity. Time (t_2), 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 30–60 min)

prolonged seizures [15] and the potential threat of brain damage in humans, the Task Force proposed the continued use of 30 min as time-point t_2 in convulsive SE. There is only limited (or no) evidence for when neuronal damage takes place in other forms of SE [8, 15]. Imaging studies in humans suggest that cytotoxic edema occurs after prolonged seizure activity, so t_2 was set at 60 min for focal status with impairment of consciousness. The timelines were set primarily for operational purposes, and the timing of the onset of brain damage may vary considerably with age, intensity of SE, and other clinical circumstances. It was the intention of the Task Force to choose time t_2 to help provide a practical safe guideline for clinical purposes [8].

The framework for the new 2015 classification was built on four axes: (1) semiology, (2) etiology, (3) EEG correlates, and (4) age. The backbone of the classification is the semiology. Here, the different clinically identifiable forms of SE were divided along two taxonomic aspects: motor activity

and impairment of consciousness, yielding two major groups: (A) SE with prominent motor symptoms, including all convulsive forms, and (B) SE without prominent motor symptoms representing the nonconvulsive forms of SE (NCSE) (Table 2.3). Each group can be divided again according to the degree of impairment of consciousness, which is highly relevant clinically. NCSE with coma represents a life-threatening condition that requires urgent and intensive treatment, whereas NCSE without coma occurs most often in the form of absence SE or focal SE with impairment of consciousness (previously called “complex partial SE”), which are often far easier to control than the forms of NCSE associated with coma [16].

The etiology of status is divided into two groups: (1) known or symptomatic, and (2) unknown or cryptogenic. The symptomatic group can be subdivided into acute symptomatic, remote symptomatic, and progressive symptomatic. A list of known causes of SE is added in an

Table 2.3 Axis 1 (Semiology): International League Against Epilepsy (ILAE) classification of status epilepticus (From Trinka et al. [8], with permission)

A. With prominent motor symptoms
1. Convulsive status epilepticus (CSE; synonym: tonic-clonic SE)
a. Generalized convulsive
b. Focal onset evolving into bilateral convulsive SE
c. Unknown whether focal or generalized
2. Myoclonic status epilepticus (prominent epileptic myoclonic jerks)
a. With coma
b. Without coma
3. Focal motor status epilepticus
a. Repeated focal motor seizures (Jacksonian)
b. <i>Epilepsia partialis continua</i>
c. Adversive status
d. Oculoclonic status
e. Ictal paresis (i.e. focal inhibitory SE)
4. Tonic status epilepticus
5. Hyperkinetic SE
B. Without prominent motor symptoms (i.e. nonconvulsive status epilepticus, NCSE)
1. NCSE with coma (including so-called “subtle” SE)
2. NCSE without coma
a. Generalized
i. Typical absence status
ii. Atypical absence status
iii. Myoclonic absence status
b. Focal
i. Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
ii. Aphasic status
iii. With impaired consciousness
c. Unknown whether focal or generalized
Autonomic SE

appendix to the classification and can be used as a syllabus; this needs to be updated periodically as new information emerges. SE often occurs in the context of genetic epilepsy syndromes, but there is essentially always a trigger for the status itself, such as fever, electrolyte disturbance, or other intrinsic factors.

The third axis includes the electroencephalography (EEG) correlates of the SE. In convulsive SE, the clinical presentation is most often clear, and artifacts obscure the EEG, rendering the EEG of little value. The opposite is true for the nonconvulsive forms of SE (category B in axis 1), where a correct diagnosis is often not possible without EEG. In the most extreme forms, the patient is in deep coma and only an EEG can show the epileptiform or rhythmic discharges leading to the diagnosis [16, 17]. Nevertheless, caution is appropriate here. There is currently no clear consensus as to which EEG patterns in coma represent SE.

Therefore, the group recommended describing the EEG correlate of status in a given patient using the following descriptors: name of pattern, morphology, location, time-related features, modulation, and effect of intervention, and to use the recently proposed terminology from the American Clinical Neurophysiology Society [18] and its diagnostic EEG criteria for NCSE [17, 19–21] as a practical guide for diagnosis. With the new definition, there is hope to give clinicians better guidance as to when to treat, how aggressively to treat, and how to avoid over- or under-treatment of SE [22].

There are, of course, other clear directions for future research, e.g., concerning the time of t1 in the absence status, myoclonic status, and other forms of SE, which are completely unknown. Also, it must be emphasized that the idea of t1 was derived from a population with drug-resistant epilepsy undergoing video-EEG monitoring. Acute

symptomatic seizures may behave differently. The same is true for t2, and the time-points given here are for operational purposes, remaining fully aware that current knowledge is very limited. This classification of SE is the first attempt to not mirror the seizure classification system *per se* [8]. It is hoped that the use of two clinically accessible taxonomic criteria, namely motor activity and disturbance of consciousness, will lead to a broad acceptance by clinicians dealing with SE. Much research is necessary to determine whether the diagnosis of SE also includes boundary syndromes such as epileptic encephalopathies, coma with non-evolving epileptiform EEG patterns, behavioral disturbances (e.g., psychosis) in patients with epilepsy, or acute confusional states (e.g., delirium) with epileptiform EEG patterns [17, 23].

The new classification has already undergone a feasibility study by two members of the Task Force. They retrospectively assessed 488 episodes of SE and classified them according to previous clinical terminology and by the new classification system. Generalized convulsive SE occurred in 230 patients (47%), and nonconvulsive SE in coma in 29 (6%); these two categories corresponded almost perfectly between the two classifications. Focal SE, however, was markedly heterogeneous, and the new classification appeared to better reflect the clinical reality, offering more relevant subdivisions, which also differed in mortality rates [24].

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