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It's Time to Revise the Definition of Status Epilepticus

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Generalized, tonic–clonic status epilepticus is well recognized as a common neurologic emergency requiring prompt treatment. The diagnosis is usually not difficult, other than for patients with prolonged seizures, who often develop increasingly subtle clinical features (1,2). There also appears to be a consensus among physicians regarding treatment (3). Nonetheless, there is a major, persistent dilemma regarding status epilepticus: its definition. Discussions concerning the precise definition of status epilepticus all too often result in agreement that current "textbook" definitions are either imprecise, at odds with clinical practice, or both. Here we propose a revised system for defining status epilepticus that addresses these problems.

References to status epilepticus prior to the mid-19th century focused on cases in which seizures lasted many hours to days (4). In 1904, Clark and Prout (5) defined status epilepticus as a state in which seizures occur so frequently that "the coma and exhaustion are continuous between the seizures." In his general textbook of neurology published in 1940, Kinnier Wilson (6) referred to status epilepticus as the severest form of seizures in which "the post-convulsive sleep of one attack is cut short by development of the next." Aspects of these definitions were mirrored in the first International Classification of Epileptic Seizures that was developed in 1964 by the International League Against Epilepsy (ILAE). Status epilepticus was defined as the situation in which "a seizure persists for a sufficient length of time or is repeated frequently enough to produce a fixed and enduring epileptic condition" (7). The same definition was retained in the revised classification published in 1970 (8), and it was modified slightly in 1981 to refer to the situation in which "a seizure persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur" (9).

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Much of the confusion with status epilepticus is that the "official" definition by the ILAE lacks a specific *duration* of seizure activity. Most authors of reviews or research reports in the modern era choose precise temporal criteria, but these criteria lack uniformity. Until recently, the most popular duration of seizures qualifying as status epilepticus has been 30 min (for examples, see references 3 and 10–12). The rationale for this duration, when stated, has generally been that 30 min represents a time during which ongoing seizures can lead to neuronal injury in certain animal models. Nonetheless, in the past few years, some clinicians suggested the duration of seizures qualifying as status epilepticus should be shorter. In a review article in 1991, Bleck (13) defined status epilepticus as continuous or repeated seizures lasting >20 min. Furthermore, the recently completed, prospective VA Cooperative Trail on Treatment of Generalized Convulsive Status Epilepticus used a duration of 10 min as inclusion criterion for status epilepticus (14).

The essential problem in the evolution of these definitions has been the limited understanding of the basic, pathophysiological mechanisms underlying status epilepticus, as well as the variations in the clinical phenotype. Resolution of this problem will require considerably more time and effort. In the meantime, we propose that the definition of generalized, convulsive status epilepticus be revised to incorporate the very practical considerations of patient management. To do this, our scheme delineates two distinct definitions: an operational definition and a mechanistic definition.

OPERATIONAL DEFINITION

Generalized, convulsive status epilepticus in adults and older children (>5 years old) refers to ≥5 min of (a) continuous seizures ***or*** *(b) two or more discrete seizures between which there is incomplete recovery of consciousness.* This definition is in contrast to serial seizures, in which there are two or more seizures over a relatively brief period (i.e., minutes to many hours), but the patient regains consciousness between the seizures.

Given the unique forms of prolonged seizures in young children and infants, especially seizures associated with fever, a longer time frame than 5 min (e.g., 10–15 min) is suggested for this younger group. However, in contrast to the availability of data on seizure durations in adults (see the following), there is a paucity of similar information from young children. We are therefore unable to find a logical basis for providing an operational definition for status epilepticus in this younger group at this time.

Our rationale for the revised, operational definition in adults is based on the following three points:

1. Defining status epilepticus based on the theoretic onset of neuronal injury, as done in the past, is of questionable value because the relation between status epilepticus and neuronal injury in humans is complex and influenced by various factors besides duration of seizure activity. The seminal work in the 1970s by Meldrum et al. (15) established that seizures lasting >82 min in unanesthesized baboons could cause irreversible brain injury. However, five animals in status epilepticus for 50–120 min had no obvious brain injury. Not surprisingly, numerous clinical studies suggested a relation between seizure duration and patient mortality (16–18). However, acute mortality in status epilepticus is usually due to systemic derangements that are directly and indirectly related to persistent seizures, not neuronal injury per se. Furthermore, various reports suggested that the etiology of status epilepticus may be an extremely important determinant of short-term outcome and response to therapy, leading to even more variability in defining the time at which irreversible brain injury occurs (17–19). Although it is often not considered in definitions of status epilepticus, age is also an important determinant of outcome, further confounding the development of a definition of status epilepticus that has general application (18).
2. The typical, generalized tonic–clonic seizure (GTCS) in adults appears to last >5 min relatively rarely. Gastaut and Broughton (20) studied the clinical phenomenology of GTCS in thousands of patients, and observed that the tonic phase lasted 1–20 s, the clonic phase lasted ~30 s, and the "postictal tonic contraction" lasted a few seconds to 4 min. Another study found that the mean duration of secondarily generalized GTCSs was 53 s (21). More recently, in a careful video-EEG analysis of 120 secondarily GTCSs in 47 hospitalized patients, Theodore et al. (22) reported that the mean duration of GTCSs was 62 s, with a range of 16–108 s. These latter two studies were concerned with a selected group of patients (those with medically intractable partial seizures), so the results are not necessarily applicable to all GTCSs. Nonetheless, these observations, combined with data from clinical studies of status epilepticus, suggest that GTCSs in adults that do not terminate within 5 min may vary considerably in duration and last from many minutes to several hours. The biologic differences between adult patients with typical GTCSs lasting at most a few minutes and patients who have seizures lasting >5 min are unknown. In young children and infants, there is relatively little known about the durations of typical "single" seizures and prolonged seizures. As in adults, the factors that govern the duration of seizures in young children are poorly understood.
3. Perhaps most important, patients with convulsions that persist beyond the duration of a typical GTCS should be treated acutely with antiepileptic drugs (AEDs), as long as complications of therapy can be safely managed. This approach is consistent with common, clinical practice. When faced with a patient who is having continuous seizures, it is unreasonable to wait 30 or even 15 min before initiating therapy. Similarly, a patient in a postictal coma who has a second GTCS would be treated acutely. Patients who are experiencing GTCSs at the time of arrival in the emergency department are treated promptly, regardless of the prior duration of seizures. All of these practices are based on empiric observations that patients with persistent seizures of any duration are potentially at greater risk for cardiorespiratory problems. It also is obvious that assessment and management of these patients is much less complicated when the seizures are stopped. Simplified management is a primary reason for the increased use of AED therapy by paramedics in the pre-hospital setting. Paramedics who are called to treat patients with seizures in the pre-hospital setting often initiate therapy if the patient continues to have seizures at the time of paramedic arrival. In the ongoing "Pre-hospital Treatment of Status Epilepticus" (PHTSE) study in San Francisco, the working definition of status epilepticus sets the duration of seizures as >5 min to match local practice (23).

MECHANISTIC DEFINITION

Generalized, convulsive status epilepticus refers to a condition in which there is a failure of the "normal" factors that serve to terminate a typical GTCS. This definition can now be considered a basic research definition because our knowledge of the mechanisms governing seizure cessation remains incomplete. These mechanisms presumably involve abnormal persistence of seizure-

induced factors, a delay in the expression of factors that suppress seizures, or both. Once the factors responsible for seizure termination are fully understood, it will be possible to focus efforts on analyzing the evolving "seizure state" of a patient based on fundamental, pathophysiological properties. Ultimately, this definition should supplant the operational definition proposed, because a precise assessment of seizure pathophysiology in a patient will guide both aspects of clinical assessment and treatment decisions.

There are a number of benefits to this revised definition scheme. First, it offers an operational definition that makes clinical sense. Most clinicians agree that prolonged seizures are accompanied by an increased risk of complications, and that we should not wait 10 min or longer before instituting a treatment protocol for status epilepticus. Second, it highlights a potentially vital but as yet unknown pathophysiological distinction between the single GTCS in adults that appears typically to last $\leq$2–4 min and more prolonged seizures. (Further studies on the clinical epidemiology of status epilepticus—in both adults and pediatric patients—will be vital to refine these temporal criteria.) Third, it serves as a more realistic definition for clinical studies of status epilepticus. This will become even more important as progress is made in the rapid diagnosis and treatment of patients with seizures in the prehospital setting. However, there may be a need for alternative clinical research definitions, having different specifications for duration of seizures or recovery of consciousness, tailored to a particular population of patients or clinical setting.

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